CARDIAC DYSFUNCTION IN OBESITY PATIENTS

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Learn from yesterday,
live for today, hope for tomorrow.
The important thing is not to
stop questioning.

Albert Einstein

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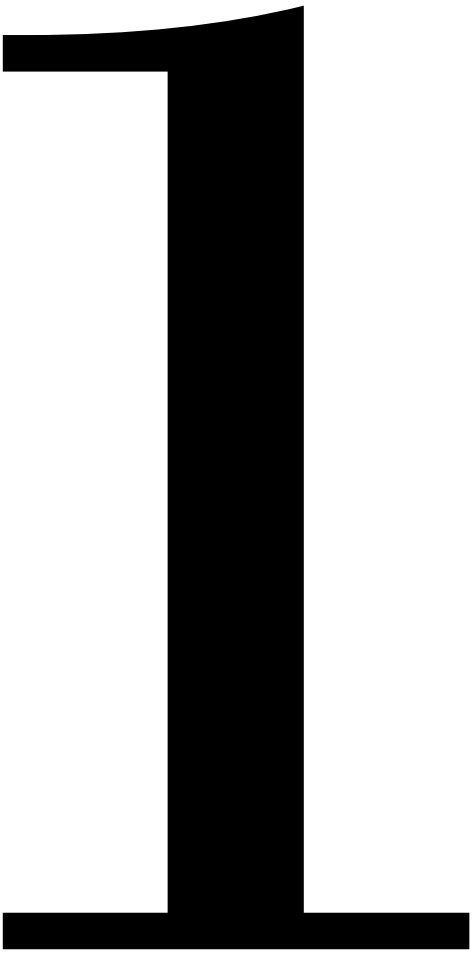
Part I

Introduction



Chapter 1

General introduction

GENERAL INTRODUCTION

Obesity

Obesity is a complex and incompletely understood disease. The World Health Organization defines obesity and overweight as "an abnormal or excessive fat accumulation to the extent that health may be impaired". Excess body fat is commonly measured by body mass index (BMI). BMI is a simple index of weight-for-height and is defined as the weight in kilograms divided by the square of the height in meters (kg/m^2). Overweight is classified as BMI ≥ 25 kg/m^2, obese as BMI ≥ 30 kg/m^2, and severely obese as BMI ≥ 35 kg/m^2.[1]

Since 1980, the prevalence of obesity has doubled in more than 70 countries,[2] and this is still increasing.[3] Moreover, more people are obese than underweight nowadays.[4] Looking at the exact numbers, in 2015 approximately 603.7 million adults were overweight worldwide, and 2.3% of men and 5.0% of women are even severely obese.[4,5] According to the "Rijksinstituut voor Volksgezondheid en Milieu" currently more than 50% of the Dutch population aged ≥ 18 years is overweight, and 15% obese.

Obesity has generally been accepted as one of the main health-threatening conditions and is a major challenge in health care practice and costs.[6] Epidemiologic studies have identified a high BMI as a risk factor for an expanding set of chronic diseases, including cardiovascular disease, hypertension, dyslipidaemia, diabetes mellitus, chronic kidney disease, many cancers, and an array of musculoskeletal disorders.[5] Also, obesity even doubles the lifetime risk of developing heart failure.[7,8]

Heart failure

Heart failure is a complex clinical syndrome that results from any structural or functional impairment of ventricular filling and/or ejection of blood,[9] which is characterized by an impaired quality of life, frequent hospitalizations, and poor outcome.[10] Heart failure is a major public health problem in developed countries,[11] affecting about 38 million people worldwide.[12] It is the most common reason for hospital admissions in patients aged 65 years or older.[13] Although the survival rate in patients with heart failure has improved, the mortality rate remains very high: more than 30% of patients die within 5 years of the diagnosis[13] despite of an overall decrease of cardiovascular mortality and morbidity with modern advances in diagnosis and therapy.[14]

The pathophysiology of heart failure is very complex. Ventricular remodelling resulting in hemodynamic and structural changes, neurohormonal system activation, and systemic

inflammation, are involved in the development and progression of the disease.[15] Estimates are that with every 1 kg/m^2 increase in BMI, the risk of developing heart failure increased by 5% in men and 7% in women.[16] It is also known that a BMI ≥30 kg/m^2 worsens the prognosis of these patients.[8] However, the relationship between these two chronic conditions is complex. Obesity is associated with diabetes mellitus, dyslipidaemia, and hypertension. However, the onset of heart failure in obesity cannot be fully explained by the presence of these traditional cardiac risk factors.[17]

Fortunately, significant advances in our understanding of the pathophysiological consequences of obesity for the cardiovascular system have been made over the past two decades, indicating that it is most likely multifactorial.[7,18] For example, myocardial lipotoxicity, thrombosis, altered endothelial function, compression by fat tissue, diastolic dysfunction, increased afterload and filling pressures may all play a role.[19]

The enormous and still growing prevalence of obesity warrants efficient screening of obesity patients with the highest need for further risk assessment, follow-up, and treatment.[20] However, the current knowledge on the role of obesity in causing cardiac dysfunction is insufficient to optimally develop such strategies for obesity patients.[18,21] New, more sensitive methods, such as advanced echocardiography may be eligible for this.

Echocardiography

Current guidelines recommend screening of obesity patients on the presence of cardiac risk factors.[18] It is expected that this will lead to an increase in the use of transthoracic echocardiography (TTE) in obesity patients.[22,23] The body habitus of obesity patients poses technical challenges regarding obtaining optimal echocardiographic image quality. However, studies in which the feasibility of obtaining echocardiographic parameters by TTE in obesity patients was reported are limited, and there are no studies regarding the applicability of speckle tracking echocardiography (STE) in this group of patients.

STE is a relatively new echocardiographic imaging modality that can quantify myocardial wall motion angle-independently.[24] Previous studies regarding detection of the early stages of cardiac dysfunction have shown the benefits of STE over left ventricular (LV) ejection fraction assessment.[25,26] Currently, STE is broadly available and echo-machines from all well-known vendors are generally equipped with speckle tracking software.[27] Strain can be assessed in three directions (longitudinal, circumferential, and radial), with the global longitudinal strain (GLS)

to be the most reproducible. It is therefore recommended to use GLS as a parameter of LV systolic function.[28]

Left ventricular hypertrophy

Left ventricular hypertrophy (LVH) occurs frequently in obesity patients, even in the absence of comorbidities such as hypertension,[29,30] and is associated with an increased risk of cardiovascular disease, morbidity, and mortality.[31-33] There is a direct relationship between body weight and left ventricular mass.[34] The presence of excess adipose as well as non-adipose tissue results in an increased blood volume, as well as a hyperdynamic circulation in response to the increased metabolic demand.[35] The change in cardiac output necessary to meet this increased metabolic demand is largely mediated through an increased stroke volume, mainly because of a higher venous return.[36] Concurrently, the increased preload leads to an increased ventricular wall tension, which chronically may lead to chamber dilatation and contribute to heart failure.[34] In addition, coexisting hypertension can increase afterload, contributing to cardiac remodelling, LVH, and eventually the development of heart failure.[36]

The estimation of left ventricular mass (LVM) is determined by echocardiography. Although echocardiography is a more sensitive tool to identify an increased LVM and thereby LVH, the standard electrocardiogram (ECG) remains widely used, because of its established clinical value, broad availability and low costs. However, the value of LVH criteria is questionable in obesity patients,[37,38] because obesity is responsible for geometrical and electrophysiological changes of the heart and ECG voltages may be attenuated by subcutaneous adipose tissue.[39,40]

Heart rate variability

The autonomic nervous system is a control system that acts largely unconsciously and regulates bodily functions such as the heart rate, digestion, respiratory rate, pupillary response, and urination through its two branches: the sympathetic and parasympathetic nervous systems. The heart rate variability (HRV) measures the effect of autonomic function on the heart. Even a slight variation in autonomic regulation of the heart changes the heart rate and rhythm. The HRV looks through beat-to-beat variation during ECG recording.[41] 24-hour recording of the standard deviation of all RR intervals (SDNN) by Holter monitoring reveals the sympathetic nervous system contribution to HRV.[42] Furthermore, the SDNN-index estimates the variability due to the factors affecting HRV within a 5 minute period.[43] A depressed HRV has been confirmed to be a prognostic marker and is correlated with morbidity and mortality.[44-46]

Furthermore, sympathetic nervous system dysfunction seems crucial in the development of heart failure.[47] Previous studies have described a decreased HRV in obesity patients.[41,48] Therefore, Holter monitoring could be used as an instrument to detect cardiac dysfunction in obesity patients.

Biomarkers

Nowadays, biomarkers play a major role in the diagnosis and management of heart failure.[49,50] Natriuretic peptides are the gold standard biomarkers for the diagnosis and prognosis of heart failure.[51] However, natriuretic peptides are decreased in obesity patients and they are therefore of less use than in non-obese patients.[52] In addition, heart failure in obesity patients appears to result not only from cardiac overload or injury but also from factors specifically related to the abundant fat tissue.[53] As such, natriuretic peptides might not be the only biomarkers relevant in cardiac dysfunction in obesity patients. Currently, a variety of biomarkers are described, reflecting several biological processes that have been hypothesized to play an important role in the occurrence of cardiac dysfunction, such as inflammation, oxidative stress, extracellular matrix remodelling, neurohormones, atherosclerosis, insulin resistance, myocyte injury, and myocyte stress.[54] Especially inflammation is recognized as an important component of the pathogenesis of heart failure and has significant prognostic implications.[36,55] In addition, obesity itself is a chronic inflammatory condition.[56] Moreover, locally produced or circulating adipokines such as leptin and adiponectin have also been demonstrated to contribute directly to the cardiac remodelling, through their effects on myocardial metabolism and structure and the composition of the myocardial extracellular matrix.[57]

The use of multiplex immunoassays that determine a broad spectrum of blood biomarkers reflecting multiple processes is gaining interest in medical science.[54,58] Therefore, it may also help to better understand the underlying pathophysiology of cardiac dysfunction in obesity patients.

Bariatric surgery

Clinically significant weight loss is difficult to achieve with lifestyle interventions and the results are often temporary. In contrast, bariatric surgery is an effective and safe treatment option resulting in large long-term weight loss.[59,60] Several studies suggest that weight loss achieved by bariatric surgery has a positive impact on heart morphology in obesity patients without heart failure.[61] For example, it is associated with a 35% reduced incidence of new-onset heart failure during long term follow-up.[62] It also offers beneficial cardiac effects on both

systolic and diastolic function, and myocardial structure in obesity patients.[63] However, little is known about the pathophysiology behind this improvement. Also, we cannot predict which patients still have cardiac dysfunction post-surgery.

Cardiac rehabilitation in obesity patients

Intentional weight loss, accomplished through behavioural weight loss and exercise, improves insulin sensitivity and associated cardio-metabolic risk factors such as: lipid measures, blood pressure, inflammation, and vascular function.[64] Besides the benefits of weight reduction, exercise itself may be possible to reverse cardiac dysfunction.[65]

Nowadays, cardiac rehabilitation (CR) is a valuable treatment for patients with a broad spectrum of cardiac disease.[66] Currently, at entry into CR over 80% of the patients are overweight, and over 40% are even obese.[67] However, usual CR programs are far from optimal in obesity patients, because they have a higher cardio metabolic risk and poorer fitness. There is growing evidence that effects achieved during usual CR in obesity patients are substantially smaller than in non-obese patients.[68] Also, CR programs do not generally include weight loss programs.[67] A novel tailor-made CR could make a positive contribution to obesity patients with cardiovascular disease.

OUTLINE OF THIS THESIS

The overarching aim of this thesis is to study the association between cardiac dysfunction and obesity, focussing on the early signs of cardiac dysfunction, the possible pathophysiology, and changes after weight loss.

Part I contains the introduction of this thesis. In **Chapter 1,** we describe the general introduction on obesity patients and cardiac dysfunction. Background information on the different diagnostics that were used, cardiovascular biomarkers, and weight loss are provided. In **Chapter 2**, we describe the study design of the CARdiac Dysfunction In OBesity – Early Signs Evaluation (CARDIOBESE)-study, which is the main study of this thesis.

In **Part II**, we focus on the applicability of different diagnostics used in daily clinical practice in obesity patients. In **Chapter 3**, we describe the feasibility and reproducibility of regular and speckle tracking echocardiography in obesity patients. In **Chapter 4,** is the accuracy of the most commonly used ECG criteria for the detection of LVH in obesity patients evaluated, and are new ECG criteria proposed and prospectively tested.

The focus in **Part III** is on cardiac dysfunction related to obesity and the impact of bariatric surgery. In **Chapter 5**, we describe the early detection of LV diastolic dysfunction using conventional and speckle tracking echocardiography in a large animal model with metabolic dysfunction. In **Chapter 6**, we focus on the prevalence and pathophysiology of subclinical cardiac dysfunction in obesity patients as detected by multimodality diagnostics. In **Chapter 7**, we investigate whether bariatric surgery is associated with changes in subclinical cardiac function, in order to gain insight into the underlying pathophysiology. Also, predictors for maintaining subclinical cardiac dysfunction one-year post-bariatric surgery were investigated.

In **Part IV**, we describe cardiovascular biomarker profiles in obesity patients. In **Chapter 8**, we compared cardiovascular biomarker profiles between obesity patients and non-obese controls, and between obesity patients with and without cardiac dysfunction. Again, with the purpose of better understanding the underlying pathophysiology of cardiac dysfunction in obesity patients. In **Chapter 9**, we studied before and after bariatric surgery changes in cardiovascular biomarker profiles between obesity patients with and without cardiac dysfunction, in order to better understand the underlying pathophysiology. In addition, we constructed a model to gain insight into which patients have cardiac dysfunction post-bariatric surgery.

In **Part V** (**Chapter 10**) we evaluated echocardiographic changes after tailor-made cardiac rehabilitation for obesity patients, to better understand the effect of weight loss and exercise on cardiac function in obesity patients with cardiovascular disease.

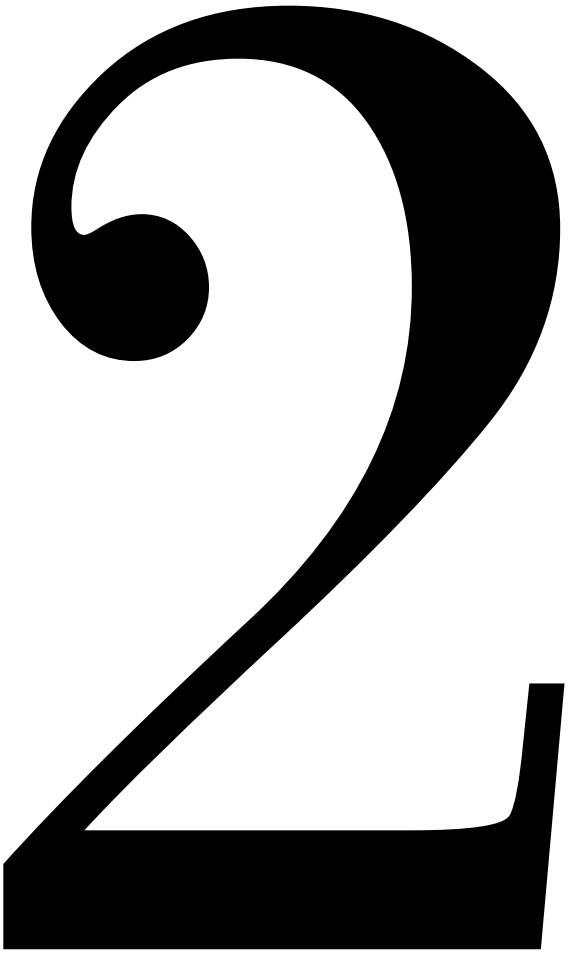
Finally, in **Part VI,** we place the results of the studies described in this thesis in a broad context, discus the implications of the findings, and provide recommendations for future research (**Chapter 11)**. Last, in **Chapter 12,** we provide a summary of the main findings of this thesis.

REFERENCES

1. Obesity: preventing and managing the global epidemic. Report of a WHO consultation. World Health Organ Tech Rep Ser 2000;894:i-xii, 1-253.
2. Afshin A, Reitsma MB, Murray CJL. Health Effects of Overweight and Obesity in 195 Countries. N Engl J Med 2017;377:1496-7.
3. Global BMIMC, Di Angelantonio E, Bhupathiraju Sh N, et al. Body-mass index and all-cause mortality: individual-participant-data meta-analysis of 239 prospective studies in four continents. Lancet 2016;388:776-86.
4. Collaboration NCDRF. Trends in adult body-mass index in 200 countries from 1975 to 2014: a pooled analysis of 1698 population-based measurement studies with 19.2 million participants. Lancet 2016;387:1377-96.
5. Collaborators GBDO, Afshin A, Forouzanfar MH, et al. Health Effects of Overweight and Obesity in 195 Countries over 25 Years. N Engl J Med 2017;377:13-27.
6. Suehs BT, Kamble P, Huang J, et al. Association of obesity with healthcare utilization and costs in a Medicare population. Curr Med Res Opin 2017;33:2173-80.
7. Bui AL, Horwich TB, Fonarow GC. Epidemiology and risk profile of heart failure. Nat Rev Cardiol 2011;8:30-41.
8. Lavie CJ, Sharma A, Alpert MA, et al. Update on Obesity and Obesity Paradox in Heart Failure. Prog Cardiovasc Dis 2016;58:393-400.
9. Yancy CW, Jessup M, Bozkurt B, et al. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2013;62:e147-239.
10. Stewart S, MacIntyre K, Hole DJ, Capewell S, McMurray JJ. More 'malignant' than cancer? Five-year survival following a first admission for heart failure. Eur J Heart Fail 2001;3:315-22.
11. Zarrinkoub R, Wettermark B, Wandell P, et al. The epidemiology of heart failure, based on data for 2.1 million inhabitants in Sweden. Eur J Heart Fail 2013;15:995-1002.
12. Writing Group M, Mozaffarian D, Benjamin EJ, et al. Heart Disease and Stroke Statistics-2016 Update: A Report From the American Heart Association. Circulation 2016;133:e38-360.
13. Braunwald E. Heart failure. JACC Heart Fail 2013;1:1-20.
14. Heidenreich PA, Trogdon JG, Khavjou OA, et al. Forecasting the future of cardiovascular disease in the United States: a policy statement from the American Heart Association. Circulation 2011;123:933-44.
15. Carbone S, Canada JM, Buckley LF, et al. Obesity Contributes to Exercise Intolerance in Heart Failure With Preserved Ejection Fraction. J Am Coll Cardiol 2016;68:2487-8.
16. Kenchaiah S, Evans JC, Levy D, et al. Obesity and the risk of heart failure. N Engl J Med 2002;347:305-13.
17. Ndumele CE, Matsushita K, Lazo M, et al. Obesity and Subtypes of Incident Cardiovascular Disease. J Am Heart Assoc 2016;5.
18. Badimon L, Bugiardini R, Cenko E, et al. Position paper of the European Society of Cardiology-working group of coronary pathophysiology and microcirculation: obesity and heart disease. Eur Heart J 2017;38:1951-8.
19. Kitzman DW, Shah SJ. The HFpEF Obesity Phenotype: The Elephant in the Room. J Am Coll Cardiol 2016;68:200-3.
20. Benjamin EJ, Muntner P, Alonso A, et al. Heart Disease and Stroke Statistics-2019 Update: A Report From the American Heart Association. Circulation 2019;139:e56-e528.
21. Finer N. Weight loss for patients with obesity and heart failure. Eur Heart J 2019.
22. Murphy NF, MacIntyre K, Stewart S, Hart CL, Hole D, McMurray JJ. Long-term cardiovascular consequences of obesity: 20-year follow-up of more than 15 000 middle-aged men and women (the Renfrew-Paisley study). Eur Heart J 2006;27:96-106.
23. Martin RP. American Society of Echocardiography president's message: echocardiography and the epidemics. J Am Soc Echocardiogr 2003;16:16A-7A.
24. van Dalen BM, Tzikas A, Soliman OI, et al. Assessment of subendocardial contractile function in aortic stenosis: a study using speckle tracking echocardiography. Echocardiography 2013;30:293-300.
25. Ersboll M, Valeur N, Mogensen UM, et al. Prediction of all-cause mortality and heart failure admissions from global left ventricular longitudinal strain in patients with acute myocardial infarction and preserved left ventricular ejection fraction. J Am Coll Cardiol 2013;61:2365-73.

26. Dalen H, Thorstensen A, Romundstad PR, Aase SA, Stoylen A, Vatten LJ. Cardiovascular risk factors and systolic and diastolic cardiac function: a tissue Doppler and speckle tracking echocardiographic study. J Am Soc Echocardiogr 2011;24:322-32 e6.
27. Menting ME, McGhie JS, Koopman LP, et al. Normal myocardial strain values using 2D speckle tracking echocardiography in healthy adults aged 20 to 72 years. Echocardiography 2016;33:1665-75.
28. Lang RM, Badano LP, Mor-Avi V, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. Eur Heart J Cardiovasc Imaging 2015;16:233-70.
29. Alpert MA, Lambert CR, Terry BE, et al. Effect of weight loss on left ventricular mass in nonhypertensive morbidly obese patients. Am J Cardiol 1994;73:918-21.
30. Himeno E, Nishino K, Nakashima Y, Kuroiwa A, Ikeda M. Weight reduction regresses left ventricular mass regardless of blood pressure level in obese subjects. Am Heart J 1996;131:313-9.
31. Havranek EP, Froshaug DB, Emserman CD, et al. Left ventricular hypertrophy and cardiovascular mortality by race and ethnicity. Am J Med 2008;121:870-5.
32. Porthan K, Kentta T, Niiranen TJ, et al. ECG left ventricular hypertrophy as a risk predictor of sudden cardiac death. Int J Cardiol 2019;276:125-9.
33. Wenger NK. Prevention of cardiovascular disease: highlights for the clinician of the 2013 American College of Cardiology/American Heart Association guidelines. Clin Cardiol 2014;37:239-51.
34. Cuspidi C, Rescaldani M, Sala C, Grassi G. Left-ventricular hypertrophy and obesity: a systematic review and meta-analysis of echocardiographic studies. J Hypertens 2014;32:16-25.
35. Bella JN, Devereux RB, Roman MJ, et al. Relations of left ventricular mass to fat-free and adipose body mass: the strong heart study. The Strong Heart Study Investigators. Circulation 1998;98:2538-44.
36. Zhai AB, Haddad H. The impact of obesity on heart failure. Curr Opin Cardiol 2017;32:196-202.
37. Robinson C, Woodiwiss AJ, Libhaber CD, Norton GR. Novel Approach to the Detection of Left Ventricular Hypertrophy Using Body Mass Index-Corrected Electrocardiographic Voltage Criteria in a Group of African Ancestry. Clin Cardiol 2016;39:524-30.
38. Domienik-Karlowicz J, Rymarczyk Z, Lisik W, et al. Questionable validity of left ventricular hypertrophy cutoff values in morbidly and super-morbidly obese patients. Ann Noninvasive Electrocardiol 2018;23:e12564.
39. Okin PM, Roman MJ, Devereux RB, Kligfield P. Electrocardiographic identification of left ventricular hypertrophy: test performance in relation to definition of hypertrophy and presence of obesity. J Am Coll Cardiol 1996;27:124-31.
40. Germano G. Electrocardiographic signs of left ventricular hypertrophy in obese patients: what criteria should be used? High Blood Press Cardiovasc Prev 2015;22:5-9.
41. Yadav RL, Yadav PK, Yadav LK, Agrawal K, Sah SK, Islam MN. Association between obesity and heart rate variability indices: an intuition toward cardiac autonomic alteration - a risk of CVD. Diabetes Metab Syndr Obes 2017;10:57-64.
42. Grant CC, van Rensburg DC, Strydom N, Viljoen M. Importance of tachogram length and period of recording during noninvasive investigation of the autonomic nervous system. Ann Noninvasive Electrocardiol 2011;16:131-9.
43. Shaffer F, Ginsberg JP. An Overview of Heart Rate Variability Metrics and Norms. Front Public Health 2017;5:258.
44. Forslund L, Bjorkander I, Ericson M, et al. Prognostic implications of autonomic function assessed by analyses of catecholamines and heart rate variability in stable angina pectoris. Heart 2002;87:415-22.
45. Bauer A, Kantelhardt JW, Barthel P, et al. Deceleration capacity of heart rate as a predictor of mortality after myocardial infarction: cohort study. Lancet 2006;367:1674-81.
46. Huikuri HV, Stein PK. Heart rate variability in risk stratification of cardiac patients. Prog Cardiovasc Dis 2013;56:153-9.
47. Florea VG, Cohn JN. The autonomic nervous system and heart failure. Circ Res 2014;114:1815-26.
48. Karason K, Molgaard H, Wikstrand J, Sjostrom L. Heart rate variability in obesity and the effect of weight loss. Am J Cardiol 1999;83:1242-7.
49. Demissei BG, Valente MA, Cleland JG, et al. Optimizing clinical use of biomarkers in high-risk acute heart failure patients. Eur J Heart Fail 2016;18:269-80.
50. Brouwers FP, van Gilst WH, Damman K, et al. Clinical risk stratification optimizes value of biomarkers to predict new-onset heart failure in a community-based cohort. Circ Heart Fail 2014;7:723-31.
51. Mueller C, McDonald K, de Boer RA, et al. Heart Failure Association of the European Society of Cardiology practical guidance on the use of natriuretic peptide concentrations. Eur J Heart Fail 2019;21:715-31.

52. Mehra MR, Uber PA, Park MH, et al. Obesity and suppressed B-type natriuretic peptide levels in heart failure. J Am Coll Cardiol 2004;43:1590-5.
53. Alpert MA, Lavie CJ, Agrawal H, Kumar A, Kumar SA. Cardiac Effects of Obesity: PATHOPHYSIOLOGIC, CLINICAL, AND PROGNOSTIC CONSEQUENCES-A REVIEW. J Cardiopulm Rehabil Prev 2016;36:1-11.
54. Braunwald E. Biomarkers in heart failure. N Engl J Med 2008;358:2148-59.
55. Gullestad L, Ueland T, Vinge LE, Finsen A, Yndestad A, Aukrust P. Inflammatory cytokines in heart failure: mediators and markers. Cardiology 2012;122:23-35.
56. Lumeng CN, Saltiel AR. Inflammatory links between obesity and metabolic disease. J Clin Invest 2011;121:2111-7.
57. Schram K, Sweeney G. Implications of myocardial matrix remodeling by adipokines in obesity-related heart failure. Trends Cardiovasc Med 2008;18:199-205.
58. Santema BT, Kloosterman M, Van Gelder IC, et al. Comparing biomarker profiles of patients with heart failure: atrial fibrillation vs. sinus rhythm and reduced vs. preserved ejection fraction. Eur Heart J 2018;39:3867-75.
59. DeMaria EJ. Bariatric surgery for morbid obesity. N Engl J Med 2007;356:2176-83.
60. Sjostrom L, Lindroos AK, Peltonen M, et al. Lifestyle, diabetes, and cardiovascular risk factors 10 years after bariatric surgery. N Engl J Med 2004;351:2683-93.
61. Vest AR, Heneghan HM, Agarwal S, Schauer PR, Young JB. Bariatric surgery and cardiovascular outcomes: a systematic review. Heart 2012;98:1763-77.
62. Jamaly S, Carlsson L, Peltonen M, Jacobson P, Karason K. Surgical obesity treatment and the risk of heart failure. Eur Heart J 2019.
63. Aggarwal R, Harling L, Efthimiou E, Darzi A, Athanasiou T, Ashrafian H. The Effects of Bariatric Surgery on Cardiac Structure and Function: a Systematic Review of Cardiac Imaging Outcomes. Obes Surg 2016;26:1030-40.
64. Ades PA, Savage PD. Potential benefits of weight loss in coronary heart disease. Prog Cardiovasc Dis 2014;56:448-56.
65. Baynard T, Carhart RL, Jr., Ploutz-Snyder LL, Weinstock RS, Kanaley JA. Short-term training effects on diastolic function in obese persons with the metabolic syndrome. Obesity (Silver Spring) 2008;16:1277-83.
66. Doimo S, Fabris E, Piepoli M, et al. Impact of ambulatory cardiac rehabilitation on cardiovascular outcomes: a long-term follow-up study. Eur Heart J 2019;40:678-85.
67. Ades PA, Savage PD, Harvey-Berino J. The treatment of obesity in cardiac rehabilitation. J Cardiopulm Rehabil Prev 2010;30:289-98.
68. Savage PD, Ades PA. The obesity epidemic in the United States: role of cardiac rehabilitation. Coron Artery Dis 2006;17:227-31.



Chapter 2

Cross-sectional and prospective follow-up study to detect early signs of cardiac dysfunction in obesity: protocol of the CARDIOBESE study

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ABSTRACT

Introduction

In view of the increasing occurrence of both obesity and heart failure, a growing overlap of these two clinical entities in the near future is expected. Significant advances in our understanding of the pathophysiological consequences of obesity for the cardiovascular system have been made over the past two decades. However, to optimise management and treatment of obesity patients, further research is required to improve early identification of cardiac dysfunction in obesity and to gain insight in the underlying pathophysiology. The CARdiac Dysfunction In OBesity – Early Signs Evaluation (CARDIOBESE) study has been designed to address these issues.

Methods and analysis

CARDIOBESE is a cross-sectional multicentre study of 100 obesity patients scheduled for bariatric surgery (body mass index (BMI) ≥35 kg/m^2) without known cardiovascular disease, and 50 age-matched and gender-matched non-obese controls (BMI<30 kg/m^2). Echocardiography, blood and urine biomarkers and Holter monitoring will be used to identify parameters that are able to show cardiac dysfunction at a very early stage in obesity patients (*primary objective*). Furthermore, a prospective follow-up study of obesity patients before and 1 year after bariatric surgery will be done to gain insight in the pathophysiology of obesity causing cardiac dysfunction (*secondary objective*).

Ethics and dissemination

The study was approved by the Medical Ethics Committee Toetsingscommissie Wetenschappelijk Onderzoek Rotterdam e.o. (TWOR). Inclusion of patients and controls is almost complete. Analyses of the investigations are currently being performed, and dissemination through peer-reviewed publications and conference presentations is expected from the first quarter of 2019. By identifying early markers of cardiac dysfunction in obesity, and by understanding the underlying pathophysiology of the abnormalities of these markers, the CARDIOBESE study may provide guidance for risk stratification, monitoring and treatment strategies for obesity patients.

INTRODUCTION

In view of the increasing occurrence of both obesity and heart failure, a growing overlap of these two clinical entities in the near future is expected.[1–3] A body mass index (BMI) ≥30 kg/m^2 worsens the prognosis of patients with cardiovascular disease and doubles the lifetime risk of developing heart failure. Significant advances in our understanding of the pathophysiological consequences of obesity for the cardiovascular system have been made over the past two decades.[4,5] Obesity is associated with diabetes mellitus, dyslipidaemia and hypertension. However, the onset of heart failure in obesity cannot be fully explained by the presence of these traditional cardiac risk factors.[6] Also, BMI may not be the optimal parameter to reflect increased cardiovascular risk in obesity.[7]

Present-day guidelines recommend screening of obesity patients on presence of cardiac risk factors and inclusion of obesity patients in cardiovascular rehabilitation programmes directed to reduce body weight and increase physical activity, thereby improving cardiac risk factors.[5] The enormous and still growing prevalence of obesity warrants efficient screening of obesity patients with the highest need for such further risk assessment, follow-up and treatment. Current knowledge on the role of obesity in causing cardiac dysfunction is insufficient to optimally develop such strategies for obesity patients.

The aim of the CARdiac Dysfunction In OBesity – Early Signs Evaluation (CARDIOBESE) study is to identify subclinical cardiac dysfunction in obesity patients by echocardiography, blood and urine tests and/or Holter monitoring (*primary objective*).

Bariatric surgery has proven to be a successful therapy for severe obese patients, both regarding weight loss and reduction of traditional cardiac risk factors.[8] Relating findings of the diagnostic techniques for assessment of cardiac dysfunction used in the CARDIOBESE study to specific features of obesity and by comparing results in obesity patients before and 1 year after bariatric surgery may help to gain insight in the pathophysiology of obesity causing cardiac dysfunction (*secondary objective*).

To the best of our knowledge, the CARDIOBESE study will be the first study in which (speckle tracking) echocardiography, blood and urine biomarkers and Holter monitoring will be combined in a cohort of obesity patients and non-obese controls.

METHODS

Study Design

Recruitment and inclusion of 100 consecutive obesity patients will take place at the bariatric surgery outpatient clinics of the Franciscus Gasthuis & Vlietland (75 patients) and the Maasstad

Ziekenhuis (25 patients). Fifty non-obese controls will be recruited using advertisements in a local newspaper or will be personnel recruited from the participating hospitals or family members or friends of personnel. Cardiologists of the Erasmus University Medical Centre with extensive expertise on early detection of cardiac dysfunction were involved in the design of the study and will be assisting in data analysis.

Primary objective

A cross-sectional study of obesity patients scheduled for bariatric surgery and age-matched and gender-matched non-obese controls will be performed to quantify the proportion of early signs of cardiac dysfunction in obesity patients and to determine if obesity patients have an elevated prevalence of cardiac dysfunction. Conventional and advanced echocardiography will be performed, blood and urine samples will be collected and a Holter monitor will be affixed for 24 hours heart rhythm registration (Figure 1).

Secondary objective

A prospective follow-up study of the obesity patients undergoing bariatric surgery will be performed to gain insight in the pathophysiology of obesity causing cardiac dysfunction (Figure 1). The aforementioned diagnostic techniques will be repeated 1 year after bariatric surgery. Before–after changes in parameters of cardiac structure and function (Table 1) will be related to before–after changes in features of obesity (Table 2).

The objective of the CARDIOBESE study is not to investigate specific effects of bariatric surgery. To fulfil the secondary objective, we also could have chosen a conservative approach for weight loss (diet and exercise programme) or study the effects of naturally occurring changes in weight. In the CARDIOBESE study, bariatric surgery is just used as an efficient method to rapidly induce significant metabolic improvement and weight loss. By studying these changes and trying to relate them to improvement in cardiac function, we expect to gain insight in the pathophysiology of obesity causing cardiac dysfunction. In this context, for the secondary objective, the obesity patient can be compared with his or her own baseline values and therefore be his or her own control.

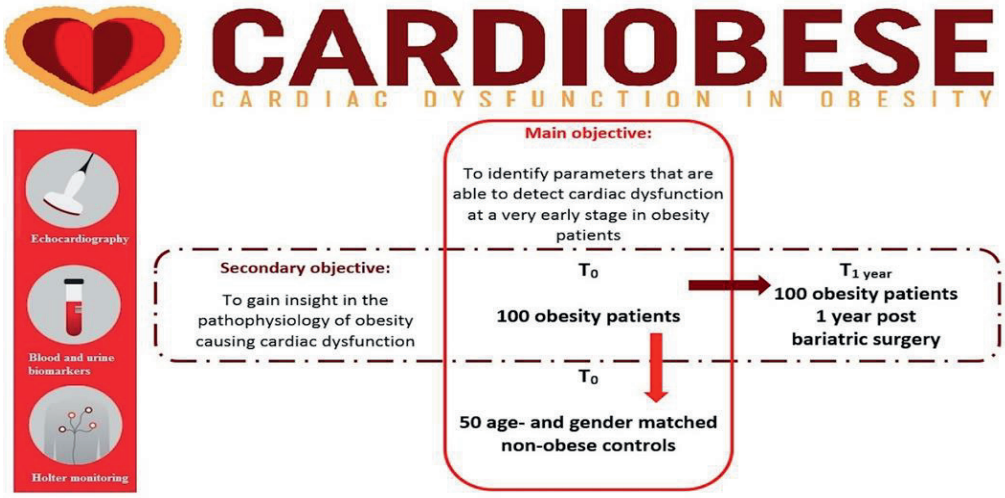


Figure 1: Overview of the design of the CARDIOBESE study.
CARDIOBESE, CARdiac Dysfunction In OBesity – Early SignsEvaluation.

Study population

Inclusion criteria

Patients: BMI ≥ 35 kg/m^2, scheduled for bariatric surgery, aged 35-65 years, and written informed consent.

Controls: BMI < 30 kg/m^2, age 35-65 years, and written informed consent.

Exclusion criteria

Patients and controls: history of cardiovascular disease.

Table 1 Parameters of cardiac structure and function

Echocardiography	Holter monitoring	Blood and urine biomarkers
LV ejection fraction	Premature atrial beats	High sensitive Troponin I
LV diastolic function	Premature ventricular beats	BNP
E/Em	Atrial fibrillation	
Septal Em	Supraventricular tachycardia	
Lateral Em	Ventricular tachycardia	
Left atrial volume index	Heart rate variability	
LV mass (area-length method)	SDNN	
TAPSE	SDNN index	
Pulsed tissue Doppler S wave tricuspid annulus	rMSSD	
Global systolic LV strain / strain rate*	PNN50	
Diastolic strain rate, early peak and late peak*	Triangle	
LV twist†	HF(norm)	
	LF(norm)	
	VLF	
		Other biomarkers will be chosen in a later phase

*Longitudinal, circumferential and radial strain will be measured.

†Peak systolic twist/twist velocity, peak diastolic untwist velocity and untwisting rate will be measured.

E/Em= ratio of peak early left ventricular filling velocity (E) over average septal and lateral mitral annulus early diastolic wave velocity (Em); *HF(norm)*= high frequency normalised; *LF(norm)*= low frequency normalised; *LV*= left ventricular; *PNN50*= percentage of successive normal sinus RR intervals >50 ms; *rMSSD*= root mean square of the successive normal sinus RR interval difference; *SDNN*= SD of all NN intervals; *SDNN index*= mean of the SD of all NN intervals for all 5 min segments of the entire recording; *TAPSE*= tricuspid annular plane systolic excursion; *Triangle*= number of all NN intervals/maximum number; *VLF*= very low frequency normalised.

Endpoints

The main study parameter is the proportion of patients/ controls with any sign of cardiac dysfunction as assessed by either echocardiography, blood/urine biomarkers or Holter monitoring (Table 1). An early sign of cardiac dysfunction is considered to be present when a studied parameter is significantly different from a well-defined cut-off value.[9,10] When such a cut-off value is not available, a studied parameter is considered to be an early sign of cardiac dysfunction when significantly different between obesity patients and non-obese controls. Secondary endpoints are: change in the proportion of obesity patients with any sign of cardiac dysfunction between study onset and 1 year after bariatric surgery and changes in cardiac dysfunction parameters in obesity patients undergoing bariatric surgery between study onset and 1 year after surgery.

Table 2 General characteristics and obesity parameters

Physical examination	Comorbidity	Medication	Laboratory tests	
Body mass index	Diabetes mellitus	Beta blocker	CRP	Transferrin
Waist circumference	Hypertension	ACE inhibitor	HbA1C	Ferritin
Systolic BP	Hyperlipidaemia	ARB	TSH	Vitamin B12
Diastolic BP	Current smoking	Diuretic	HDL-cholesterol	Folic acid
Heart Rate	COPD	CCA	LDL-cholesterol	Albumin
	OSAS	Statin	Triglycerides	Magnesium
	Arthralgia	Aspirin	Total cholesterol	Vitamin B1
	Alcohol abuse	Other antiplatelet	Lipoprotein A	Vitamin B6
	Drug abuse	Insulin	Apo B100	Vitamin D
		Oral anti-diabetics	Sodium	Haemoglobin
		Anti-inflammatory	Potassium	Haematocrit
		agents	Calcium	Erythrocytes
			Creatinine	MCV
			MDRD	Leukocytes
			ALAT	Thrombocytes

Comorbidity as reported by the patient or the general practitioner.

ALAT= alanine amino-transferase; *ARB*= angiotensin receptor blocker; BP= blood pressure, *CCA*= calcium channel antagonist, *COPD*= chronic obstructive pulmonary disease; *CRP*= C reactive protein; *HbA1c*= Glycosylated Hemoglobin; *HDL*= high-density lipoprotein; *LDL*= low-density lipoprotein; *MDRD*= modification of diet in renal disease; *OSAS*= obstructive sleep apnoea syndrome; *TSH*= Thyroid-stimulating hormone.

Sample size calculation

The fact that the combination of parameters that we will use to identify subclinical cardiac dysfunction has not been investigated in obesity before complicates a well-defined and evidence-based sample size calculation.

A conservative estimate would be that cardiac dysfunction based on conventional echocardiography is present in 20% of obesity patients and 2.5% of age-matched and gender-matched non-obese controls.[11] Given these estimates, to be able to reject the null hypothesis that cardiac dysfunction rates are equal between patients and controls, at least 97 obesity patients and 49 non-obese controls have to be included in the analysis (alpha: 0.05 (two sided), power: 0.80, 2:1 ratio of patients:controls). The use of more sensitive techniques in the CARDIOBESE study may increase the proportion of non-obese controls with an early sign of cardiac dysfunction. Nevertheless, the proportion of obesity patients with an early sign of cardiac dysfunction is expected to increase even more, assuring that the previous sample size calculation will still suffice.

Study procedures

Echocardiography

Two-dimensional greyscale harmonic images will be obtained in the left lateral decubitus position using a commercially available ultrasound system (EPIQ 7, Philips, Best, The Netherlands), equipped with a broadband (1-5MHz) X5-1 transducer. All acquisitions and measurements will be performed according to current guidelines.[9,10,12]

Interobserver and intraobserver, and test–retest reproducibility of the assessment of cardiac dimensions and function in obesity by echocardiography will be investigated in a substudy.

Blood and urine biomarkers

Blood and urine samples will be taken both for the study and as part of regular care. Urine supernatant, serum, citrate plasma and EDTA plasma will be prepared by centrifugation at 4°C and frozen in aliquots at −80°C for future analysis within 2 hours. In addition to the regular care path blood tests, high sensitive troponin I, C reactive protein and brain natriuretic peptide will be determined immediately. Other biomarkers may be selected later and can subsequently be determined from the stored blood and/or urine samples.

Holter monitoring

Heart rhythm will be recorded for 24 consecutive hours using a portable digital recorder (GE SEER Light, Chicago, Illinois, USA). The digital recorder will be connected using stickers that are placed on the chest.

Statistical analysis

The proportion of obesity patients/non-obese controls with any sign of cardiac dysfunction will be compared as prevalence difference (95% CI) and prevalence ratio (95% CI). The unpaired Student's t-test for continuous variables will be used to compare parameters with normal distributions, the non-parametric Mann-Whitney U test for continuous parameters with skewed distributions and the χ^2 test/Fisher's exact test for categorical variables. Statistical significance is considered as a two-tailed p value <0.05. Bonferroni correction for multiple testing will be applied. For each individual test parameter, presence/absence of a sign of cardiac dysfunction will be evaluated using multiple linear and logistic regression analysis

(method: backwards stepwise analysis). Covariates to be included are the matching factors (age and gender), group definition (obesity patient/non-obese control), baseline characteristics considered to be potentially related to cardiac dysfunction (continuous variables such as BMI

and body weight and categorical variables such as diabetes, hypertension, hyperlipidaemia and smoking) and other studied parameters identified to be significantly different between obesity patients and healthy volunteers by univariate analysis.

The change in the proportion of obesity patients with any sign of cardiac dysfunction between study onset and 1 year after bariatric surgery will be tested with the McNemar test.

Multiple logistic regression analysis will be used to investigate which parameters contribute to the likelihood of a sign of cardiac dysfunction at 1 year after bariatric surgery. Covariates to be included are the same as mentioned before. Changes in individual parameters of cardiac dysfunction between study onset and 1 year after bariatric surgery will be studied using paired Student's t-test, the non-parametric Wilcoxon signed rank test and McNemar test. Statistical analyses will be performed with SPSS V.25.0 or higher.

Patient and public involvement

Before the finalisation of the protocol for the CARDIOBESE study,[25] obesity patients that visited the outpatient clinic for screening for bariatric surgery were asked whether they would be willing to undergo some extra tests (echocardiogram, extra blood samples and Holter monitoring) when asked to participate in a study to investigate early signs of cardiac dysfunction in obesity. Without exception patients confirmed willingness to potentially participate. Patients recognised the importance of such a study and a majority of patients even reported that fear of developing heart disease was one of the major reasons to consider bariatric surgery.

On completion of the study, the results will be summarised in layman's terms and distributed to participants and patient support groups. We will also promote the transfer of knowledge to the general public (e.g., including short, user-friendly articles/briefings in relevant newsletters, magazines and periodicals and user groups/forums).

DISCUSSION

Obesity is becoming a global epidemic.[13] Beyond being related to an unfavourable cardiovascular risk factor profile, obesity also directly affects heart structure and function.[14] However, proper clinical evaluation of obesity patients may be hampered by the morphology of the patient.[15] Also, knowledge on the exact pathophysiology of obesity causing cardiac dysfunction is limited.[16] The CARDIOBESE study has been designed to address these issues.

Early signs of cardiac dysfunction in obesity

Echocardiography

It is well known that there is a relationship between obesity and left ventricular (LV) diastolic dysfunction (appendix 1). However, the latest improvement in echocardiography regarding early recognition of cardiac dysfunction has been the development of speckle tracking echocardiography. Each region of the myocardium has its own unique speckle pattern that remains stable enough to permit spatial and temporal image processing by dedicated software packages, allowing assessment of myocardial deformation parameters such as LV strain and twist, which are well-known measures of subtle LV dysfunction.[10,12,17]

Speckle tracking echocardiography data in obesity patients are relatively scarce and only concern LV strain and not twist (appendix 1). Although availability of speckle tracking echocardiography may still be limited, echo-machines from all well-known vendors are currently routinely equipped with speckle tracking software. Also, the technique has been significantly improved the past decennium, and inter-vendor differences have been minimised,[12] optimising clinical applicability. In the CARDIOBESE study, LV strain and twist will be thoroughly studied in obesity patients.

Blood and urine biomarkers

Focus in obesity research has mainly been on biomarkers of inflammation, insulin resistance and kidney/liver damage. Exploration of the value of blood and urine biomarkers for detection of subclinical cardiac dysfunction in obesity patients has been limited. There are some studies in which high-sensitive troponin T was measured in obesity patients but with conflicting results.[18,19]

Studies concerning natriuretic peptides in obesity patients without known cardiovascular disease demonstrated that higher BMI is associated with lower circulating natriuretic peptide concentrations (appendix 1).[20,21] The mechanism of this inverse relationship is not fully understood. It is thought to be related to either decreased production or increased peripheral metabolism of natriuretic peptides.[22] Despite its inverse relationship with BMI, natriuretic peptides do provide significant prognostic information regarding the risk of developing heart failure in obesity.[23]

In the CARDIOBESE study, blood and urine biomarkers will be compared with echocardiography and Holter monitoring parameters in order to assess the diagnostic value of the biomarkers and to better understand the underlying pathophysiology of changes in the concentration (or presence) of the biomarkers. Because of the rapid development of new blood

and urine biomarkers of cardiac dysfunction, spare samples from each patient and control will be stored in order to choose optimal biomarkers at a later stage.

Holter monitoring

In community and population-based cohort studies, obesity has consistently emerged as a risk factor for atrial fibrillation.[24] Identification of precursors of atrial fibrillation may lead to early detection of atrial fibrillation. Frequent premature atrial complexes are known to be associated with a risk of developing atrial fibrillation.[25] Despite this, the usefulness of searching for atrial fibrillation or its electrical precursors as early markers of cardiac dysfunction in obesity has never been investigated. Therefore, this will be done in the CARDIOBESE study.

Obesity patients have an increased sympathetic nervous system activity shown by an increase in mean heart rate, whereas heart rate variability parasympathetic indicators are decreased.[26] Since autonomic dysfunction may play a role in development of cardiac dysfunction, in the CARDIOBESE study parameters of heart rate variability will be investigated.

Pathophysiology of cardiac dysfunction in obesity

The pathophysiology of cardiac dysfunction in obesity is incompletely understood and most likely multifactorial. Myocardial lipotoxicity, thrombosis, altered endothelial function, compression by fat tissue, diastolic dysfunction, increased afterload and filling pressures may all play a role.[27] Changes in cardiac parameters after bariatric surgery have been studied before, showing improvement of LV structure, LV diastolic function, LV global strain and strain rate, natriuretic peptide levels and heart rate variability (appendix 1). However, in none of these studies information from echocardiography, blood and urine biomarkers and Holter monitoring have been combined. In the CARDIOBESE study, correlating findings of these different diagnostic techniques and comparing results before and 1 year after bariatric surgery may help to gain insight in the pathophysiology of obesity causing cardiac dysfunction.

Ethics and dissemination

Inclusion of patients and controls is almost complete. CARDIOBESE enrolled 92 obesity patients between 1 January 2017 and 23 July 2018, and 46 non-obese controls between 20 November 2017 and 23 July 2018. Analyses of the investigations are currently being performed, and dissemination through peer-reviewed publications and conference presentations is expected from the first quarter of 2019. By identifying early markers of cardiac dysfunction in obesity, and by understanding the underlying pathophysiology of the abnormalities of these markers,

the CARDIOBESE study may provide guidance for risk stratification, monitoring and treatment strategies for obesity patients.

REFERENCES

1. Lavie CJ, Sharma A, Alpert MA, et al. Update on obesity and obesity paradox in heart failure. Prog Cardiovasc Dis 2016;58:393–400.
2. Webber L, Divajeva D, Marsh T, et al. The future burden of obesityrelated diseases in the 53 WHO European-Region countries and the impact of effective interventions: a modelling study. BMJ Open2014;4:e004787.
3. Horwich TB, Fonarow GC, Clark AL. Obesity and the obesity paradox in heart failure. Prog Cardiovasc Dis 2018;61:151–6.
4. Bui AL, Horwich TB, Fonarow GC. Epidemiology and risk profile of heart failure. Nat Rev Cardiol 2011;8:30–41.
5. Badimon L, Bugiardini R, Cenko E, et al. Position paper of the European Society of Cardiology-working group of coronary pathophysiology and microcirculation: obesity and heart disease. Eur Heart J 2017;38:1951–8.
6. Ndumele CE, Matsushita K, Lazo M, et al. Obesity and subtypes of incident cardiovascular disease. J Am Heart Assoc 2016;5.
7. Azhari Z, Ismail MD, Zuhdi ASM, et al. Association between body mass index and outcomes after percutaneous coronary intervention in multiethnic South East Asian population: a retrospective analysis of the Malaysian National Cardiovascular Disease Database-Percutaneous Coronary Intervention (NCVD-PCI) registry. BMJ Open 2017;7:e017794.
8. Sjöström L, Lindroos AK, Peltonen M, et al. Lifestyle, diabetes, and cardiovascular risk factors 10 years after bariatric surgery. N Engl J Med 2004;351:2683–93.
9. Lang RM, Badano LP, Mor-Avi V, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the american society of echocardiography and the European association of cardiovascular imaging. Eur Heart J Cardiovasc Imaging 2015;16:233–71.
10. Nagueh SF, Smiseth OA, Appleton CP, et al. Recommendations for the evaluation of left ventricular diastolic function by echocardiography: an update from the american society of echocardiography and the european association of cardiovascular imaging. Eur Heart J Cardiovasc Imaging 2016;17:1321–60.
11. Pascual M, Pascual DA, Soria F, et al. Effects of isolated obesity on systolic and diastolic left ventricular function. Heart 2003;89:1152–6.
12. Voigt JU, Pedrizzetti G, Lysyansky P, et al. Definitions for a common standard for 2D speckle tracking echocardiography: consensus document of the EACVI/ASE/Industry Task Force to standardize deformation imaging. Eur Heart J Cardiovasc Imaging 2015;16:1–11.
13. Engeland A, Bjørge T, Søgaard AJ, et al. Body mass index in adolescence in relation to total mortality: 32-year followup of 227,000 Norwegian boys and girls. Am J Epidemiol 2003;157:517–23.
14. Alpert MA, Karthikeyan K, Abdullah O, et al. Obesity and cardiac remodeling in adults: mechanisms and clinical implications. Prog Cardiovasc Dis 2018;61:114–23.
15. Piché ME, Poirier P, Lemieux I, et al. Overview of epidemiology and contribution of obesity and body fat distribution to cardiovascular disease: an update. Prog Cardiovasc Dis 2018;61:103–13.
16. Aune D, Sen A, Norat T, et al. Body mass index, abdominal fatness, and heart failure incidence and mortality: a systematic review and dose-response meta-analysis of prospective studies. Circulation 2016;133:639–49.
17. van Dalen BM, Tzikas A, Soliman OI, et al. Left ventricular twist and untwist in aortic stenosis. Int J Cardiol 2011;148:319–24.
18. Ndumele CE, Coresh J, Lazo M, et al. Obesity, subclinical myocardial injury, and incident heart failure. JACC Heart Fail 2014;2:600–7.
19. Siervo M, Ruggiero D, Sorice R, et al. Body mass index is directly associated with biomarkers of angiogenesis and inflammation in children and adolescents. Nutrition 2012;28:262–6.
20. Buckley LF, Canada JM, Del Buono MG, et al. Low NT-proBNP levels in overweight and obese patients do not rule out a diagnosis of heart failure with preserved ejection fraction. ESC Heart Fail 2018;5:372–8.
21. Meijers WC, Hoekstra T, Jaarsma T, et al. Patients with heart failure with preserved ejection fraction and low levels of natriuretic peptides. Neth Heart J 2016;24:287–95.
22. Shah Z, Wiley M, Sridhar AM, et al. Inverse correlation of venous brain natriuretic peptide levels with body mass index is due to decreased production. Cardiology 2017;137:159–66.
23. Ndumele CE, Matsushita K, Sang Y, et al. N-terminal pro-brain natriuretic peptide and heart failure risk among individuals with and without obesity: The Atherosclerosis Risk in Communities (ARIC) Study. Circulation 2016;133:631–8.

24. Frost L, Hune LJ, Vestergaard P. Overweight and obesity as risk factors for atrial fibrillation or flutter: the Danish Diet, Cancer, and Health Study. Am J Med 2005;118:489–95.
25. Acharya T, Tringali S, Bhullar M, et al. Frequent atrial premature complexes and their association with risk of atrial fibrillation. Am J Cardiol 2015;116:1852–7.
26. Yadav RL, Yadav PK, Yadav LK, et al. Association between obesity and heart rate variability indices: an intuition toward cardiac autonomic alteration - a risk of CVD. Diabetes Metab Syndr Obes 2017;10:57–64.
27. Kitzman DW, Shah SJ. The HFpEF obesity phenotype: the elephant in the room. J Am Coll Cardiol 2016;68:200–3.

APPENDIX

Appendix 1 Previous studies concerning echocardiography, biomarkers or holter monitoring in obesity patients

	Ref.	Patients/ Controls	Main findings
Echocardiography	[1]	30 / 30	Geometrical and structural ventricular remodelling negatively influenced LV function in obesity
	[2]	40 / 40	Obese dyslipidemic adolescents had impaired LV and RV strain
	[3]	34	Abnormal cardiac structure was related to LV systolic and diastolic dysfunction in overweight and obesity
	[4]	60 / 50	Childhood obesity was associated with an alteration in longitudinal LV function
	[5]	44 / 14	Subclinical ventricular dysfunction was associated with the severity of obesity
	[6]	50 / 46	LV longitudinal strain was impaired in obesity, even in the absence of other comorbidities.
	[7]	132	Obesity was associated with LV diastolic dysfunction
	[8]	35 / 30	Impaired LA mechanical functions were related to BMI in obesity patients
before-after bariatric surgery	[9]	41	Weight loss through bariatric surgery was accompanied by significant improvements in cardiac structure
	[10]	28 /35	LV and RV global strain and strain rate abnormalities can be reversed after weight reduction following bariatric surgery
	[11]	61	One year after bariatric surgery favourable changes in LV geometry and related haemodynamic status were observed
	[12]	60 / 20	Weight reduction after bariatric surgery was related to reduction of LV hypertrophy and improvement of LV diastolic function
	[13]	43	LV relaxation impairment was normalized 9 months after bariatric surgery
	[14]	57 / 57	Body weight changes were associated with changes in LV structure independent of obesity-related comorbidities
	[15]	23	LV function improved 3 years after bariatric surgery
	[16]	43	LV function improved 1 year after bariatric surgery
	[17]	52	Bariatric surgery had an important effect on reversing LV and RV remodelling and it substantially improved RV longitudinal strain

	[18]	37	Significant weight loss by bariatric surgery was associated with improved LV structure and function
	[19]	53	Sleeve gastrectomy improved LV systolic function and contributed to reversed LV remodelling
	[20]	13	Almost complete normalization of myocardial functional and structural alterations after weight loss
	[21]	24 / 50	Weight loss produced comparable changes in cardiac morphology and function in those with and without congestive heart failure
Biomarkers	[22]	2.448 / 1.141	Among individuals without cardiovascular disease, higher BMI was associated with increased hs-TnT levels
	[23]	57 / 25	Obese children with the metabolic syndrome had increased concentrations of hs-TnT
	[24]	38 / 113	There was a lack of association between BMI and hs-TnT or natriuretic peptides
	[25]	34 / 77	NT-proBNP plasma levels in obese heart failure patients were lower when compared with non-obese patients
	[26]	3.475 / 3.802	Natriuretic peptides provided significant prognostic information regarding the risk of developing heart failure in obesity
	[27]	1.912 / 567	Lower natriuretic peptide concentrations were associated with increased BMI
	[28]	157	Heart failure patients with low natriuretic peptide levels had a higher body mass index
	[29]	30	NT-proBNP was below the proposed diagnostic cut-off point in half of this obese study cohort of patients with heart failure with preserved ejection fraction
before-after bariatric surgery	[30]	70 / 33	Despite significant improvements in LV diastolic function following bariatric surgery, natriuretic peptide levels increased
	[31]	40	Natriuretic peptide levels increased 12 and 24 months after bariatric surgery
	[32]	22	Bariatric surgery rapidly altered natriuretic peptide release, not related to extent of weight loss or changes in metabolic parameters
ECG and/or holtermonitoring	[33]	47.589	The risk of atrial fibrillation increased substantially as BMI increased in both men and women
	[34]	30 / 29	Obesity was strongly associated with reduced cardiac parasympathetic and increased sympathetic activity
	[8]	35 / 30	Delayed atrial electromechanical interval was related to BMI in obesity patients

	[35]	1.341 / 176	Prevalence of atrial fibrillation 1.9% among patients undergoing bariatric surgery; risk related to age and gender, but not BMI
	[36]	5282	Obesity was an important risk factor for atrial fibrillation, probably mediated by LA dilatation
	[37]	1200	SDNN decreased with an increase in the number of metabolic syndrome components after adjusting for other covariates
before-after bariatric surgery	[38]	10 / 7	Weight loss after bariatric surgery enhanced heart rate variability and decreases mean and minimal heart rate
	[39]	11	Post-surgery improvement in QT variability index implied that weight loss reduced the risk of ventricular arrhythmic events
	[40]	153 / 188	Marked weight loss after bariatric surgery resulted in decreased resting heart rate and an enhancement in heart rate recovery

For studies without a control group only the number of obesity patients is given. *LV*= left ventricular, *RV*= right ventricular, *LA*= left atrial, *BMI*= body mass index, *hs-TnT*= high sensitive Troponine T, *SDNN*= Standard deviation of all NN intervals

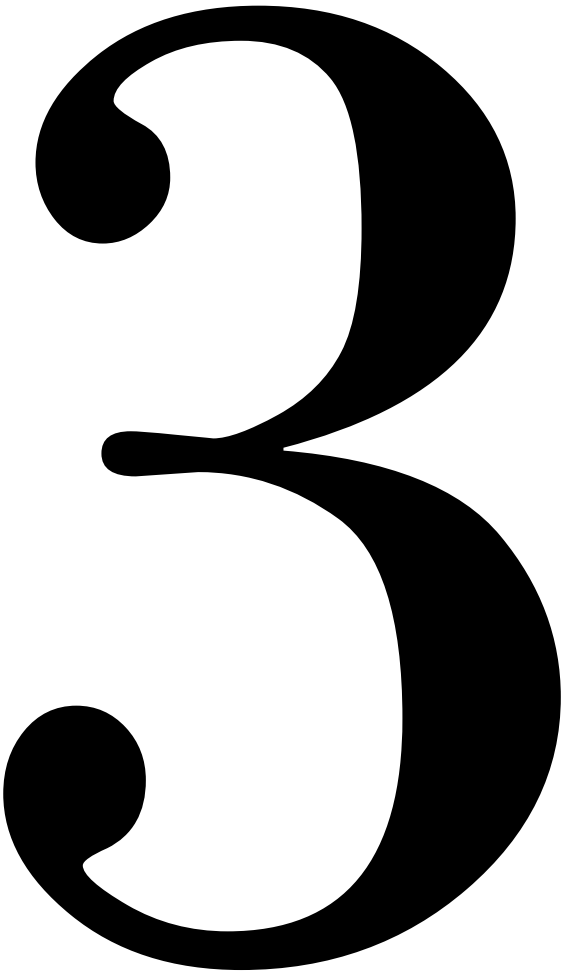
REFERENCES APPENDIX

1. Monte IP, Mangiafico S, Buccheri S, et al. Early changes of left ventricular geometry and deformational analysis in obese subjects without cardiovascular risk factors: a three-dimensional and speckle tracking echocardiographic study. Int J Cardiovasc Imaging 2014;30(6):1037-47. doi: 10.1007/s10554-014-0429-5
2. Vitarelli A, Martino F, Capotosto L, et al. Early myocardial deformation changes in hypercholesterolemic and obese children and adolescents: a 2D and 3D speckle tracking echocardiography study. Medicine (Baltimore) 2014;93(12):e71. doi: 10.1097/MD.0000000000000071
3. Zhang Y, Han L, Huang H, et al. [Research on Cardiac Structure and Function in the Overweight and Obese population and Influence Factors]. Sheng Wu Yi Xue Gong Cheng Xue Za Zhi 2016;33(1):126- 31, 43.
4. Kibar AE, Pac FA, Ece I, et al. Effect of obesity on left ventricular longitudinal myocardial strain by speckle tracking echocardiography in children and adolescents. Balkan Med J 2015;32(1):56-63. doi: 10.5152/balkanmedj.2015.15136
5. Sanchez AA, Levy PT, Sekarski TJ, et al. Markers of cardiovascular risk, insulin resistance, and ventricular dysfunction and remodeling in obese adolescents. J Pediatr 2015;166(3):660-5. doi: 10.1016/j.jpeds.2014.11.012
6. Barbosa JA, Mota CC, Simoes ESAC, et al. Assessing pre-clinical ventricular dysfunction in obese children and adolescents: the value of speckle tracking imaging. Eur Heart J Cardiovasc Imaging 2013;14(9):882-9. doi: 10.1093/ehjci/jes294
7. Tavares Ida S, Sousa AC, Menezes Filho RS, et al. Left ventricular diastolic function in morbidly obese patients in the preoperative for bariatric surgery. Arq Bras Cardiol 2012;98(4):300-6.
8. Erdem FH, Ozturk S, Baltaci D, et al. Detection of atrial electromechanical dysfunction in obesity. Acta Cardiol 2015;70(6):678-84. doi: 10.2143/AC.70.6.3120180
9. Luaces M, Cachofeiro V, Garcia-Munoz-Najar A, et al. Anatomical and functional alterations of the heart in morbid obesity. Changes after bariatric surgery. Rev Esp Cardiol (Engl Ed) 2012;65(1):14-21. doi: 10.1016/j.recesp.2011.06.018
10. Koshino Y, Villarraga HR, Somers VK, et al. Changes in myocardial mechanics in patients with obesity following major weight loss after bariatric surgery. Obesity (Silver Spring) 2013;21(6):1111-8. doi: 10.1002/oby.20168
11. Luaces M, Martinez-Martinez E, Medina M, et al. The impact of bariatric surgery on renal and cardiac functions in morbidly obese patients. Nephrol Dial Transplant 2012;27 Suppl 4:iv53-7. doi: 10.1093/ndt/gfs529
12. Ikonomidis I, Mazarakis A, Papadopoulos C, et al. Weight loss after bariatric surgery improves aortic elastic properties and left ventricular function in individuals with morbid obesity: a 3-year follow-up study. J Hypertens 2007;25(2):439-47. doi: 10.1097/HJH.0b013e3280115bfb
13. Leichman JG, Wilson EB, Scarborough T, et al. Dramatic reversal of derangements in muscle metabolism and left ventricular function after bariatric surgery. Am J Med 2008;121(11):966-73. doi: 10.1016/j.amjmed.2008.06.033
14. Garza CA, Pellikka PA, Somers VK, et al. Structural and functional changes in left and right ventricles after major weight loss following bariatric surgery for morbid obesity. Am J Cardiol 2010;105(4):550-6. doi: 10.1016/j.amjcard.2009.09.057
15. Cunha Lde C, da Cunha CL, de Souza AM, et al. Evolutive echocardiographic study of the structural and functional heart alterations in obese individuals after bariatric surgery. Arq Bras Cardiol 2006;87(5):615-22.
16. Valezi AC, Machado VH. Morphofunctional evaluation of the heart of obese patients before and after bariatric surgery. Obes Surg 2011;21(11):1693-7. doi: 10.1007/s11695-011-0431-0
17. Kaier TE, Morgan D, Grapsa J, et al. Ventricular remodelling post-bariatric surgery: is the type of surgery relevant? A prospective study with 3D speckle tracking. Eur Heart J Cardiovasc Imaging 2014;15(11):1256-62. doi: 10.1093/ehjci/jeu116
18. Shin SH, Lee YJ, Heo YS, et al. Beneficial Effects of Bariatric Surgery on Cardiac Structure and Function in Obesity. Obes Surg 2017;27(3):620-25. doi: 10.1007/s11695-016-2330-x
19. Kemaloglu Oz T, Unal Dayi S, Seyit H, et al. The effects of weight loss after sleeve gastrectomy on left ventricular systolic function in men versus women. J Clin Ultrasound 2016;44(8):492-9. doi: 10.1002/jcu.22361
20. Di Bello V, Santini F, Di Cori A, et al. Effects of bariatric surgery on early myocardial alterations in adult severely obese subjects. Cardiology 2008;109(4):241-8. doi: 10.1159/000107787

21. Alpert MA, Terry BE, Mulekar M, et al. Cardiac morphology and left ventricular function in normotensive morbidly obese patients with and without congestive heart failure, and effect of weight loss. Am J Cardiol 1997;80(6):736-40.
22. Ndumele CE, Coresh J, Lazo M, et al. Obesity, subclinical myocardial injury, and incident heart failure. JACC Heart Fail 2014;2(6):600-7. doi: 10.1016/j.jchf.2014.05.017
23. Pervanidou P, Akalestos A, Bastaki D, et al. Increased circulating High-Sensitivity Troponin T concentrations in children and adolescents with obesity and the metabolic syndrome: a marker for early cardiac damage? Metabolism 2013;62(4):527-31. doi: 10.1016/j.metabol.2012.09.012
24. Siervo M, Ruggiero D, Sorice R, et al. Body mass index is directly associated with biomarkers of angiogenesis and inflammation in children and adolescents. Nutrition 2012;28(3):262-6. doi: 10.1016/j.nut.2011.06.007
25. Rivera M, Cortes R, Salvador A, et al. Obese subjects with heart failure have lower N-terminal pro-brain natriuretic peptide plasma levels irrespective of aetiology. Eur J Heart Fail 2005;7(7):1168-70. doi: 10.1016/j.ejheart.2005.04.003
26. Ndumele CE, Matsushita K, Sang Y, et al. N-Terminal Pro-Brain Natriuretic Peptide and Heart Failure Risk Among Individuals With and Without Obesity: The Atherosclerosis Risk in Communities (ARIC) Study. Circulation 2016;133(7):631-8. doi: 10.1161/CIRCULATIONAHA.115.017298
27. Fox ER, Musani SK, Bidulescu A, et al. Relation of obesity to circulating B-type natriuretic peptide concentrations in blacks: the Jackson Heart Study. Circulation 2011;124(9):1021-7. doi: 10.1161/CIRCULATIONAHA.110.991943
28. Meijers WC, Hoekstra T, Jaarsma T, et al. Patients with heart failure with preserved ejection fraction and low levels of natriuretic peptides. Neth Heart J 2016;24(4):287-95. doi: 10.1007/s12471-016-0816-8
29. Buckley LF, Canada JM, Del Buono MG, et al. Low NT-proBNP levels in overweight and obese patients do not rule out a diagnosis of heart failure with preserved ejection fraction. ESC Heart Fail 2018;5(2):372-78. doi: 10.1002/ehf2.12235
30. Martin J, Bergeron S, Pibarot P, et al. Impact of bariatric surgery on N-terminal fragment of the prohormone brain natriuretic peptide and left ventricular diastolic function. Can J Cardiol 2013;29(8):969-75. doi: 10.1016/j.cjca.2012.11.010
31. Marney AM, Brown NJ, Tamboli R, et al. Changes in B-type natriuretic peptide and BMI following Roux-en-Y gastric bypass surgery. Diabetes Care 2014;37(4):e70-1. doi: 10.2337/dc13-2449
32. Abrahamsson N, Engstrom BE, Sundbom M, et al. Gastric bypass surgery elevates NT-ProBNP levels. Obes Surg 2013;23(9):1421-6. doi: 10.1007/s11695-013-0889-z
33. Frost L, Hune LJ, Vestergaard P. Overweight and obesity as risk factors for atrial fibrillation or flutter: the Danish Diet, Cancer, and Health Study. Am J Med 2005;118(5):489-95. doi: 10.1016/j.amjmed.2005.01.031
34. Yadav RL, Yadav PK, Yadav LK, et al. Association between obesity and heart rate variability indices: an intuition toward cardiac autonomic alteration - a risk of CVD. Diabetes Metab Syndr Obes 2017;10:57-64. doi: 10.2147/DMSO.S123935
35. Shoemaker MB, Gidfar S, Pipilas DC, et al. Prevalence and predictors of atrial fibrillation among patients undergoing bariatric surgery. Obes Surg 2014;24(4):611-6. doi: 10.1007/s11695-013-1123-8
36. Wang TJ, Parise H, Levy D, et al. Obesity and the risk of new-onset atrial fibrillation. JAMA 2004;292(20):2471-7. doi: 10.1001/jama.292.20.2471
37. Yoo HJ, Hwang SY, Choi KM, et al. Clinical implication of body size phenotype on heart rate variability. Metabolism 2016;65(11):1589-96. doi: 10.1016/j.metabol.2016.08.002
38. Nault I, Nadreau E, Paquet C, et al. Impact of bariatric surgery--induced weight loss on heart rate variability. Metabolism 2007;56(10):1425-30. doi: 10.1016/j.metabol.2007.06.006
39. Alam I, Lewis MJ, Lewis KE, et al. Influence of bariatric surgery on indices of cardiac autonomic control. Auton Neurosci 2009;151(2):168-73. doi: 10.1016/j.autneu.2009.08.007
40. Wasmund SL, Owan T, Yanowitz FG, et al. Improved heart rate recovery after marked weight loss induced by gastric bypass surgery: two-year follow up in the Utah Obesity Study. Heart Rhythm 2011;8(1):84-90. doi: 10.1016/j.hrthm.2010.10.023

Part II

Diagnostics in obesity patients



Chapter 3

Feasibility and reproducibility of transthoracic echocardiography in obesity patients

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ABSTRACT

Background

Obesity patients are considered technically difficult to evaluate by transthoracic echocardiography (TTE).

Purpose

The aim of our study was to evaluate the feasibility, inter- and intra-observer variability and test-retest variability of parameters of cardiac function and dimension by TTE in obesity patients as compared to non-obese controls.

Methods

We prospectively enrolled 100 obesity patients (body mass index ≥ 35kg/m^2) and 50 non-obese controls (body mass index < 30kg/m^2) without known cardiovascular disease. Feasibility of echocardiographic parameters was assessed by categorizing image quality and evaluation of available parameters. Intra-observer reproducibility was assessed by one observer on the same echocardiographic loop in 50 patients. A second observer assessed interobserver reproducibility in the same patients. To investigate test-retest variability, two physicians obtained images in 37 obesity patients and 17 non-obese controls.

Results

Image quality was excellent in 11% of the obesity patients as compared to 60% of the non-obese controls ($p<0.001$). All investigated parameters of cardiac function and dimension were available in both groups, except for global longitudinal strain (GLS). GLS was obtained in 93% of obesity patients versus 98% of non-obese controls ($p=0.20$). Comparable inter- and intra-observer variability between obesity patients and non-obese controls in the vast majority of parameters was observed. No significant differences on test-retest variability were observed.

Conclusion

Although non-obese controls on average had better echocardiographic image quality than obesity patients, feasibility of assessment of a broad variety of parameters of cardiac function and dimension was excellent in obesity patients and there were no important differences regarding variability of measurements.

INTRODUCTION

Worldwide, approximately 603.7 million adults are overweight (body mass index (BMI) ≥ 25 kg/m^2) and 2.3% of men and 5.0% of women are even severely obese (BMI ≥35 kg/m^2).[1,2] Obesity has generally been accepted as one of the main health threatening conditions, and a major challenge in health care practice and costs.[3] Cardiovascular disease is the leading cause of death and disability-adjusted life-years related to obesity with 2.7 million deaths and 66.3 million disability-adjusted life-years worldwide.[2] As a result of this, current guidelines recommend screening of obesity patients on the presence of cardiac risk factors.[4] It is expected that this will lead to an increase of the use of transthoracic echocardiography (TTE) in obesity patients.[5,6]

However, it may be technically challenging to adequately evaluate obesity patients by TTE, and for this reason these patients may be excluded from this simple, cost-effective, and safe diagnostic test. So far no study has been performed with the specific aim to investigate both feasibility and reproducibility of TTE in this group of patients. Additionally, speckle tracking echocardiography (STE) has been introduced for better quantification of left ventricular (LV) dysfunction. In previous studies subclinical LV dysfunction was detected in obesity patients by global longitudinal strain (GLS) analysis using STE.[7-9] Interestingly, the applicability of GLS has not been investigated before specifically in obesity patients.

The aim of our study was to evaluate the feasibility, inter- and intra-observer variability and test-retest variability of parameters of cardiac function and dimension by conventional TTE and GLS by STE in obesity patients as compared to non-obese controls.

METHODS

Study group

We prospectively studied 100 obesity patients who were referred for bariatric surgery in the Franciscus Gasthuis & Vlietland, Rotterdam, the Netherlands. Patients were included if they were between 35 and 65 years old and had a BMI of ≥35 kg/m^2. Patients with known cardiovascular disease were excluded. Fifty non-obese (BMI<30 kg/m^2) subjects were enrolled as controls. The study protocol was approved by the ethics committee and written informed consent was obtained from all participants.[10]

Transthoracic echocardiography

Two-dimensional grayscale harmonic images were obtained in the left lateral decubitus position using a commercially available ultrasound system (EPIQ 7, Philips, Best, the Netherlands),

equipped with a broadband (1-5MHz) X5-1 transducer. To optimize speckle tracking echocardiography, apical images were obtained at a frame rate of 60 to 80 frames/s.

Conventional echocardiographic measurements

All acquisitions and measurements were performed according to the current guidelines.[11,12] Interventricular septal thickness (IVSd), posterior wall thickness (PWd) and left ventricular dimension (LVEDD) were all measured at end-diastole. The left ventricular mass (LVM) was calculated according to the Deveraux formula: LVM (g) = 0.80 × {1.04[(IVSd + LVEDD + PWd)^3 - (LVEDD)]^3}+ 0.6. We performed pulsed-wave Doppler examination from the (apical) 4-chamber view, to obtain peak mitral inflow velocities at early (E) and late (A) diastole and E deceleration time. Tissue Doppler imaging was performed to obtain myocardial tissue velocity at the septal and lateral mitral annulus at early diastole (e'). E/A ratio and the E/e′ ratio were calculated using the septal e'. Left atrial volume was measured using the modified biplane area-length method. Left atrial volume index (LAVI) was calculated by dividing left atrial volume by body surface area.

Speckle-tracking analysis

Three consecutive cardiac cycles were acquired from all apical views (4-chamber, 2-chamber and 3-chamber). Subsequently, these cycles were transferred to a QLAB workstation (version 10.2, Philips, Best, the Netherlands) for off-line speckle tracking analysis. Off-line analyses were performed by 2 independent observers. In end-diastole, automated border tracking was enabled, before manual adjustment using a 'point and click approach' to ensure that the endocardial and epicardial borders were included in the region of interest. When tracking was suboptimal, fine-tuning was performed manually. Peak regional longitudinal strain was measured in 16 myocardial regions and a weighted mean was used to derive GLS.

Feasibility

Feasibility of echocardiographic parameters was assessed by categorizing image quality and by evaluating availability of echocardiographic parameters in all 100 obesity patients and 50 non-obese controls. The quality of each echocardiogram was rated on a rating scale from 1–4, with 1 being poor image quality and 4 excellent image quality, as determined subjectively by the 2 independent observers. Availability of each echocardiographic parameter was listed for all 100 obesity patients and all 50 non-obese controls.

Reproducibility

Intra-observer reproducibility of the echocardiographic parameters was assessed in 50 obesity patients and 25 non-obese controls with an interval of 6 months by one observer (SS) on the same echocardiographic loop. A second observer (JY) who was unaware of the results, also assessed inter-observer reproducibility.

In 37 obesity patients and 17 non-obese controls images were obtained by two physicians (SS and BD) to investigate test-retest variability.

Statistical analysis

Values in obesity patients and non-obese controls were compared using the Student's t-test. Image quality between groups was compared using the chi-square test. Variability was calculated as the mean per cent error, defined as the absolute difference between the two sets of measurements, divided by the mean of the measurements. A p-value of <0.05 was considered statistically significant. Test-retest reproducibility was displayed using Bland-Altman plots.[13] Statistical analyses was performed with SPSS version 25.0 or higher (SPSS Inc., Chicago, USA).

RESULTS

Patient characteristics

No significant differences were observed in the two study groups regarding age (48±7 years in obesity patients versus 49±9 years in non-obese controls, p=0.41) and gender (both 70% female). The mean BMI in the obesity group was 43±4 kg/m^2 and 25±3 kg/m^2 in the non-obese controls ($p<0.001$).

Feasibility of echocardiographic parameters in obesity patients and non-obese controls

Only 11% of the obesity patients had excellent-quality ultrasound images compared to 60% of the non-obese controls. However, apart from GLS and left ventricular ejection fraction (LVEF), all investigated parameters of cardiac function and dimension were available in both groups (Table 1). LVEF was available in 98% of the obesity patients and in all of the non-obese controls. GLS was available in 93% of obesity patients versus 98% of non-obese controls. Missing values were because of poor image quality.

Table 1 Image quality and availability of various echocardiographic parameters in obesity patients versus non-obese controls

	Obese (n=100)	Non-obese (n=50)
Image quality		
1 – poor	12 (12%)	1 (2%)ǂ
2 – moderate	44 (44%	4 (8%)*
3 – good	33 (33%)	15 (30%)
4 – excellent	11 (11%)	30 (60%)*
Image quality sufficient for parameter availability		
IVSd	100 (100%)	50 (100%)
LVEDD	100 (100%)	50 (100%)
PWd	100 (100%)	50 (100%)
LVM	100 (100%)	50 (100%)
E-wave	100 (100%)	50 (100%)
A-wave	100 (100%)	50 (100%)
E/A ratio	100 (100%)	50 (100%)
Septal e'velocity	100 (100%)	50 (100%)
Lateral e'velocity	100 (100%)	50 (100%)
E/e'ratio	100 (100%)	50 (100%)
Deceleration time	100 (100%)	50 (100%)
LA-volume index	100 (100%)	50 (100%)
TAPSE	100 (100%)	50 (100%)
LVEF	98 (98%)	50 (100%)
GLS	93 (93%)	49 (98%)

Values represent n (%)

ǂp<0.05, *p<0.001. All p-values regarding image quality sufficient for parameter availability are non-significant

IVSd= interventricular septal thickness at end-diastole, *LVEDD*= left ventricular dimension at end-diastole, *LVEF*= left ventricular ejection fraction, *PWd*= posterior wall thickness at end-diastole, *LVM*= left ventricular mass, *E-wave*= early diastolic transmitralflow velocity, *A-wave*= late diastolic transmitralflow velocity, *e'*= early diastolic mitral annular velocity, *LA-volume index*= left atrial volume index, *TAPSE*= Tricuspid annular plane systolic excursion, *GLS*= Global Longitudinal Strain

Inter- and intra-observer variability of echocardiographic parameters in obesity patients and non-obese controls

The inter- and intra-observer variability was comparable between obesity patients and non-obese controls for the vast majority of parameters (Table 2). However, intra-observer variability of IVSd was increased in obesity patients (10.6±6.3% versus 6.8±6.3%, p=0.019). There were small differences regarding inter-observer variability of the lateral e' (10.6±9.1% in obesity patients versus 6.5±3.9% in non-obese controls, p=0.036) and E/e'ratio (9.3±9.2% in obesity patients versus 5.0±4.0% non-obese controls, p=0.033).

Table 2 Variability and intraclass correlation coefficients of various echocardiographic parameters in obesity patients versus non-obese controls.

	Intra-observer				**Inter-observer**				**Test-retest variability**			
Echo parameters	**Obese (n=50)**		**Non-obese (n=25)**		**Obese (n=50)**		**Non-obese (n=25)**		**Obese (n=37)**		**Non-obese (n=17)**	
	Variability	ICC	Variability	ICC	Variability	ICC	Variability	ICC	Variability	ICC	Variability	ICC
IVSd	10.6±6.3	0.77	6.8±6.3*	0.81	10.8±6.9	0.76	8.5±4.5	0.86	11.1±9.0	0.77	10.1±6.4	0.76
LVEDD	5.4±4.7	0.84	6.7±5.3	0.76	5.5±3.7	0.89	5.5±3.3	0.87	6.7±5.1	0.69	6.1±5.2	0.55
PWd	12.4±9.0	0.62	13.7±9.6	0.67	11.5±9.7	0.77	9.7±6.7	0.76	12.4±9.4	0.68	9.8±6.4	0.80
LVM	13.6±9.4	0.86	11.3±10.8	0.90	10.8±7.7	0.93	10.6±9.1	0.85	10.3±8.73	0.92	8.9±4.5	0.94
E-wave	4.7±3.9	0.85	3.1±2.1	0.97	5.3±4.3	0.93	5.3±3.1	0.90	9.3±6.0	0.88	6.1±3.9	0.86
A-wave	5.4±5.4	0.92	5.1±9.6	0.99	5.5±4.7	0.89	5.4±2.5	0.96	9.2±6.5	0.85	5.8±4.6	0.97
E/A ratio	5.9±9.6	0.94	2.1±3.0	0.99	4.9±5.0	0.80	3.8±3.4	0.98	8.9±5.7	0.91	8.5±5.7	0.86
Septal e'velocity	5.4±4.2	0.91	3.5±3.6	0.96	7.5±7.4	0.85	5.3±2.4	0.94	9.7±7.3	0.86	7.7±4.6	0.93
Lateral e'velocity	8.2±7.3	0.84	5.9±7.6	0.91	10.6±9.1	0.84	6.5±3.9*	0.95	13.9±12.2	0.80	9.1±9.4	0.97
E/e'ratio	7.8±7.8	0.86	4.9±4.1	0.96	9.3±9.2	0.90	5.0±4.0*	0.94	11.6±7.6	0.92	10.1±11.6	0.91
Deceleration time	8.4±6.6	0.81	5.3±6.4	0.91	10.2±8.9	0.80	6.9±4.7	0.88	16.2±14.2	0.57	14.1±12.3	0.55
LA-volume index	12.3±7.8	0.76	8.7±6.5	0.82	11.0±6.9	0.91	9.2±4.8	0.91	13.6±11.8	0.77	10.1±6.3	0.87
TAPSE	7.3±5.4	0.77	5.1±4.1	0.84	9.5±7.2	0.76	7.0±3.1	0.92	7.4±6.6	0.82	9.7±3.3	0.75
LVEF	7.3±5.4	0.76	8.2±5.8	0.22	7.7±5.2	0.78	4.2±3.7†	0.69	9.7±8.7	0.41	5.3±2.6	0.42
GLS	6.8±5.2	0.91	5.6±4.6	0.66	6.4±4.9	0.93	5.6±4.6	0.71	8.8±7.6	0.81	6.9±5.3	0.49

Values represent mean ± standard deviation

*$p<0.05$

IVSd= Interventricular septal thickness at end-diastole, *LVEDD*= left ventricular dimension at end-diastole, *LVEF*=left ventricular ejection fraction, *PWd*= posterior wall thickness at end-diastole, *LVM*= Left ventricular mass, *E-wave*= early diastolic transmitralflow velocity, *A-wave*= late diastolic transmitralflow velocity, *e'*=early diastolic mitral annular velocity, *LA-volume index*= left atrial volume index, *TAPSE*= Tricuspid annular plane systolic excursion, *GLS*= Global Longitudinal Strain

Test-retest variability of echocardiographic parameters in obesity patients and non-obese controls

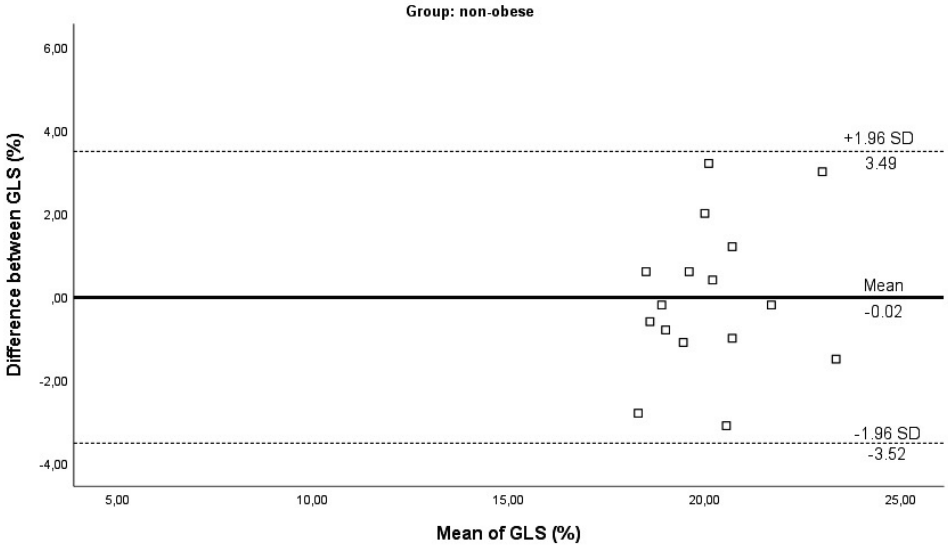
No significant differences were observed between obesity patients and non-obese controls regarding test-retest variability. Bland–Altman analysis was performed (Figure 1) to graphically display the test-retest reproducibility for GLS, LVM, E/e' ratio, left atrial volume index and tricuspid annular plane systolic excursion for both groups.

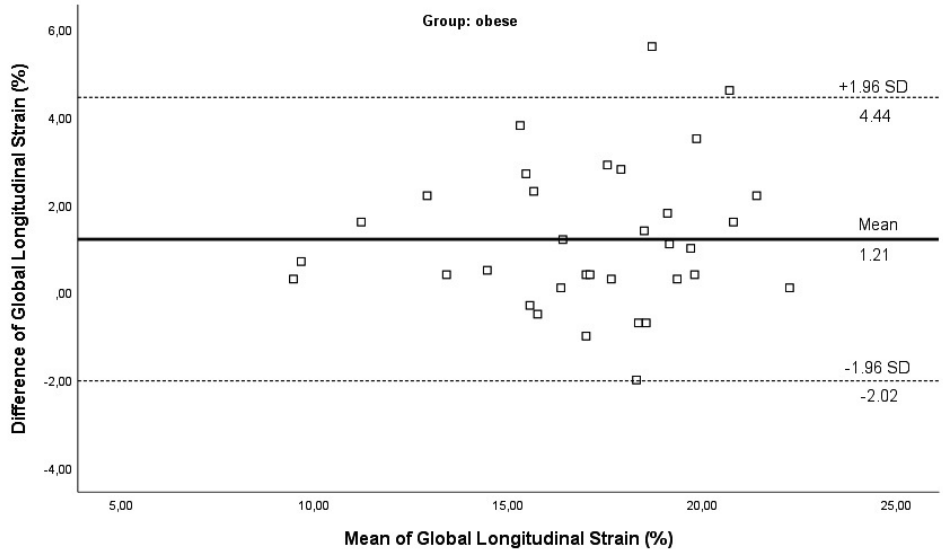
DISCUSSION

The current study demonstrates that although non-obese controls had better overall echocardiographic image quality than obesity patients, feasibility of assessment of a broad variety of parameters of cardiac function and dimensions were excellent in obesity patients. No important differences regarding variability of measurements were observed. GLS had good feasibility and reproducibility in obesity patients.

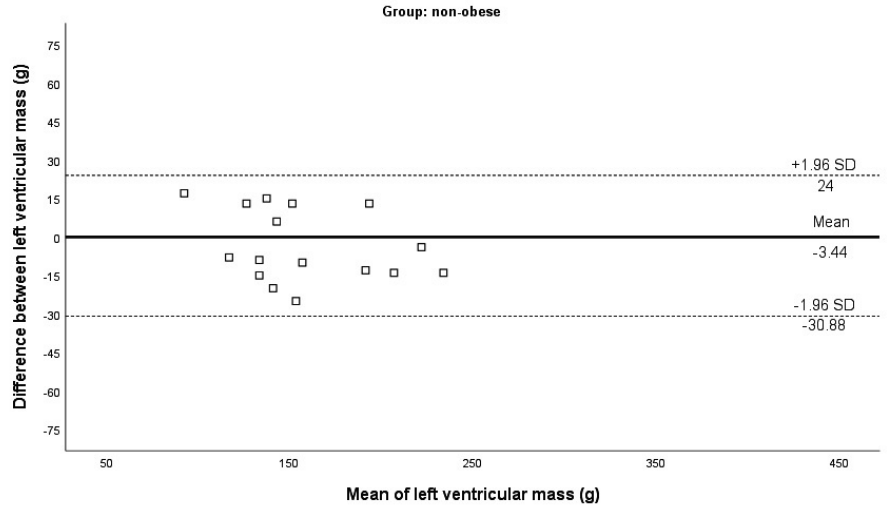
Nowadays, obesity is a common condition and therefore echocardiographic examination of these patients is part of daily clinical practice.[1] However, the body habitus of obesity patients poses technical challenges regarding obtaining optimal echocardiographic image quality. However, studies in which feasibility of obtaining echocardiographic parameters by TTE in obesity patients was reported are limited. As early as in 1982, Zema et al.[14] examined the feasibility of M-Mode echocardiography in 50 obese adults and concluded that M-Mode echocardiography allows detailed evaluation of obese subjects. Both Shah et al.[15] and Supariwala et al.[16] reported good feasibility of stress-echocardiography in obesity patients. On the contrary, Siadecki et al.[17] found a correlation between increasing BMI and decreased image quality in focused bedside echocardiography. Only one previous study was performed to investigate interobserver variability of echocardiography in obesity patients. Jhang et al.[18] concluded in 1997 that the interobserver variability of determination of LVM assessed by M-Mode was poor in obesity patients.

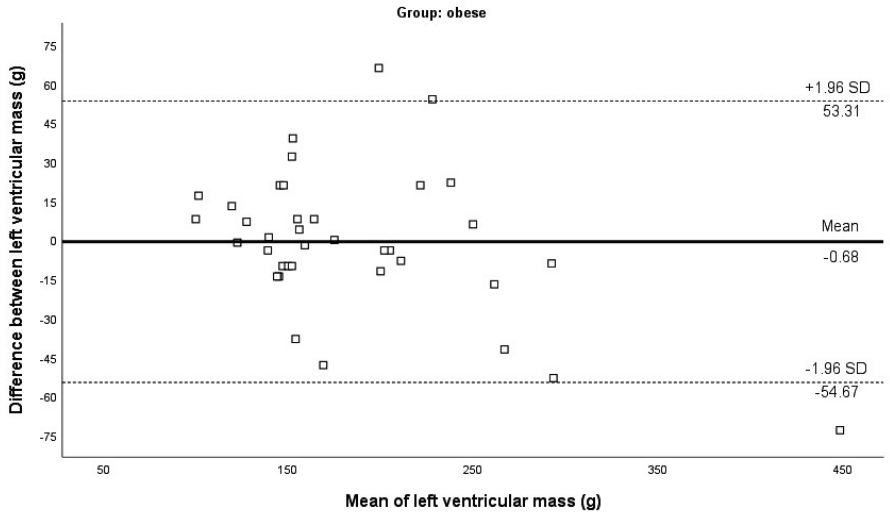
a) Global longitudinal strain (GLS)



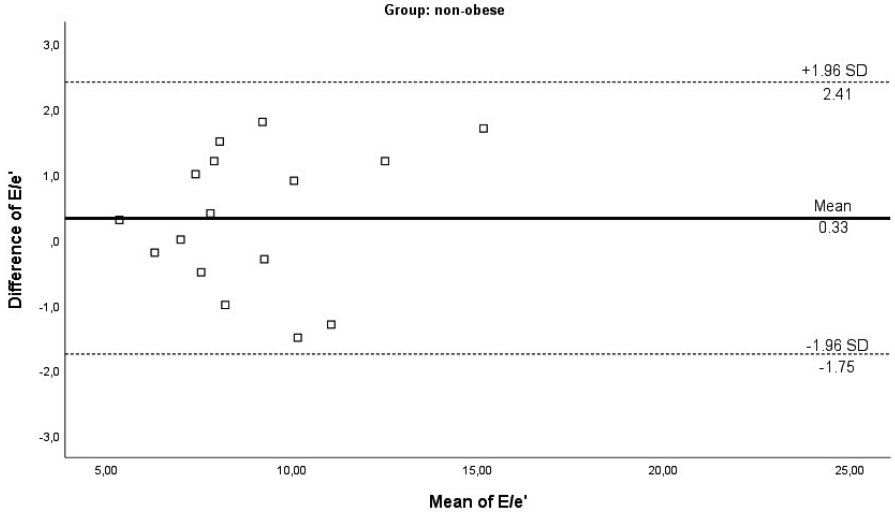


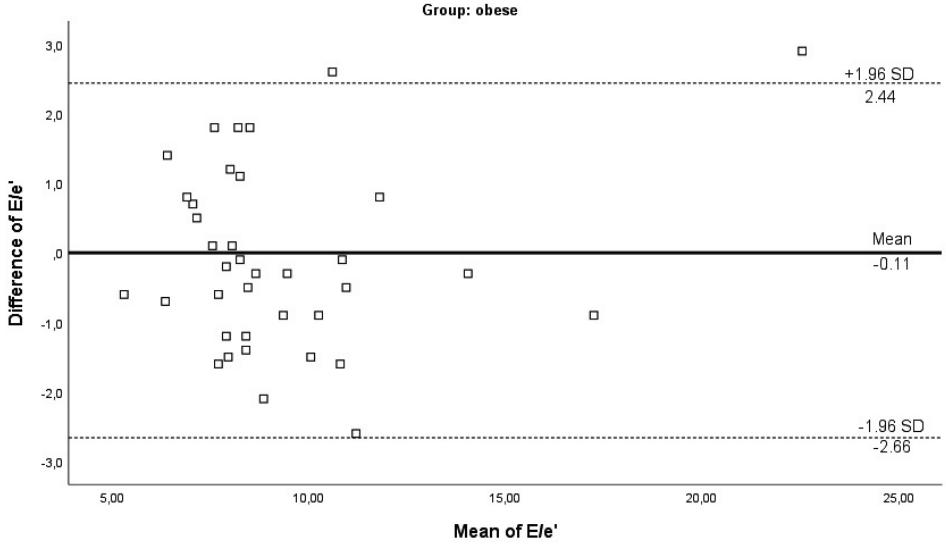
b) Left ventricular mass



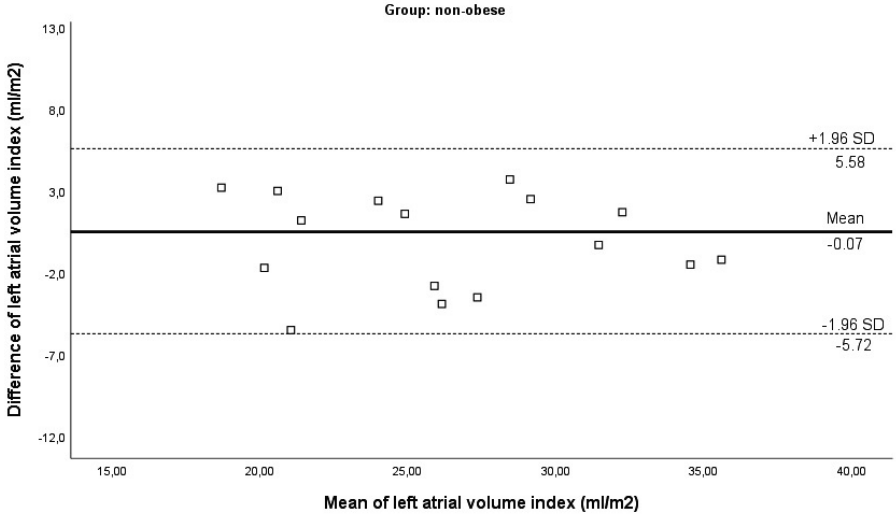


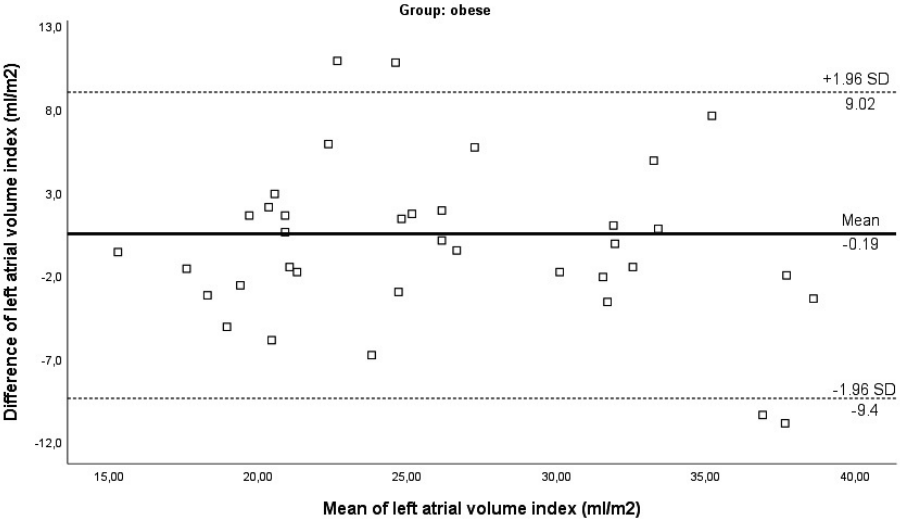
c) E/e'


Group: non-obese
Difference of E/e'
Mean of E/e'
+1.96 SD
2.41
Mean
0.33
-1.96 SD
-1.75
3,0
2,0
1,0
,0
-1,0
-2,0
-3,0
5,00
10,00
15,00
20,00
25,00


Group: obese
Difference of E/e'
Mean of E/e'
+1.96 SD
2.44
Mean
-0.11
-1.96 SD
-2.66
3,0
2,0
1,0
,0
-1,0
-2,0
-3,0
5,00
10,00
15,00
20,00
25,00

d) Left atrial volume index





e) TAPSE

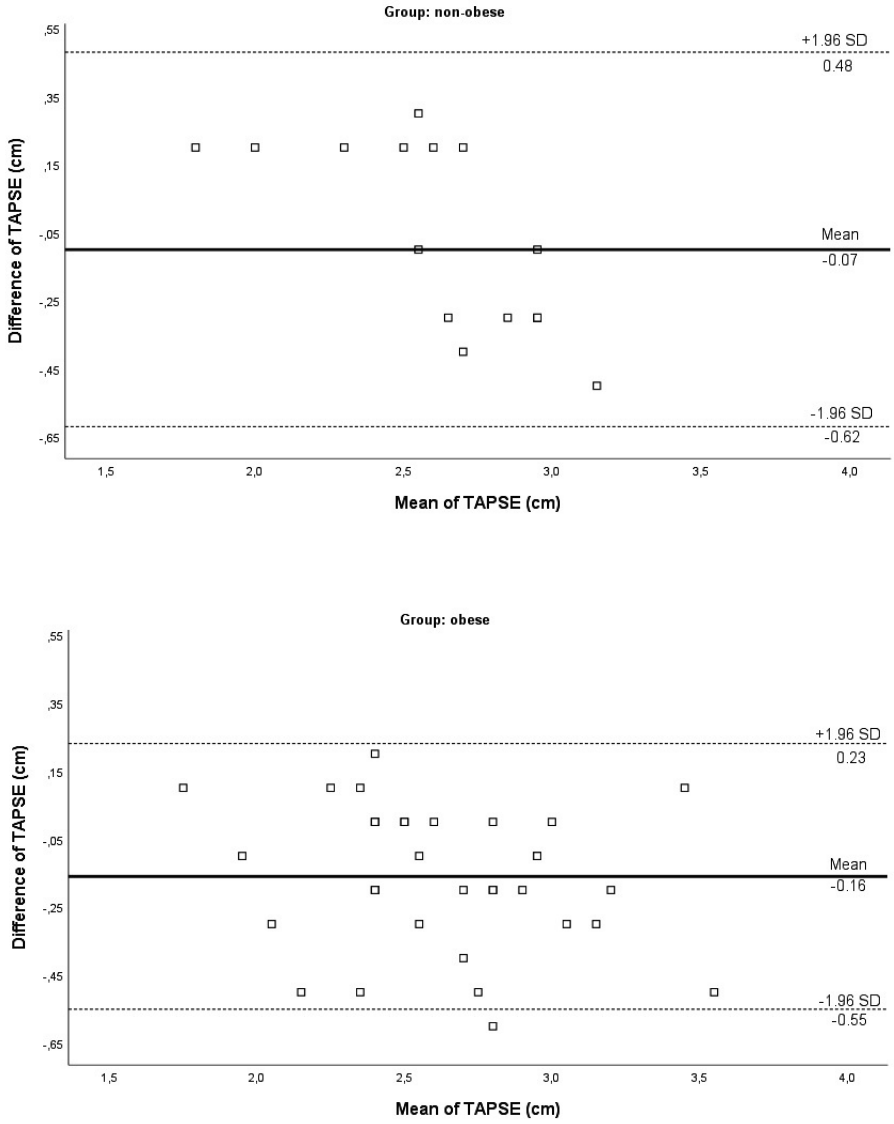


Figure 1: Bland Altman analysis of global longitudinal strain (a), left ventricular mass (b), E/e' (c), left atrial volume index (d), TAPSE (e)

There is a strong perception in the clinical community that TTE, even with the latest technology, does not provide adequate diagnostic images in obesity patients. Indeed, value of echocardiographic imaging in obesity patients may be limited due to poor acoustic windows.[16] The ultrasound energy is markedly attenuated by subcutaneous fat, and as a result of this, the presence of adipose tissue can significantly limit the ability to obtain high-quality ultrasound images.[17] Also, body morphology of obesity patients may hamper the ability to identify the acoustic window with the most optimal image quality. Nevertheless, in our study we showed that feasibility of parameters of cardiac function and dimension by TTE in obesity patients is excellent, with acceptable reproducibility compared to non-obese subjects. A possible explanation for this somewhat unexpected finding may be that, since the images were obtained for research purposes, physicians used all the time necessary to identify the optimal echocardiographic windows, not being hampered by time pressure. The extra time needed to obtain most optimal images in obesity patients may often not be available in common daily clinical practice. Also, the widespread idea of echocardiography usually being non-diagnostic in obesity patients may lead to a self-fulfilling prophecy; poor image quality during acquisition of images may be more easily accepted by the operator, and further search for the optimal echocardiographic window and optimization of the machine settings may therefore be omitted.

Recent improvement for the evaluation of left ventricular function by echocardiography has been the development of strain imaging by STE.[19] Currently, STE is broadly available and echo-machines from all well-known vendors are generally equipped with speckle tracking software.[17] Strain can be assessed in three principle directions (longitudinal, circumferential, and radial), with longitudinal strain to be the most reproducible. It is therefore recommended to use GLS as one of the parameters of LV systolic function.[11] Until now it has been unclear how well this method would perform in obesity patients as no earlier studies have been performed specifically focusing on feasibility and/or reproducibility. Although image quality was relatively poor in obesity patients, we demonstrated an overall good feasibility and reproducibility for GLS and suggest the use of this parameter in daily clinical practice.

Limitations

In the current study, we primarily focused on parameters of global left- and right ventricular function and dimension. Feasibility and reproducibility of regional wall motion abnormalities or valve function was not assessed. Subjects had no known cardiac history and presence of regional wall motion abnormalities or valve dysfunction was therefore expected to be limited.

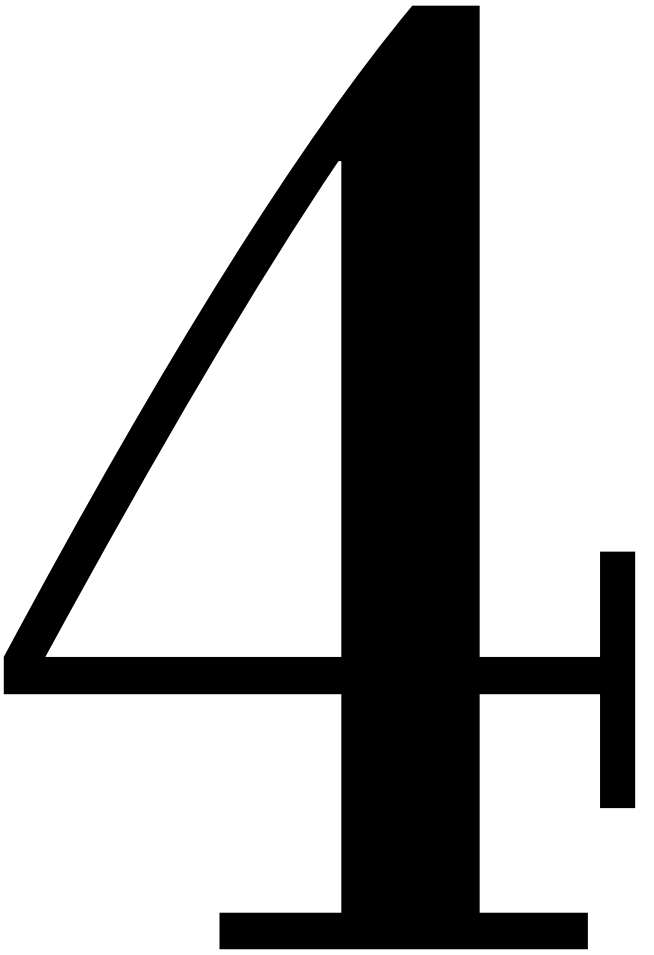
Additionally, the results do not reflect a more acutely ill or intensive care population, in which the ability to perform adequate echocardiography may be more challenging. Last, we did not record the duration of our TTE examinations.

CONCLUSIONS

The current study demonstrates that assessment of a broad variety of parameters of cardiac function and dimension by TTE was feasible in obesity patients. No important differences regarding variability of measurements were observed. GLS had good feasibility and reproducibility in obesity patients and we suggest that this parameter may also be used in daily clinical practice in these patients.

REFERENCES

1. Collaboration NCDRF. Trends in adult body-mass index in 200 countries from 1975 to 2014: a pooled analysis of 1698 population-based measurement studies with 19.2 million participants. Lancet 2016;387:1377-96.
2. Collaborators GBDO, Afshin A, Forouzanfar MH, Reitsma MB, Sur P, Estep K, et al. Health Effects of Overweight and Obesity in 195 Countries over 25 Years. N Engl J Med 2017;377:13-27.
3. Suehs BT, Kamble P, Huang J, Hammer M, Bouchard J, Costantino ME, et al. Association of obesity with healthcare utilization and costs in a Medicare population. Curr Med Res Opin 2017;33:2173-80.
4. Badimon L, Bugiardini R, Cenko E, Cubedo J, Dorobantu M, Duncker DJ, et al. Position paper of the European Society of Cardiology-working group of coronary pathophysiology and microcirculation: obesity and heart disease. Eur Heart J 2017;38:1951-8.
5. Murphy NF, MacIntyre K, Stewart S, Hart CL, Hole D, McMurray JJ. Long-term cardiovascular consequences of obesity: 20-year follow-up of more than 15 000 middle-aged men and women (the Renfrew-Paisley study). Eur Heart J 2006;27:96-106.
6. Martin RP. American Society of Echocardiography president's message: echocardiography and the epidemics. J Am Soc Echocardiogr 2003;16:16A-7A.
7. Barbosa MM, Beleigoli AM, de Fatima Diniz M, Freire CV, Ribeiro AL, Nunes MC. Strain imaging in morbid obesity: insights into subclinical ventricular dysfunction. Clin Cardiol 2011;34:288-93.
8. Monte IP, Mangiafico S, Buccheri S, Arcidiacono AA, Lavanco V, Privitera F, et al. Early changes of left ventricular geometry and deformational analysis in obese subjects without cardiovascular risk factors: a three-dimensional and speckle tracking echocardiographic study. Int J Cardiovasc Imaging 2014;30:1037-47.
9. Koopman LP, McCrindle BW, Slorach C, Chahal N, Hui W, Sarkola T, et al. Interaction between myocardial and vascular changes in obese children: a pilot study. J Am Soc Echocardiogr 2012;25:401-10 e1.
10. Snelder SM, de Groot-de Laat LE, Biter LU, Castro Cabezas M, van de Geijn GJ, Birnie E, et al. Cross-sectional and prospective follow-up study to detect early signs of cardiac dysfunction in obesity: protocol of the CARDIOBESE study. BMJ Open 2018;8:e025585.
11. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. Eur Heart J Cardiovasc Imaging 2015;16:233-70.
12. Nagueh SF, Smiseth OA, Appleton CP, Byrd BF, 3rd, Dokainish H, Edvardsen T, et al. Recommendations for the Evaluation of Left Ventricular Diastolic Function by Echocardiography: An Update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. Eur Heart J Cardiovasc Imaging 2016;17:1321-60.
13. Bland JM, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. Lancet 1986;1:307-10.
14. Zema MJ, Caccavano M. Feasibility of detailed M-mode echocardiographic examination in markedly obese adults: prospective study of 50 patients. J Clin Ultrasound 1982;10:31-4.
15. Shah BN, Zacharias K, Pabla JS, Karogiannis N, Calicchio F, Balaji G, et al. The clinical impact of contemporary stress echocardiography in morbid obesity for the assessment of coronary artery disease. Heart 2016;102:370-5.
16. Supariwala A, Makani H, Kahan J, Pierce M, Bajwa F, Dukkipati SS, et al. Feasibility and prognostic value of stress echocardiography in obese, morbidly obese, and super obese patients referred for bariatric surgery. Echocardiography 2014;31:879-85.
17. Siadecki SD, Frasure SE, Lewiss RE, Saul T. High Body Mass Index is Strongly Correlated with Decreased Image Quality in Focused Bedside Echocardiography. J Emerg Med 2016;50:295-301.
18. Jhang JS, Diamond JA, Phillips RA. Interobserver Variability of Left Ventricular Measurements in a Population of Predominantly Obese Hypertensives Using Simultaneously Acquired and Displayed M-Mode and 2-D Cine Echocardiography. Echocardiography 1997;14:9-14.
19. Amundsen BH, Helle-Valle T, Edvardsen T, Torp H, Crosby J, Lyseggen E, et al. Noninvasive myocardial strain measurement by speckle tracking echocardiography: validation against sonomicrometry and tagged magnetic resonance imaging. J Am Coll Cardiol 2006;47:789-93.
20. Menting ME, McGhie JS, Koopman LP, Vletter WB, Helbing WA, van den Bosch AE, et al. Normal myocardial strain values using 2D speckle tracking echocardiography in healthy adults aged 20 to 72 years. Echocardiography 2016;33:1665-75.



Chapter 4

Optimized electrocardiographic criteria for the detection of left ventricular hypertrophy in obesity patients

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ABSTRACT

Background

Despite a generally high specificity, electrocardiographic(ECG) criteria for the detection of left ventricular hypertrophy (LVH) lack sensitivity, particularly in obesity patients.

Objectives

The aim of the study was to evaluate the accuracy of the most commonly used ECG criteria (Cornell voltage and Sokolow-Lyon index), the recently introduced Peguero-Lo Presti criteria and the correction of these criteria by body mass index (BMI) to detect LVH in obesity patients and to propose adjusted ECG criteria with optimal accuracy.

Methods

The accuracy of the ECG criteria for detection of LVH was retrospectively tested in a cohort of obesity patients referred for a transthoracic echocardiogram based on clinical grounds (test cohort, n=167). Adjusted ECG criteria with optimal sensitivity for the detection of LVH were developed. Subsequently, the value of these criteria was prospectively tested in an obese population without known cardiovascular disease (validation cohort, n=100).

Results

Established ECG criteria had a poor sensitivity in obesity patients in both the test cohort (ranged from 0-16%) and the validation cohort (ranged from 0-20%). The adjusted criteria showed improved sensitivity, with optimal values for males using the Cornell voltage corrected for BMI (RaVL+SV3)*BMI ≥700mm*kg/m^2; sensitivity 47% test cohort, 40% validation cohort), for females the Sokolow-Lyon index corrected for BMI (SV1+RV5/RV6)*BMI ≥885mm*kg/m^2; sensitivity 26% test cohort, 23% validation cohort.

Conclusions

Established ECG criteria for the detection of LVH lack sufficient sensitivity in obesity patients. We propose new criteria for the detection of LVH in obesity patients with improved sensitivity, approaching known sensitivity of the most commonly used ECG criteria in lean subjects.

INTRODUCTION

The prevalence of obesity has increased rapidly, and nowadays more people are obese than underweight.[1] Left ventricular hypertrophy (LVH) occurs frequently in obesity patients, even in the absence of comorbidities such as hypertension[2,3] and is associated with increased risk of cardiovascular disease, morbidity, and mortality.[4-6] Although echocardiography is a more sensitive tool to identify LVH, the standard electrocardiogram (ECG) remains widely used, because of its established clinical value, broad availability, and low costs.[7] ECG criteria for the diagnosis of LVH have been used since 1914.[8] Nowadays, the two most commonly used ECG criteria are the Cornell voltage[9] and the Sokolow-Lyon index.[10] Despite a generally high specificity, most ECG criteria for LVH lack sensitivity.[11] The value of these criteria is particularly questionable in obesity patients[12,13] because obesity is responsible for geometrical and electrophysiological changes of the heart and ECG voltages may be attenuated by subcutaneous adipose tissue.[14,15] Recently, Peguero and Lo-Presti introduced more sensitive ECG criteria for the detection of LVH.[16] Until now, these criteria have not been specifically tested in obese subjects. Finally, Angeli et al.[17] introduced a correction to the Cornell voltage by body mass index (BMI) to improve the performance of traditional ECG criteria.

The aim of the current study was to retrospectively evaluate the accuracy of various ECG criteria to detect LVH in obesity patients and to propose adjusted ECG criteria with optimal sensitivity for this group of patients. Subsequently, the identified optimal criteria were prospectively tested in an obese population without suspicion of or known cardiovascular disease.

METHODS

The accuracy of the Cornell voltage, Sokolow–Lyon index, Peguero-Lo-Presti criteria and the correction of Cornell voltage by BMI for detection of LVH was retrospectively tested in obesity patients who were referred for a transthoracic echocardiogram based on clinical grounds (suspicion on or history of cardiovascular disease) (test cohort). From these data, ECG criteria with optimal sensitivity for the detection of LVH were developed by adjusting the cut-off values and correcting all voltage criteria for BMI. After this, the value of these criteria was prospectively tested in an obese population without a suspicion on or history of cardiovascular disease (validation cohort).

Test cohort

All obesity patients (BMI ≥35 kg/m^2) who came to the Franciscus Gasthuis & Vlietland (Rotterdam, the Netherlands) in 2017 and underwent both an ECG and transthoracic echocardiography in the same week were included in the analysis. Patients with conditions potentially effecting the ECG voltage amplitude, such as a left or right bundle branch block, a paced rhythm, imaging evidence of myocardial infarction or pericardial effusion, were excluded.

Validation cohort

All obese participants of the CARDIOBESE study[18] were recruited for the validation cohort. In short, the CARDIOBESE study was designed to detect early signs of cardiac dysfunction in obesity patients without a suspicion on or known cardiovascular disease. Patients with a BMI ≥35 kg/m^2 scheduled for bariatric surgery were included. A history of cardiovascular disease was an exclusion criterion. All research data acquisition was approved by the local research ethics committee and informed written consent was obtained from each participant.

ECG recording and analysis

A standard 12-lead ECG was recorded at a paper speed of 25 mm/s and an amplification of 10 mm/mV. Heart rate, QRS duration, R-wave and S-wave heights and QRS axis were measured. Left axis deviation was determined as QRS axis between −30° and −90°. Measurements were taken to the nearest 1 mm. The most commonly used ECG criteria were analyzed (Figure 1): the Cornell voltage, RaVL + SV3 (considered positive ≥28 mm in male subjects and ≥20 mm in female subjects)[9]; Sokolow–Lyon index, SV1 + RV5/RV6 (RV5 or RV6, whichever is greater; considered positive ≥35 mm)[10]; the Peguero–Lo Presti criteria, SV4 + Sdeepest (considered positive ≥28 mm in males and ≥23 mm in females)[16]; and the correction of Cornell voltage by BMI, (RaVL + SV3)* BMI (considered positive ≥604 mm*kg/m^2).[17] Finally, we multiplied the Sokolow–Lyon index and Peguero–Lo Presti criteria by BMI.

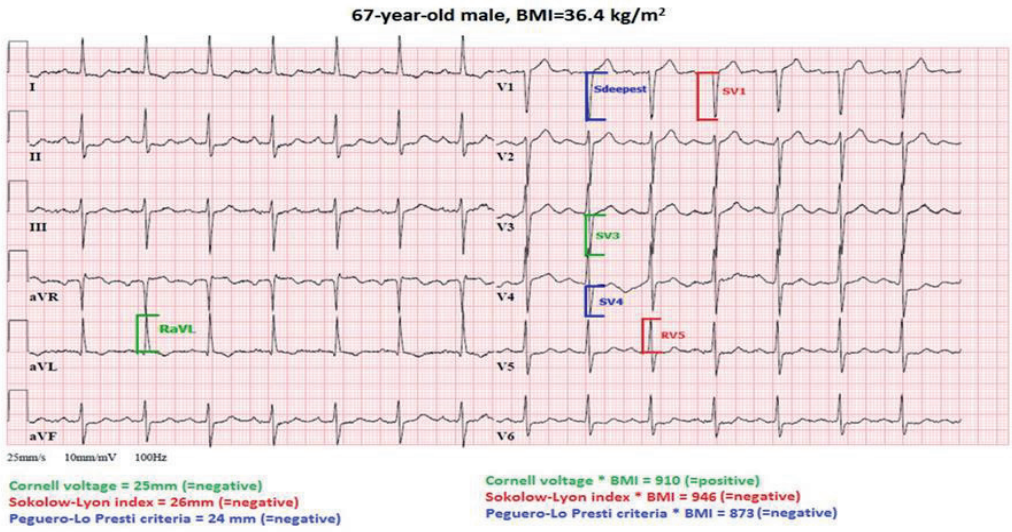


Figure 1: Electrocardiogram of a 67-year-old male obesity patient that meets the criteria for left ventricular hypertrophy based on the adjusted Cornell voltage*BMI, (RaVL+SV3)*BMI ≥700 mm*kg/m^2. The diagnosis of left ventricular hypertrophy was confirmed by an echocardiogram. Note that none of the other criteria were positive.

BMI= body mass index

Echocardiography

Two-dimensional grayscale harmonic images were obtained in the left lateral decubitus position using a commercially available ultrasound system (EPIQ 7, Philips, Best, the Netherlands), equipped with a broadband (1-5MHz) X5-1 transducer. All acquisitions and measurements were performed according to current guidelines.[19,20] Estimation of left ventricular mass (LVM) as determined by echocardiography was used as the golden standard. Interventricular septal thickness (IVSd), posterior wall thickness (PWd) and left ventricular dimension (LVEDD) were all measured at end-diastole. The LVM was calculated according to the Deveraux formula using these measurements: LVM (g) = 0.80 × {1.04[(IVSd + LVEDD + PWd)^3 - (LVEDD)^3]}+ 0.6. The LVM was divided by the body surface area (BSA) to calculate the LVM-index (LVMI). BSA was calculated by the Mosteller formula.[21] LVH was defined as LVMI ≥102g/m^2 for males and ≥88g/m^2 for females.[19]

Statistical analysis

To compare baseline characteristics between the two cohorts, the Student *t* test was used for continuous variables and the χ^2 test for categorical variables. Continuous values were expressed

as mean ± SD and categorical values as percentages. The sensitivity, specificity, positive predictive values (PPV) and negative predictive values (NPV) and their 95% confidence intervals were calculated for the ECG criteria in both groups. Differences in sensitivity and specificity between cohorts were tested with the χ^2test. A *P* value <.05 was considered statistically significant. Optimal cut-off values for all ECG criteria were manually calculated for both genders by a receiver operating curve (ROC) curve, using a fixed specificity of 95%.[10,14,22,23] Statistical analyses was performed with SPSS version 25.0 or higher (SPSS Inc., Chicago, USA).

RESULTS

Patient characteristics

A total of 194 patients were included in the test cohort and 100 in the validation cohort. Twenty-seven patients were excluded in the test cohort; five patients because of a paced rhythm, 15 patients because of a bundle branch block, and seven patients showed wall motion abnormalities on echocardiography. No patients were excluded due to poor echocardiographic windows.

Patients in the test cohort were older, had a higher heart rate and more comorbidities such as diabetes mellitus and hypertension (Table 1). Patients in the validation cohort had a higher BSA (2.3 ± 0.2 vs 2.5 ± 0.2 m^2, *P* < .001) compared to the test cohort. LVM (197 ± 67 vs 196 ± 63 g, *P* = .83), and LVMI (94 ± 81 vs 79 ± 22 g/m^2, *P* = .13) were not significantly different between groups. However, the prevalence of LVH (defined as an increased LVMI) was higher in the test cohort (31.7% vs 19.2%, *P* < .05). LVH criteria as measured by ECG and echocardiography were stratified by gender as well (Table 2). There were no significant differences between male and female patients in both groups regarding abnormal ECG criteria. Also, although LVMI was increased in males as compared to females, prevalence of abnormal LVMI was comparable.

Accuracy of established criteria for detection of LVH in obesity patients (test cohort)

The BMI adjusted Cornell voltage had the highest sensitivity (53% male, 32% female) followed by the Peguero-Lo Presti criteria (16% male, 9% female). The Sokolow-Lyon index had very poor sensitivity (0% male, 3% female) in this obese population (Table 3). On the other hand, the specificity of the criteria not multiplied by BMI was high (ranged from 96% to 100%), but relatively low for the BMI adjusted Cornell voltage (72% male, 85% female).

Table 1: Patient characteristics

	Test cohort (n=167)	Validation cohort (n=100)	p-value
Age (years)	601 ± 13	48 ± 8	**<0.001**
Female, n (%)	123 (74%)	70 (70%)	0.49
Length (m)	1.67 ± 0.1	1.71 ± 0.1	0.84
Weight (kg)	110 ± 15	127 ± 18	0.27
BMI (kg/m^2)	39 ± 4	43 ± 4	0.20
BSA (m^2)	2.3 ± 0.2	2.5 ± 0.2	**<0.001**
Systolic BP (mmHg)	147 ± 25	142 ± 21	0.09
Diastolic BP (mmHg)	76 ± 12	80 ± 12	0.51
Heart rate (beats/min)	78 ± 16	71 ± 13	**0.048**
Diabetes mellitus, n (%)	112 (67%)	21 (21%)	**<0.001**
Hypertension, n (%)	80 (48%)	31 (31%)	**0.008**
Left axis deviation, n (%)	16 (10%)	5 (5%)	0.22
RaVL + SV3 (mm) (Cornell voltage)	11.8 ± 6	9.6 ± 5	**0.002**
SV1 + RV5/RV6 (mm) (Sokolow-Lyon index)	15.9 ± 6	15.7 ± 6	0.81
SV4 + Sdeepest (mm) (Peguero-Lo presti criteria)	14.5 ± 5	12.1 ± 6	**0.001**
LVM (g)	197 ± 67	196 ± 63	0.83
LVM abnormal, n (%)	121 (72%)	69 (69%)	0.63
LVM-index (g/m^2)	94 ± 81	79 ± 22	0.13
LVMI abnormal, n (%)[a]	53 (32%)	19 (19%)	**0.026**

Values represent mean ± SD or n (%).
BMI= body mass index, *BSA*= body surface area, *BP*= blood pressure, *LVM*= left ventricular mass, *LVMI*= left ventricular mass index
[a] Used as the definition for LVH as defined by echocardiography.

Table 2: Criteria for LVH measured by ECG and echocardiography stratified by gender

	Test cohort (n=167)			Validation cohort (n=100)		
	Male (n=44)	Female (n=123)	p-value	Male (n=30)	Female (n=70)	p-value
ECG criteria						
Cornell voltage (mm)	14.8 ± 5.6	10.8 ± 5.6	**<0.001**	11.1 ± 5.9	9.0 ± 0.4	0.06
Cornell voltage abnormal, n (%)	3 (7%)	3 (2%)	0.18	1 (3%)	1 (1%)	0.37
Sokolow-Lyon index (mm)	15.4 ± 5.5	1.73 ± 7.6	0.09	15.5 ± 5.5	15.8 ± 6.1	0.82
Solow-Lyon abnormal, n (%)	1 (2%)	1 (1%)	0.45	0	1 (1%)	0.51
Peguero-Lo Presti criteria (mm)	17.7 ± 5.8	13.4 ± 4.6	**<0.001**	12.7 ± 6.4	11.8 ± 5.3	0.45
Peguero-Lo Presti abnormal, n (%)	3 (7%)	4 (3%)	0.31	2 (7%)	4 (6%)	0.88
Echocardiography criteria						
LVM (g)	258 ± 80	174 ± 43	**<0.001**	242 ± 56	176 ± 55	**<0.001**
LVM abnormal, n (%)	36 (82%)	85 (69%)	0.11	26 (87%)	43 (61%)	**0.015**
LVM-index (g/m^2)	124 ± 130	84 ± 49	**0.004**	92 ± 21	75 ± 26	**0.002**
LVMI abnormal, n (%)	19 (43%)	34 (28%)	0.06	5 (17%)	14 (20%)	0.67

Values represent mean ± SD or n (%).

LVM= left ventricular mass, *LVMI*= left ventricular mass index

Accuracy of adjusted criteria for detection of LVH in obesity patients (test cohort)

New cut-off values for both males and females were defined for all criteria, with a fixed 95% specificity. The new cut-off values for the Cornell voltage, Sokolow-Lyon index, and Peguero-Lo Presti criteria were, respectively, ≥20, 24, and 19 mm for females and ≥27, 27, and 23 mm for males. All criteria were multiplied by BMI. The optimal cut-off values for the Cornell voltage*BMI, Sokolow-Lyon index*BMI, and Peguero-Lo Presti criteria*BMI were, respectively, ≥795, 885, and 780 mm*kg/m^2 for females and ≥700, 984, and 900 mm*kg/m^2 for males. Using these adjusted cut-off values, the Cornell voltage*BMI, (RaVL+SV3)*BMI ≥700 mm*kg/m^2, had the best sensitivity for males (47%, CI: 25%-70%), specificity 96% (CI: 78%-100%), ROC AUC 0.65, PPV 90% (CI: 54%-99%), and NPV 71% (CI: 52%-84%). the Sokolow- Lyon index*BMI, (SV1 + RV5/RV6)*BMI ≥885 mm*kg/m^2, had the best sensitivity for females (26%, CI: 14%-45%), specificity 93% (CI: 85%-97%), ROC AUC 0.69, PPV 60% (CI: 33%-83%), and NPV 77% (CI: 68%-84%).

Prospective validation of the adjusted criteria for detection of LVH in obesity patients (validation cohort)

When the new criteria were tested in the validation cohort, again the adjusted Cornell voltage*BMI had the best sensitivity for males (40%, CI: 7%-83%), specificity 92% (CI: 71%-99%), ROC AUC 0.78, PPV 50% (CI: 9%-91%), and NPV 88% (CI: 68%-97%). The Sokolow-Lyon index*BMI again had the best sensitivity for females (23%, CI: 6%-54%), specificity 83% (CI: 70%-91%), ROC AUC 0.57, PPV 25% (CI:7-57%), and NPV 81% (CI: 68%-90%). None of the male patients in the validation cohort had a positive Sokolow-Lyon index at a cut-off value of 27 mm. There were no substantial differences between the sensitivity and specificity in the test cohort and validation cohort.

Table 3: Accuracy of the Cornell voltage, Sokolow-Lyon index, Peguero-Lo Presti criteria and the BMI adjusted Cornell voltage for detection of left ventricular hypertrophy in obesity patients using both the conventional cut-off points and the adjusted criteria

Test Cohort	Gender	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
Original criteria					
Cornell voltage	Male	16 (4-40)	100 (83-100)	100 (31-100)	61 (45-75)
	Female	3 (0-17)	98 (91-100)	33 (2-87)	73 (63-80)

Sokolow–Lyon index	Male	0 (0-21)	96 (78-100)	0 (0-95)	56 (40-71)
	Female	3 (0-17)	100 (95-100)	100 (5-100)	73 (64-80)
Peguero–Lo Presti criteria	Male	16 (4-40)	100 (83-100)	100 (31-100)	61 (45-75)
	Female	9 (2-25)	99 (93-100)	75 (22-99)	74 (65-81)
Cornell voltage * BMI	Male	53 (29-75)	72 (50-87)	59 (33-81)	67 (46-83)
	Female	32 (2-37)	85 (76-92)	46 (26-67)	80 (72-87)
Adjusted Criteria					
Cornell voltage	Male	16 (4-40)	100 (83-100)	100 (30-100)	61 (45-75)
	Female	6 (1-21)	97 (90-99)	40 (7-83)	73 (64-80)
Sokolow-Lyon index	Male	21 (7-46)	92 (72-99)	67 (24-94)	61 (43-76)
	Female	18 (7-35)	97 (90-99)	67 (31-910	75 (66-82)
Peguero–Lo Presti criteria	Male	32 (14-57)	96 (78-100)	86 (42-99)	65 (47-79)
	Female	24 (11-42)	93 (85-97)	57 (30-81)	76 (67-84)
Cornell voltage * BMI	Male	47 (25-70)	96 (78-100)	90 (54-99)	71 (52-84)
	Female	9 (2-25)	96 (88-99)	43 (12-80)	73 (64-81)
Sokolow–Lyon index * BMI	Male	32 (14-57)	96 (78-100)	86 (42-99)	65 (47-79)
	Female	26 (14-45)	93 (85-97)	60 (33-83)	77 (68-84)
Peguero–Lo Presti criteria *BMI	Male	32 (14-57)	96 (78-100)	86 (42-99)	65 (47-79)
	Female	24 (11-41)	96 (88-99)	67 (35-89)	77 (35-89)
Validation Cohort					
Original criteria					
Cornell voltage	Male	20 (1-70)	100 (83-100)	100 (5-100)	86 (66-95)
	Female	8 (0-38)	100 (92-100)	100 (5-100)	82 (70-90)
Sokolow–Lyon index	Male	0 (0-54)	100 (83-100)	- *	83 (64-93)
	Female	0 (0-28)	98 (89-100)	0 (0-95)	80 (68-89)
Peguero–Lo Presti criteria	Male	20 (1-70)	96 (77-100)	50 (3-97)	85 (65-95)
	Female	15 (3-46)	96 (86-100)	50 (9-91)	82 (70-90)
Cornell voltage * BMI	Male	40 (7-83)	88 (67-98)	40 (7-83)	88 (67-97)
	Female	23 (6-54)	87 (74-94)	30 (8-65)	82 (69-91)
Adjusted Criteria					
Cornell voltage	Male	20 (1-70)	100 (83-100)	100 (5-100)	86 (66-95)
	Female	8 (4-38)	98 (88-100)	50 (3-97)	81 (69-90)
Sokolow-Lyon index	Male	- *	100 (83-100)	- *	83 (64-93)
	Female	15 (2-46)	90 (78-96)	29 (5-70)	81 (68-90)
Peguero–Lo Presti criteria	Male	20 (1-70)	96 (77-100)	50 (3-97)	85 (65-95)
	Female	15 (3-46)	94 (83-99)	40 (7-83)	82 (70-90)
Cornell voltage * BMI	Male	40 (7-83)	92 (71-99)	50 (9-91)	88 (68-97)
	Female	8 (0-38)	96 (86-99)	33 (2-87)	81 (69-89)
Sokolow–Lyon index * BMI	Male	0 (0-54)	92 (72-99)	0 (0-80)	81 (61-93)
	Female	23(6-54)	83 (70-91)	25 (7-57)	81 (68-90)
Peguero–Lo Presti criteria *BMI	Male	20 (1-70)	96 (77-100)	50 (3-97)	85 (65-95)
	Female	23 (6-54)	92 (81-98)	43 (12-79)	83 (71-91)

BMI= body mass index, *PPV*= positive predictive value, *NPV*= negative predictive value.

* None of the male patients in the validation cohort had a positive Sokolow-Lyon index.

DISCUSSION

In the current study we demonstrated that in obesity patients, established ECG criteria for the detection of LVH lack sufficient sensitivity for application in daily clinical practice. We propose new criteria (RaVL+SV3)*BMI ≥ 700mm*kg/m^2 for males and (SV1+RV5/RV6)*BMI ≥885mm*kg/m^2 for females for the detection of LVH in obesity patients with improved sensitivity, without losing specificity.

The explanation of the poor sensitivity of the established ECG criteria for detection of LVH (3-9% in females and 0-16% in males) may be that obesity patients commonly have reduced voltages in the precordial ECG leads, probably because the ECG voltages at the skin level are attenuated by the subcutaneous adipose tissue.[14] The sensitivity of these criteria may be improved by adjustment of the cut-off values and correction for BMI. Applying this, the Cornell voltage*BMI for males and Sokolow-Lyon index*BMI for females, showed an important improvement of the sensitivity of an ECG for the detection of LVH to 47% and 26%, respectively, using the optimal cut-of values (both identified in analysis using a fixed specificity of 95%).

Because in obesity patients with cardiac disease there may often already be a clinical indication for an echocardiogram, an ECG as a screening tool for detection of LVH may have the most value in obesity patients without known cardiac disease. In the current study for the first time, adjusted ECG criteria for detection of LVH were tested in such a relatively low-risk obese population. Even in these subjects, the proposed new criteria performed fairly very well (sensitivity of 40% for the Cornell voltage*BMI in males and 23% for the Sokolow-Lyon index*BMI in females, using the optimal cut-of values). Although these sensitivity values appear to be rather poor, also in lean subjects the sensitivity of ECG criteria for LVH is known to be limited. A review of multiple studies in different healthcare settings found that the sensitivity of the Cornell voltage and Sokolow-Lyon index ranged from 2 to 52% with a specificity ranging from 71 to 100%.[24] Therefore, in our study it was shown that sensitivity of an ECG to detect LVH in obesity patients without known cardiac disease may be comparable to known sensitivity in lean subjects when using the proposed new criteria.

When adjusting the Cornell voltage by BMI as designed by Angeli et al.[17] the sensitivity of an ECG to detect LVH increased even to 53%, however the specificity decreased to 72%. In previous studies[10,14,22,23] a fixed specificity level of 95% was chosen because this is supposed to be sufficient to render an ECG a cost-effective alternative to echocardiography in screening populations for presence of LVH. Therefore, we also used this 95% fixed specificity and

identified optimal sensitivity values by adjusting the cut-off values of the criteria. Moreover, in the study by Angeli et al. this criterion was not specifically tested in a group of obese patients. The mean BMI in their cohort was 26.7 kg/m^2, which is much lower than the mean BMI of our test- and validation cohort (39.3 kg/m^2 and 42.9 kg/m^2 respectively).

Some other studies regarding the optimization of ECG criteria for the detection of LVH in obesity patients have been performed before. Rider et al. made an adjustment to the cut-off value of the Sokolow-Lyon index (+8 mm). This improved the sensitivity to 27% (specificity 93%) in their test cohort and 25% in their validation cohort.[24] Also, Robinson et al. designed a new criterion [RaVL + (BMI − 29) × 0.017], which improved the sensitivity to 42%, however, with a relatively decreased specificity of 83%.[12] Finally, Rodrigues et al. made an adjustment to the Cornell voltage (cut-off value ≥27 mm) which improved the sensitivity to 21% with a specificity of 95%.[23] Nevertheless, in none of these studies, the sensitivity of the established ECG criteria for the detection of LVH in lean subjects was approached.

All adjusted criteria in our study had better sensitivities in males than in females. This difference is possibly because of the abundant breast tissue in obese women,[26] which may also explain why the Cornell voltage performed relatively poor in women (Table 3). The positioning of lead V3, an important lead for the Cornell voltage, is usually on a location of relatively plentiful breast tissue as compared to the position of V1 and V5 used for the Sokolow-Lyon index, which appeared to be the best performing criterion in female obesity patients. An explanation could also be that in general women have a smaller LVM (in our obese population 175 ± 48 g in females vs 252 ± 72 g in males, $P < .001$) leading to smaller S wave amplitude in V3, which measures posteriorly directed myocardial electrical activity.[9,27]

Finally, it may seem difficult to implement our proposed criteria into daily practice since, apart from the necessity to assess BMI, it would require the use of different criteria in males and females. However, nowadays ECG devices already use programmed algorithms for standard interpretation. It will be a relatively minor issue to add our proposed new criteria to these modern devices, allowing easy clinical use without extra effort.

Limitations

LVM was estimated by 2D echocardiography, despite reports demonstrating superior accuracy of cardiac magnetic resonance imaging, especially in obesity patients.[28,29] However, echocardiography is known to have good reproducibility for the diagnosis of LVH and remains the most frequently used method in clinical practice.[30] Also, LVH diagnosed by ECG is known to be a marker of adverse electric remodelling even without LVH diagnosed by

echocardiography. Thus, also without association with echocardiographic LVH, some ECG criteria may still be associated with prognosis.[31,32] Although obesity is usually defined as BMI ≥30 kg/m^2, all patients included in our study had a BMI ≥35 kg/m^2 because this was an inclusion criterion for the CARDIOBESE study. Therefore, the conclusions may only be applied to morbidly obese patients and not to obesity patients in general. The sample size was relatively small. The validation cohort had a relatively low prevalence of LVH; therefore, the PPV values even for the new criteria were low. However, as mentioned before, in the current study for the first time, adjusted ECG criteria for the detection of LVH were validated in a relatively low-risk obese population without known or suspicion of cardiovascular disease. Racial differences in the diagnosis of LVH were not addressed in this study. Also, the abilities of the proposed criteria to predict outcomes (eg, incident cardiovascular morbidity) are not known. Finally, we included only BMI as an obesity index and could not assess whether, for example, waist circumference or epicardial fat thickness is superior to BMI to adjust the voltage ECG criteria.

CONCLUSIONS

Established ECG criteria for the detection of LVH lack sufficient sensitivity in obesity patients. We propose new criteria, (RaVL+SV3)*BMI ≥700 mm*kg/m^2 for males and (SV1 + RV5/RV6)*BMI ≥885 mm*kg/m^2 for females, for the detection of LVH in obesity patients with improved sensitivity (47% in males and 26% in females), approaching known sensitivity of the most commonly used ECG criteria in lean subjects.

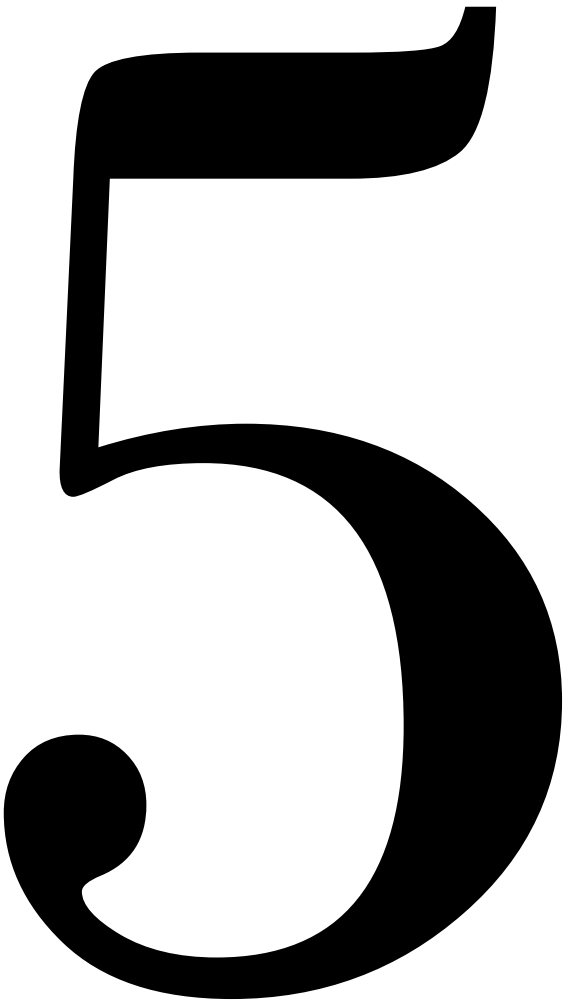
REFERENCES

1. Collaboration NCDRF. Trends in adult body-mass index in 200 countries from 1975 to 2014: a pooled analysis of 1698 population-based measurement studies with 19.2 million participants. Lancet. 2016; 387:1377-1396.
2. Alpert MA, Lambert CR, Terry BE, et al. Effect of weight loss on left ventricular mass in nonhypertensive morbidly obese patients. Am J Cardiol. 1994;73:918-921.
3. Himeno E, Nishino K, Nakashima Y, Kuroiwa A, Ikeda M. Weight reduction regresses left ventricular mass regardless of blood pressure level in obese subjects. Am Heart J. 1996;131:313-319.
4. Havranek EP, Froshaug DB, Emserman CD, et al. Left ventricular hypertrophy and cardiovascular mortality by race and ethnicity. Am J Med. 2008;121:870-875.
5. Porthan K, Kentta T, Niiranen TJ, et al. ECG left ventricular hypertrophy as a risk predictor of sudden cardiac death. Int J Cardiol. 2019; 276:125-129.
6. Wenger NK. Prevention of cardiovascular disease: highlights for the clinician of the 2013 American College of Cardiology/American Heart Association guidelines. Clin Cardiol. 2014;37:239-251.
7. de Vries SO, Heesen WF, Beltman FW, et al. Prediction of the left ventricular mass from the electrocardiogram in systemic hypertension. Am J Cardiol. 1996;77:974-978.
8. Lewis T.Observations upon ventricular hypertrophywith special reference to preponderance of one or the other chamber. Heart. 1914;5:367-402. 9.
9. Casale PN, Devereux RB, Kligfield P, et al. Electrocardiographic detection of left ventricular hypertrophy: development and prospective validation of improved criteria. J Am Coll Cardiol. 1985;6:572-580.
10. Sokolow M, Lyon TP. The ventricular complex in left ventricular hypertrophy as obtained by unipolar precordial and limb leads. Am Heart J. 1949;37:161-186.
11. Verdecchia P, Angeli F, Reboldi G, et al. Improved cardiovascular risk stratification by a simple ECG index in hypertension. Am J Hypertens. 2003;16:646-652.
12. Robinson C, Woodiwiss AJ, Libhaber CD, Norton GR. Novel approach to the detection of left ventricular hypertrophy using body mass index-corrected electrocardiographic voltage criteria in a Group of African Ancestry. Clin Cardiol. 2016;39:524-530.
13. Domienik-Karlowicz J, Rymarczyk Z, Lisik W, et al. Questionable validity of left ventricular hypertrophy cutoff values in morbidly and supermorbidly obese patients. Ann Noninvasive Electrocardiol. 2018;23:e12564.
14. Okin PM, Roman MJ, Devereux RB, Kligfield P. Electrocardiographic identification of left ventricular hypertrophy: test performance in relation to definition of hypertrophy and presence of obesity. J Am Coll Cardiol. 1996;27:124-131.
15. Germano G. Electrocardiographic signs of left ventricular hypertrophy in obese patients: what criteria should be used? High Blood Press Cardiovasc Prev. 2015;22:5-9.
16. Peguero JG, Lo Presti S, Perez J, Issa O, Brenes JC, Tolentino A. Electrocardiographic criteria for the diagnosis of left ventricular hypertrophy. J Am Coll Cardiol. 2017;69:1694-1703.
17. Angeli F, Verdecchia P, Iacobellis G, Reboldi G. Usefulness of QRS voltage correction by body mass index to improve electrocardiographic detection of left ventricular hypertrophy in patients with systemic hypertension. Am J Cardiol. 2014;114: 427-432.
18. Snelder SM, de Groot-de Laat LE, Biter LU, et al. Cross-sectional and prospective follow-up study to detect early signs of cardiac dysfunction in obesity: protocol of the CARDIOBESE study. BMJ Open 2018;8:e025585.
19. Lang RM, Badano LP, Mor-Avi V, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. Eur Heart J Cardiovasc Imaging. 2015;16:233-270.
20. Nagueh SF, Smiseth OA, Appleton CP, et al. Recommendations for the evaluation of left ventricular diastolic function by echocardiography: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. Eur Heart J Cardiovasc Imaging. 2016;17:1321-1360.
21. Mosteller RD. Simplified calculation of body-surface area. N Engl J Med. 1987;317:1098.

22. Norman JE Jr, Levy D. Adjustment of ECG left ventricular hypertrophy criteria for body mass index and age improves classification accuracy. The effects of hypertension and obesity. J Electrocardiol. 1996; 29(Suppl):241-247.
23. Rodrigues JC, McIntyre B, Dastidar AG, et al. The effect of obesity on electrocardiographic detection of hypertensive left ventricular hypertrophy: recalibration against cardiac magnetic resonance. J Hum Hypertens. 2016;30:197-203.
24. Pewsner D, Juni P, Egger M, Battaglia M, Sundstrom J, Bachmann LM. Accuracy of electrocardiography in diagnosis of left ventricular hypertrophy in arterial hypertension: systematic review. BMJ. 2007;335:711.
25. Rider OJ, Ntusi N, Bull SC, et al. Improvements in ECG accuracy for diagnosis of left ventricular hypertrophy in obesity. Heart. 2016;102: 1566-1572.
26. Rautaharju PM, Park L, Rautaharju FS, Crow R. A standardized procedure for locating and documenting ECG chest electrode positions: consideration of the effect of breast tissue on ECG amplitudes in women. J Electrocardiol. 1998;31:17-29.
27. Xu CF, Tan ES, Feng L, et al. Electrocardiographic criteria for left ventricular hypertrophy in Asians differs from criteria derived from Western populations-community-based data from an Asian population. Ann Acad Med Singapore. 2015;44:274-283.
28. Bacharova L, Ugander M. Left ventricular hypertrophy: the relationship between the electrocardiogram and cardiovascular magnetic resonance imaging. Ann Noninvasive Electrocardiol. 2014;19: 524-533.
29. Oseni AO, Qureshi WT, Almahmoud MF, et al. Left ventricular hypertrophy by ECG versus cardiac MRI as a predictor for heart failure. Heart. 2017;103:49-54.
30. Palmieri V, Dahlof B, DeQuattro V, et al. Reliability of echocardiographic assessment of left ventricular structure and function: the PRESERVE study. Prospective Randomized Study Evaluating Regression of Ventricular Enlargement. J Am Coll Cardiol. 1999;34: 1625-1632.
31. Sundstrom J, Lind L, Arnlov J, Zethelius B, Andren B, Lithell HO. Echocardiographic and electrocardiographic diagnoses of left ventricular hypertrophy predict mortality independently of each other in a population of elderly men. Circulation. 2001;103:2346-2351.
32. Narayanan K, Reinier K, Teodorescu C, et al. Electrocardiographic versus echocardiographic left ventricular hypertrophy and sudden cardiac arrest in the community. Heart Rhythm. 2014;11:1040-1046.

Part III

Cardiac dysfunction related to obesity and the impact of bariatric surgery



Chapter 5

Early detection of left ventricular diastolic dysfunction using conventional and speckle tracking echocardiography in a large animal model of metabolic dysfunction

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ABSTRACT

Left ventricular (LV) diastolic dysfunction is one of the important mechanisms responsible for symptoms in patients with heart failure. The aim of the current study was to identify parameters that may be used to detect early signs of LV diastolic dysfunction in diabetic pigs on a high fat diet, using conventional and speckle tracking echocardiography. The study population consisted of 16 healthy Göttingen minipigs and 18 minipigs with experimentally induced metabolic dysfunction. Echocardiography measurements were performed at baseline and 3-month follow-up. the ratio of peak early (E) and late filling velocity (E/A ratio) and the ratio of E and the velocity of the mitral annulus early diastolic wave (E/Em ratio) did not change significantly in both groups. Peak untwisting velocity decreased in the metabolic dysfunction group (− 30.1±18.5 vs. − 23.4±15.5 °/ms) but not in controls (−38.1±23.6 vs. − 42.2±23.0 °/ms), being significantly different between the groups at the 3-month time point ($p<0.05$). In conclusion, whereas E/A ratio and E/Em ratio did not change significantly after 3 months of metabolic dysfunction, peak untwisting velocity was significantly decreased. Hence, peak untwisting velocity may serve as an important marker to detect early changes of LV diastolic dysfunction.

INTRODUCTION

Heart failure is a major public health problem in developed countries.[1] Left ventricular (LV) diastolic dysfunction is one of the important mechanisms responsible for symptoms in patients with heart failure, irrespective of the presence or severity of systolic LV dysfunction.[2] Diastolic dysfunction and filling pressures can be assessed by two-dimensional and Doppler echocardiography.[3-5] Speckle tracking echocardiography can be used to quantify several subtle changes in LV mechanics, for example LV twist and untwisting. As the base of the heart rotates clockwise along the LV long-axis, the apex rotates counter clockwise. This results into a wringing motion of the heart, defined as LV systolic twist and diastolic untwisting.[6] LV untwisting plays an important role in the mechanics of early LV filling.[7]

Diabetes mellitus is an important risk factor for the development of LV diastolic dysfunction.[8-11] In previous studies on the use of speckle tracking for detection of LV dysfunction in diabetes mellitus, including two studies using a small animal model,[12-13] focus has been on assessment of LV strain and not on LV untwisting, and contrasting results were reported.[14-23]

The aim of the current study was to identify parameters that may be used to detect early signs of LV diastolic dysfunction in a large animal model of metabolic dysfunction, using conventional and speckle tracking echocardiography.

Although it was shown in previous studies[24-26] that LV untwisting may be a meaningful parameter of diastolic function, its potential as an early marker of diastolic dysfunction is unclear. By longitudinally investigating a large animal exposed to important risk factors for development of diastolic dysfunction, our study may provide important added information in this regard. The hypothesis of our study was that LV untwisting may be useful for detecting LV diastolic dysfunction at a very early stage.

METHODS

Porcine model of metabolic dysfunction

The study population consisted of 16 healthy Göttingen minipigs (mean age 17.8 ± 0.8 months, mean weight 31.1±1.6 kg) and 18 minipigs with metabolic dysfunction (mean age 17.7±0.6 months, mean weight 31.0±1.3 kg). Diabetes was induced with intravenous (ear catheter) injections of streptozotocin (25 mg/kg/day) over 3 days (total dose 75 mg/kg). One week after diabetes induction, a high fat diet (25% of saturated fats and 1% of cholesterol) was gradually introduced for diabetic pigs, whereas control pigs continued on a normal chow diet.[27] Pigs were group-housed (a total of 9 pigs at the same time) with a separate individual ad libitum access to food for 1 h/meal, twice daily for the entire 3-month study duration.

Studies were performed in accordance with the NIH Guide for the Care and Use of Laboratory Animals (8th edition, National Research Council. Washington, DC: The National Academies Press, 2011) and were approved by the Animal Care Committee at Erasmus University Medical Center Rotterdam.

Echocardiography

Echocardiography measurements were performed at baseline and 3-months follow-up. Two-dimensional grayscale harmonic images were obtained in the right lateral decubitus position using a commercially available ultrasound system (iE33, Philips, Best, The Netherlands), equipped with a broadband (1–5 MHz) S5-1 transducer (frequency transmitted 1.7 MHz, received 3.4 MHz) (Figure 1). Left atrial volume was calculated using the biplane area-length formula and indexed for body surface area.[28] From the mitral-inflow pattern, peak early (E) and late (A) filling velocities, E/A ratio, and E-velocity deceleration time (DT) were measured. Tissue Doppler imaging was applied by placing the sample volume at the side of the medial mitral annulus in an apical 4-chamber view.[29] Gain and filter settings were adjusted as needed to eliminate background noises and to allow for a clear tissue signal. To acquire the highest tissue velocities, the angle between the Doppler beam and the longitudinal motion of the investigated structure was adjusted to a minimal level. The velocity of the mitral annulus early diastolic wave (Em) was recorded at a sweep speed of 100 mm/s.

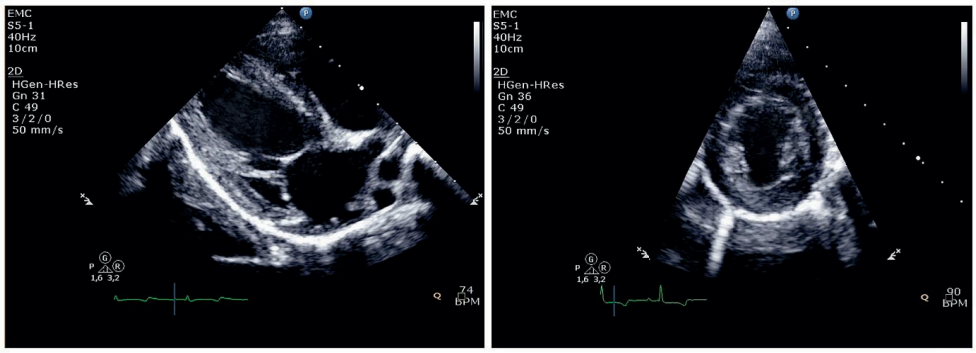

Figure 1: Example of a long-axis and short-axis echocardiographic image in a pig

Data analysis

Speckle tracking analysis of the datasets was performed using QLAB Advanced Quantification Software (version 10.0, Philips, Best, The Netherlands). In order to assess LV apical and basal rotation, tracking points were placed automatically and could be manually adjusted afterwards on an end-diastolic frame in each parasternal short-axis image, close to the endocardium. Rotation was defined as the mean angular displacement of all tracking points, relative to the centre of a circle through these tracking points. Clockwise rotation as viewed from the apex was expressed as a positive value, counter clockwise rotation was expressed as a negative value. LV twist was calculated as the difference between LV apical and basal rotation. Data were exported to a spread sheet program (Excel, Microsoft Corporation, Redmond, WA) to determine peak basal and apical rotation, peak twist, peak untwist velocity, and the timing of these parameters. Also, circumferential strain and strain rate (short-axis images) and longitudinal strain and strain rate (long-axis images) were measured.

Statistical analysis

Statistical analyses were performed with SAS 9.3 program (SAS Institute, Cary, NC), using two-way ANOVA for repeated measures, with time (baseline vs. 3-month time point) and diabetes (controls vs. diabetic animals) as factors. If significant main effects or interactions were found, pairwise differences were identified with the Tukey–Kramer post hoc correction. A p value<0.05 was considered statistically significant. Measurements were presented as mean±SD. A Pearson's R correlation test was conducted to examine whether there was a relationship between parameters that changed significantly from baseline to 3 months follow-up.

RESULTS

Characteristics of the study population

Baseline characteristics are shown in Table 1. Diabetic pigs on a high fat diet developed significantly elevated glucose and lipid levels.

Conventional echocardiography

Baseline versus 3 months conventional echocardiography characteristics are shown in Table 2. E-wave velocity increased significantly after 3 months of metabolic dysfunction (52±6 vs. 58±10 cm/s) but not in controls (54±9 vs. 53±9 cm/s) whereas A-wave velocity increased significantly in both groups (43±9 vs. 47±11 cm/s in diabetic pigs on a high fat diet and 40±7

vs. 46±10 in controls). E/A ratio and E/Em ratio did not change significantly in both groups, although there was a trend towards an increase of E/Em ratio in the diabetic pigs on a high fat diet from 6.9±1.5 at baseline to 7.7±1.3 at 3 months (p=0.06).

Table 1 General and blood characteristics of diabetic pigs on a high fat diet (n=18) and healthy controls (n=16)

	Baseline	3 months
Age at study onset (months)		
DM	17.7±2.5	-
Control	17.8±3.0	-
Body weight (kg)		
DM	31.0±5.6	35.9±7.3***
Control	31.1±6.5	34.9±5.4***
Glucose (mmol/l)		
DM	5.1±1.0	12.9±6.0#
Control	6.0±1.1	5.5±1.1
Triglycerides (mmol/l)		
DM	0.28±0.09	0.94±1.01#
Control	0.31±0.08	0.29±0.07
Total cholesterol (mmol/l)		
DM	0.94±0.23	6.25±4.51#
Control	0.93±0.28	1.14±0.27
LDL-C (mmol/l)		
DM	0.40±0.11	3.76±3.79#
Control	0.43±0.18	0.44±0.18
HDL-C (mmol/l)		
DM	0.55±0.09	2.76±1.24#
Control	0.52±0.14	0.73±0.16

Values represent mean ± standard deviation
DM= diabetic pigs on a high fat diet
***p<0.0001 as time effect; # p<0.01 as compared to controls at 3-months

Speckle tracking echocardiography

LV twist and untwist data are shown in Table 3. Most importantly, peak untwisting velocity (Figure 2) decreased significantly after 3 months of metabolic dysfunction (− 30.1±18.5 vs. − 23.4±15.5 °/ms) but not in controls (− 38.1±23.6 vs. − 42.2±23.0 °/ms) resulting in a significant group difference at the 3-month time point (p<0.05) while baseline values were not different (p =0.698). No significant correlation was found between E or E/Em ratio and peak untwisting velocity (R2= − 0.473, p=0.111 and R2= − 0.183, p=0.481, respectively) or (delta) E or E/Em ratio and (delta) peak untwisting velocity (R2= − 0.397, p=0.121 and R2= − 0.369,

p=0.145, respectively). LV longitudinal and circumferential strain and strain rate did not change significantly from baseline to 3 months in diabetic pigs on a high fat diet and healthy control pigs.

Table 2 Conventional echocardiographic characteristics of left ventricular diastolic function in diabetic pigs on a high fat diet (n=18) and healthy controls (n=16)

	Baseline	**3 months**
Left atrial volume (ml)		
DM	23±6	25±9
Control	26±7	27±8
Normalized left atrial volume (ml/kg)		
DM	0.77±0.17	0.72±0.29
Control	0.89±0.20	0.79±0.22
E-wave velocity (cm/s)		
DM	52±6	58±10*
Control	54±9	53±9
A-wave velocity (cm/s)		
DM	43±9	47±11#
Control	40±7	46±10#
E/A ratio		
DM	1.3±0.3	1.3±0.4
Control	1.4±0.3	1.2±0.2
E-wave velocity deceleration time (ms)		
DM	123±30	126±31
Control	118±21	123±28
Em septal (cm/s)		
DM	7.8±1.4	7.7±1.6
Control	7.7±1.5	7.6±1.5
E/Em ratio		
DM	6.9±1.5	7.7±1.3
Control	7.2±1.4	7.2±1.2

Values represent mean ± standard deviation.
DM= diabetic metabolic derangement, *E-wave velocity*= peak early phase filling velocity, *A-wave velocity*= peak atrial phase filling velocity, *Em*= peak early diastolic wave velocity.
*p<0.05 as compared to baseline, #p<0.05 as time effect

Table 3 Speckle tracking echocardiography parameters in diabetic pigson a high fat diet (n=18) and healthy controls (n=16)

	Baseline	3 months
Systolic		
Peak rotation basal (°)		
DM	1.2±1.2	0.8±1.8
Control	0.7±1.5	0.7±1.5
Peak rotation apical (°)		
DM	4.4±4.2	3.8±4.2
Control	4.2±2.6	4.1±2.8
Peak velocity basal rotation (°/ms)		
DM	4.3±3.0	8.8±12.6
Control	5.5±4.9	7.3±5.6
Peak velocity apical rotation (°/ms)		
DM	-26.6 ± 22.0	-28.1±32.7
Control	-31.9±29.7	-21.1±18.2
Peak twist (°)		
DM	4.1±4.4	3.6±4.4
Control	4.3±3.8	3.7±2.4
Time to peak twist (s)		
DM	0.4±0.2	0.4±0.1
Control	0.4±0.1	0.4±0.1
Diastolic		
Peak untwist velocity (°/ms)		
DM	-30.1±18.5	-23.4±15.5*
Control	-38.1±23.6	-42.2±23.0
Time to peak untwist velocity (s)		
DM	0.4±0.1	0.4±0.1
Control	0.4±0.1	0.5±0.1

Values represent mean ± standard deviation
DM= diabetic pigs on a high fat diet
* P<0.05 as compared to controls at 3-months

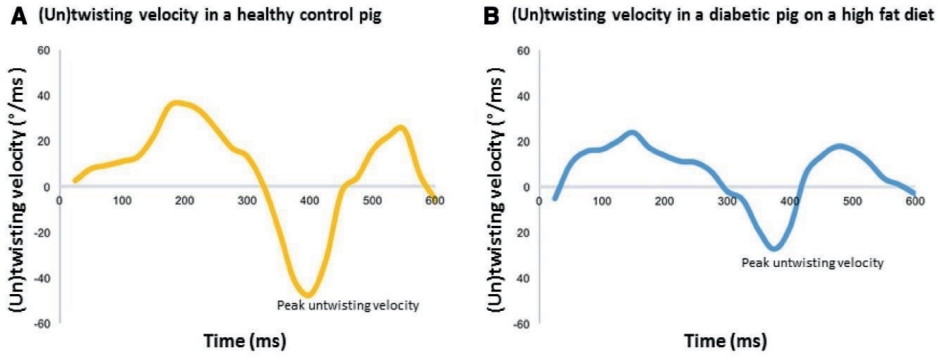

Figure 2: (Un)twisting velocity curves in a healthy control pig (A) and a diabetic pig on a high fat diet (B)

DISCUSSION

Peak untwisting velocity was significantly decreased in diabetic pigs on a high fat diet compared to healthy animals as assessed at 3-months from metabolic dysfunction onset. To the best of our knowledge, the current study is the first to show these early changes of LV diastolic dysfunction in a large animal model. These findings suggest that peak untwisting velocity may serve as an important marker to detect early changes of LV diastolic dysfunction.

Under normal physiological conditions, over 40% of diastolic LV untwisting has been completed after the first 15% of diastole, thereby contributing to the large and rapid pressure decay during the isovolumic relaxation phase.[6] This rapid, early LV untwisting process is the result of both active and passive mechanisms. There is a temporal dispersion in endocardial and epicardial repolarization, with in early diastole still depolarized endocardial fibres (as opposite to the already repolarized epicardial fibres) that may actively untwist the LV (normally the action of these fibres are overruled by the epicardial fibres).[7] However, the effective force of contraction of myocardial fibres is expected to be minimal during this part of the cardiac cycle. Nevertheless, dissimilarities of apparent stiffness of the endocardium and epicardium caused by differences in detachment of actinmyosin cross-bridges may be of influence. Furthermore, high levels of stored potential energy from the active systolic twist are transformed into kinetic energy, adding a passive component to rapid early diastolic untwisting.[30] Subendocardial dysfunction in the diabetic pigs on a high fat diet may lead to loss of the active part of diastolic untwisting.[10] Also, increased stiffness of the LV may lead to a decreased potential to transform the potential energy stored in systolic twisting into rapid LV untwisting. Both of these phenomena may explain the decreased peak untwisting velocity found in the diabetic pigs on a high fat diet.

E-wave velocity increased significantly after 3 months of metabolic dysfunction and A-wave velocity increased in both groups. A possible explanation for this may be the increased circulating volume related to the increase in body weight over time in both groups, because the mitral inflow pattern is well-known to heavily depend on circulating volume status.[4] However, this leaves unexplained why E-wave velocity only changed in diabetic pigs on a high fat diet. It cannot be excluded that the latter does have to do with the development of LV diastolic dysfunction in these pigs. Nevertheless, in daily clinical practice qualification of LV diastolic function is based much more on E/A ratio than on the individual E-wave velocity or A-wave velocity values. Importantly, E/A ratio did not change significantly in both groups. Although E/Em ratio increased by almost 12% after 3 months of metabolic dysfunction, this group difference failed to reach statistical significance. Increased E/Em ratio is essentially a marker

of increased left atrial pressure. When LV diastolic dysfunction develops, LV filling will be impaired, subsequently leading to increased left atrial pressure.[4] Maybe the 3 month period was too short to allow development of significantly increased left atrial pressure. The results of our study show that at a time when peak untwisting velocity was already significantly decreased, E/ Em ratio and E/A ratio failed to show significant differences between diabetic pigs on a high fat diet and controls.

After the 3 month period, both diabetic pigs on a high fat diet and control pigs were randomized to either a training program or an untrained, sedentary lifestyle. Unpublished data from our laboratory indicate that in this model at 5 months E/Em ratio was increased in untrained pigs with metabolic syndrome compared to untrained controls (8.6±1.8 and 7.1±0.9, respectively, $p < 0.05$). Therefore, development of diastolic dysfunction in the diabetic pigs on a high fat diet was confirmed by conventional echocardiography after 5 months.

In previous studies, abnormal values of LV strain, especially longitudinal systolic strain, in patients with diabetes mellitus have been reported.[14-23] Yet, in the current study we could not identify a decrease of longitudinal or circumferential systolic strain in the diabetic pigs on a high fat diet at a time when peak untwisting velocity was already significantly decreased. LV dysfunction is expected to start with diastolic dysfunction. Our finding therefore underscores the notion that the large animal model investigated in the current study may truly be a model of early LV dysfunction. Extension of the period of metabolic dysfunction may eventually lead to development of abnormal systolic LV strain values. Further studies are needed to test this hypothesis.

Limitations

The study population is relatively small. Also, it is uncertain whether the findings in this large animal model may be extrapolated to humans. Therefore, the true potential of LV untwisting as an early marker of LV diastolic dysfunction should be confirmed in a prospective clinical study, for example in patients at high risk of development of LV diastolic dysfunction but with a normal echocardiogram according to conventional parameters.

CONCLUSION

In this study, based on comprehensive conventional and speckle tracking echocardiography analyses of the LV in a large animal model of metabolic dysfunction, LV peak untwisting velocity was found to be a parameter for early detection of LV diastolic dysfunction.

REFERENCES

1. Zarrinkoub R, Wettermark B, Wandell P, Mejhert M, Szulkin R, Ljunggren G et al (2013) The epidemiology of heart failure, based on data for 2.1 million inhabitants in Sweden. Eur J HeartFail 15(9):995–1002
2. Dougherty AH, Naccarelli GV, Gray EL, Hicks CH, Goldstein RA (1984) Congestive heart failure with normal systolic function. Am J Cardiol 54(7):778–782
3. Oh JK, Hatle L, Tajik AJ, Little WC (2006) Diastolic heart failure can be diagnosed by comprehensive two-dimensional and Doppler echocardiography. J Am Coll Cardiol 47(3):500–506
4. Nagueh SF, Smiseth OA, Appleton CP, Byrd BF, Dokainish H, Edvardsen T et al (2016) Recommendations for the evaluation of left ventricular diastolic function by echocardiography: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. Eur Heart J Cardiovasc Imaging 22(2):107–133. http://www.ncbi.nlm.nih.gov/pubmed/27422899
5. van Dalen BM, Strachinaru M, van der Swaluw J, Geleijnse ML (2016) A simple, fast and reproducible echocardiographic approach to grade left ventricular diastolic function. Int J Cardiovasc Imaging 32(5):743–752
6. van Dalen BM, Soliman OII, Vletter WB, ten Cate FJ, Geleijnse ML (2009) Insights into left ventricular function from the time course of regional and global rotation by speckle tracking echocardiography. Echocardiography 26(4):371–377
7. Sengupta PP, Khandheria BK, Narula J (2008) Twist and untwist mechanics of the left ventricle. Heart Fail Clin 4(3):315–324
8. Leung M, Phan V, Leung DY (2014) Endothelial function and left ventricular diastolic functional reserve in type 2 diabetes mellitus. Open Hear 1(1):e000113
9. Zabalgoitia M, Ismaeil MF, Anderson L, Maklady FA (2001) Prevalence of diastolic dysfunction in normotensive, asymptomatic patients with well-controlled type 2 diabetes mellitus. Am J Cardiol 87(3):320–323
10. von Bibra H, St John Sutton M (2010) Diastolic dysfunction in diabetes and the metabolic syndrome: promising potential for diagnosis and prognosis. Diabetologia 53(6):1033–1045
11. Noh JH, Doh JH, Lee SY, Kim TN, Lee H, Song HY et al (2010) Risk factors associated with left ventricular diastolic dysfunction in type 2 diabetic patients without hypertension. Korean Diabetes J 34(1):40–46
12. Shepherd DL, Nichols CE, Croston TL, McLaughlin SL, Petrone AB, Lewis SE et al (2016) Early detection of cardiac dysfunction in the type 1 diabetic heart using speckle-tracking based strain imaging. J Mol Cell Cardiol 90:74–83
13. Li R, Yang J, Yang Y, Ma N, Jiang B, Sun Q et al (2014) Speckle tracking echocardiography in the diagnosis of early left ventricular systolic dysfunction in type II diabetic mice. BMC Cardiovasc Disord 14:141
14. Bjornstad P, Truong U, Pyle L, Dorosz JL, Cree-Green M, Baumgartner A et al (2016) Youth with type 1 diabetes have worse strain and less pronounced sex differences in early echocardiographic markers of diabetic cardiomyopathy compared to their normoglycemic peers: a resistance to insulin in type 1 and type 2 diabetes (resistant) study. J Diabetes Complicat 30(6):1103–1110
15. Altun G, Babaoglu K, Binnetoglu K, Ozsu E, Yesiltepe Mutlu RG, Hatun S (2016) Subclinical left ventricular longitudinal and radial systolic dysfunction in children and adolescents with type 1 diabetes mellitus. Echocardiography 33(7):1032–1039
16. Mochizuki Y, Tanaka H, Matsumoto K, Sano H, Shimoura H, Ooka J et al (2017) Impact of left ventricular longitudinal functional mechanics on the progression of diastolic function in diabetes mellitus. Int J Cardiovasc Imaging. https://doi.org/10.1007/ s10554-017-1198-8
17. Jedrzejewska I, Krol W, Swiatowiec A, Wilczewska A, Grzywanowska-Laniewska I, Dluzniewski M et al (2016) Left and right ventricular systolic function impairment in type 1 diabetic young adults assessed by 2D speckle tracking echocardiography. Eur Heart J Cardiovasc Imaging 17(4):438–446
18. Wang Q, Gao Y, Tan K, Xia H, Li P (2015) Assessment of left ventricular function by three-dimensional speckle-tracking echocardiography in well-treated type 2 diabetes patients with or without hypertension. J Clin Ultrasound 43(8):502–511
19. Ernande L, Bergerot C, Girerd N, Thibault H, Davidsen ES, Gautier Pignon-Blanc P et al (2014) Longitudinal myocardial strain alteration is associated with left ventricular remodeling in asymptomatic patients with type 2 diabetes mellitus. J Am Soc Echocardiogr 27(5):479–488
20. Zoroufian A, Razmi T, Taghavi-Shavazi M, Lotfi-Tokaldany M, Jalali A (2014) Evaluation of subclinical left ventricular dysfunction in diabetic patients: longitudinal strain velocities and left ventricular dyssynchrony by two-dimensional speckle tracking echocardiography study. Echocardiography 31(4):456–463

21. Roos CJ, Scholte AJ, Kharagjitsingh AV, Bax JJ, Delgado V (2014) Changes in multidirectional LV strain in asymptomatic patients with type 2 diabetes mellitus: a 2-year follow-up study. Eur Heart J Cardiovasc Imaging 15(1):41–47
22. Zhang X, Wei X, Liang Y, Liu M, Li C, Tang H (2013) Differential changes of left ventricular myocardial deformation in diabetic patients with controlled and uncontrolled blood glucose: a threedimensional speckle-tracking echocardiography-based study. J Am Soc Echocardiogr 26(5):499–506
23. Ng ACT, Delgado V, Bertini M, van der Meer RW, Rijzewijk LJ, Shanks M et al (2009) Findings from left ventricular strain and strain rate imaging in asymptomatic patients with type 2 diabetes mellitus. Am J Cardiol 104(10):1398–1401
24. Buchalter MB, Weiss JL, Rogers WJ, Zerhouni EA, Weisfeldt ML, Beyar R, Shapiro EP (1990) Noninvasive quantification of left ventricular rotational deformation in normal humans using magnetic resonance imaging myocardial tagging. Circulation 81:1236–1244
25. Dong SJ, Hees PS, Siu CO, Weiss JL, Shapiro EP (2001 Nov) MRI assessment of LV relaxation by untwisting rate: a new isovolumic phase measure of tau. Am J Physiol Heart Circ Physiol 281(5):H2002–H2009
26. Notomi Y, Lysyansky P, Setser RM, Shiota T, Popovic ZB, Martin-Miklovic MG et al (2005) Measurement of ventricular torsion by two-dimensional ultrasound speckle tracking imaging. J Am Coll Cardiol 45(12):2034–2041
27. Sorop O, van den Heuvel M, van Ditzhuijzen NS, de Beer VJ, Heinonen I, van Duin RWB et al (2016) Coronary microvascular dysfunction after long-term diabetes and hypercholesterolemia. Am J Physiol Heart Circ Physiol 311(6):H1339–H1351
28. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L et al (2015) Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. Eur Heart J Cardiovasc Imaging 16(3):233–270
29. Nagueh SF, Middleton KJ, Kopelen HA, Zoghbi WA, Quinones MA (1997) Doppler tissue imaging: a noninvasive technique for evaluation of left ventricular relaxation and estimation of filling pressures. J Am Coll Cardiol 30(6):1527–1533
30. Rademakers FE, Buchalter MB, Rogers WJ, Zerhouni EA, Weisfeldt ML, Weiss JL et al (1992) Dissociation between left ventricular untwisting and filling. accentuation by catecholamines. Circulation 85(4):1572–1581

6

Chapter 6

Subclinical cardiac dysfunction in obesity patients is linked to autonomic dysfunction: findings from the CARDIOBESE study

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ABSTRACT

Aims

Obesity doubles the lifetime risk of developing heart failure. Current knowledge on the role of obesity in causing cardiac dysfunction is insufficient for optimal risk stratification. The aim of this study was first to estimate the prevalence of subclinical cardiac dysfunction in obesity patients and second to investigate the underlying pathophysiology.

Methods

The CARDIOBESE-study is a cross-sectional multicentre study of 100 obesity patients (BMI ≥35 kg/m^2) without known cardiovascular disease, and 50 age- and gender-matched non-obese controls (BMI ≤30 kg/m^2). Echocardiography was performed, blood samples were collected and a Holter monitor was affixed.

Results

59 obesity patients (48 (42-50) years, 70% female) showed subclinical cardiac dysfunction: 57 patients had decreased global longitudinal strain (GLS), two patients with normal GLS had either diastolic dysfunction or increased brain natriuretic peptide. Only one non-obese control had diastolic dysfunction, none had another sign of cardiac dysfunction. Multivariable logistic analysis identified male gender and SDNN-index, which is a measure of autonomic dysfunction, as independent significant risk factors for subclinical cardiac dysfunction in obesity patients.

Conclusions

There was a high prevalence (61%) of subclinical cardiac dysfunction in obesity patients without known cardiovascular disease, which appeared to be best identified by GLS. Subclinical cardiac dysfunction in obesity was linked to autonomic dysfunction and male gender, and not to the presence of traditional cardiac risk factors, increased CRP, increased BNP, increased hs troponin I, or increased left ventricular mass.

INTRODUCTION

Obesity doubles the lifetime risk of developing heart failure,[1] and is becoming a global epidemic.[2] In 2015, a total of 107.7 million children and 603.7 million adults were obese (body mass index (BMI) ≥30 kg/m^2) worldwide. Since 1980, the prevalence of obesity has doubled in more than 70 countries.[3] Both overweight and obesity are associated with an increased risk of cardiovascular disease.[4] Despite the relatively consistent finding of increased prevalence of heart failure in obesity, the reason for this association remains unclear and it seems to be a heterogeneous disorder.[5,6] Many factors have been suggested, such as insulin resistance, hypertension, and reduced high-density lipoprotein cholesterol (HDL-C).[7] However, the onset of heart failure in obesity patients cannot be fully explained by the presence of traditional cardiovascular risk factors.[8] The enormous and growing prevalence of obesity warrants efficient screening of obesity patients with the highest risk of cardiac dysfunction who may need further risk assessment, follow-up, or even treatment.[9] Current knowledge on the role of obesity in causing cardiac dysfunction is insufficient to optimally develop such strategies for obesity patients.[10] Previous studies regarding the detection of the early stages of cardiac dysfunction have shown the benefits of newer diagnostic techniques such as speckle tracking echocardiography over left ventricular (LV) ejection fraction assessment.[11,12] For example in patients with obstructive sleep apnoea syndrome without overt LV dysfunction.[13] The CARdiac Dysfunction In OBesity – Early Signs Evaluation (CARDIOBESE) study is the first study in which conventional and speckle tracking echocardiography, blood biomarkers, and Holter monitoring have been combined to study subclinical cardiac dysfunction in a cohort of obesity patients without known cardiovascular disease and non-obese controls. The aim of the study was first to identify the prevalence of subclinical cardiac dysfunction in both groups and second to investigate the underlying pathophysiology by comparing obesity patients with and without cardiac dysfunction.

METHODS

Study design

The protocol of the CARDIOBESE study has been described before.[14] In short, the CARDIOBESE-study is a multicentre cross-sectional study in which we prospectively enrolled 100 consecutive obesity patients who were referred for bariatric surgery in the Franciscus Gasthuis & Vlietland (75 patients) and Maasstad Ziekenhuis (25 patients), both in Rotterdam, the Netherlands. Patients were enrolled if they were between 35 and 65 years old, had a BMI of ≥35 kg/m^2, and gave written informed consent. Patients with a suspicion of or known

cardiovascular disease based on the patient's history (as determined by questioning the patient and reviewing available medical files) were excluded. Fifty age- and gender-matched non-obese (BMI <30 kg/m^2) controls, also without suspicion of cardiovascular disease were enrolled. Controls were recruited using advertisements in a local newspaper or were personnel from the participating hospitals or family members or friends of personnel.

Conventional and advanced echocardiography was performed, blood samples were collected and a Holter monitor was affixed for 24 hours for heart rhythm registration in both the obesity patients and the non-obese controls. This was done both to quantify the proportion of early signs of cardiac dysfunction, and to determine if the prevalence of cardiac dysfunction in obesity patients is increased compared to the non-obese controls. Also, a broad variety of parameters known to be related to obesity was collected to investigate the relation between cardiac dysfunction and obesity. The study complies with the Declaration of Helsinki and the protocol was approved by the Medical Ethics Committee Toetsingscommissie Wetenschappelijk Onderzoek Rotterdam e.o. (TWOR).[14]

Sample size calculation

The combination of parameters used to identify subclinical cardiac dysfunction has not been investigated in obesity patients before. A conservative estimate would be that cardiac dysfunction based on conventional echocardiography is present in 20% of obesity patients and 2.5% of age-matched and gender-matched non-obese controls.[15] Given these estimates, to be able to reject the null hypothesis that cardiac dysfunction rates are equal between patients and controls, at least 97 obesity patients and 49 non-obese controls have to be included in the analysis (alpha: 0.05 (two-sided), power: 0.80, 2:1 ratio of patients:controls). The use of more sensitive techniques may increase the proportion of non-obese controls with an early sign of cardiac dysfunction. Nevertheless, the proportion of obesity patients with an early sign of cardiac dysfunction is expected to increase even more, assuring that the previous sample size calculation will still suffice.

Transthoracic echocardiography

Two-dimensional grayscale harmonic images were obtained in the left lateral decubitus position using a commercially available ultrasound system (EPIQ 7, Philips, the Netherlands), equipped with a broadband (1-5MHz) X5-1 transducer. All acquisitions and measurements were performed according to the current guidelines.[16,17]

Speckle tracking echocardiography is a new echocardiographic imaging modality that is able to relatively angle-independently quantify myocardial wall motion. Gray-scale echocardiographic images consist of a speckled pattern. This pattern is not the actual image of the scatterers in the tissue itself, but the interference pattern generated by the reflected ultrasound. Each region of the myocardium has its own unique speckle pattern that remains stable enough to allow spatial and temporal image processing with selection and recognition of speckles on the ultrasound image by dedicated software packages. The geometric position of the speckles changes from frame to frame with the surrounding tissue motion. Therefore, the geometric shift of each speckle represents local tissue motion and by tracking these speckles, myocardial deformation parameters, such as strain, can be calculated.18 To optimize speckle tracking echocardiography, apical images were obtained at a frame rate of 60 to 80 frames/s. Three consecutive cardiac cycles were acquired from all apical views (4-chamber, 2-chamber, and 3-chamber). Subsequently, these cycles were transferred to a QLAB workstation (version 10.2, Philips, the Netherlands) for off-line speckle tracking analysis. Off-line analyses were performed by 2 independent observers. In end-diastole, automated border tracking was enabled, before manual adjustment using a 'point and click approach' to ensure that the endocardial and epicardial borders were included in the region of interest. When tracking was suboptimal, fine-tuning was performed manually. Peak regional longitudinal strain was measured in 17 myocardial regions and a weighted mean was used to derive global longitudinal strain (GLS) (Figure 1).[16]

Blood tests

Non-fasting blood samples were taken both for the study and as part of regular care which included; sodium, potassium, calcium, glucose, glycosylated haemoglobin (HbA1C), creatinine, estimated glomerular filtration rate (eGFR), alanine aminotransferase (ALAT), Apo-lipoprotein B100, Lipoprotein a (Lp(a)), total cholesterol, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), triglycerides, ferritin, active vitamin B12, folic acid, vitamin B1, vitamin B6, albumin, magnesium, vitamin D, haemoglobin, erythrocytes, thrombocytes, leukocytes, and thyroid-stimulating hormone (TSH). In addition to the regular care path, high sensitive troponin I (hs-cTnI), C-reactive protein (CRP) and brain natriuretic peptide (BNP) were determined. Hs-cTnI was considered positive when ≥34 ng/L for male and > 16 ng/L for female subjects.

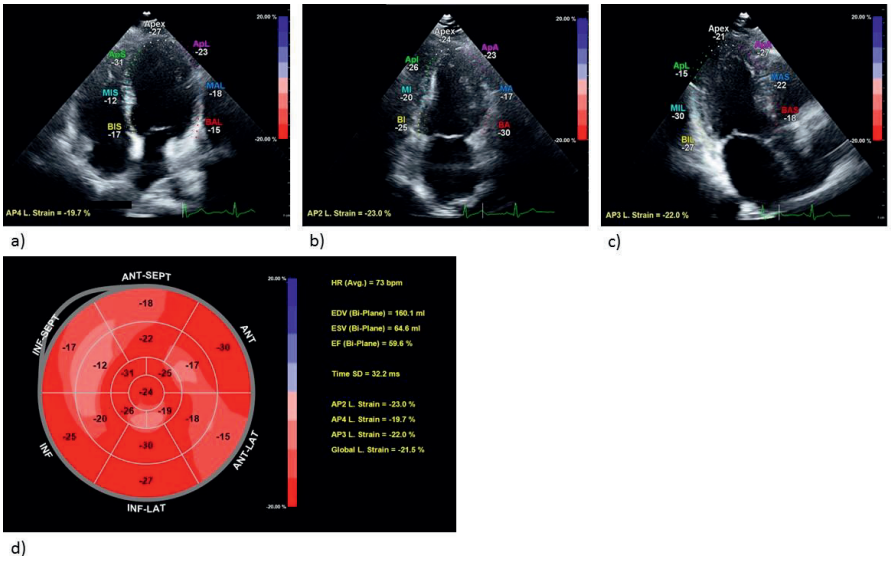

Figure 1: Measurement of global longitudinal strain (GLS) by speckle tracking analysis in an obesity patient (45 year old female, BMI 38.4 kg/m^2).

a) Apical 4-chamber view with measurement of longitudinal strain.
b) Apical 2-chamber view with measurement of longitudinal strain.
c) Apical 3-chamber view with measurement of longitudinal strain.
d) Bull's eye graph showing longitudinal strain for all myocardial segments, of which a weighted mean was used to derive GLS.

Holter monitoring

Heart rhythm was recorded for 24 consecutive hours using a portable digital recorder (GE HEER Light, USA). The digital recorder was connected using stickers that were placed on the chest. Average heart rate, minimal heart rate, maximum heart rate, total premature atrial contractions (PAC), total premature ventricular contractions (PVC), the standard deviation of all NN (often also referred to as RR) intervals (SDNN) and SDNN-index were measured. 24-hour recording of the SDNN reveals the sympathetic nervous system contribution to heart rate variability.[19] The SDNN-index estimates the variability due to the factors affecting heart rate variability (HRV) within a 5 minute period. It is calculated by first dividing the 24 hours record into 288 5-minute-segments and then calculating the standard deviation of all NN intervals contained within each segment.[20]

Cardiac dysfunction

Using echocardiography, Holter monitoring and blood tests, cardiac dysfunction was in the current study defined as either reduced LV ejection fraction (<52%),16 decreased GLS (<95th

percentile of the non-obese controls, see Statistical analysis), diastolic dysfunction,[17] sustained supraventricular or (non)sustained ventricular arrhythmia or an increased BNP (>30 pmol/L) or hs-cTnI (≥34 ng/L for male and > 16 ng/L for female subjects).

Statistical analysis

Normally distributed data are presented as means and standard deviation, skewed data as medians and interquartile range, and categorical variables as percentages and frequencies. The normality of the data was checked by the Shapiro–Wilk test. Differences in both the clinical characteristics and parameters of cardiac function between obesity patients and the non-obese controls were estimated by using generalized linear mixed models with obesity as the independent variable, and parameters entered consecutively as the dependent variable, the matched pairs were used as random intercepts. Missing variables were omitted. Differences in both clinical characteristics and parameters of cardiac function in obesity patients were tested by univariable logistic regression with cardiac dysfunction as the dependent variable. The Benjamini–Hochberg procedure, with a 5% false discovery rate, was used to correct for the multiple testing.[21]

Patient characteristics statistically significant different between obesity patients with and without cardiac dysfunction in the univariable analyses were added to multivariable logistic regression analysis (method: backward stepwise analysis). Predicted probabilities of cardiac dysfunction in obesity patients obtained from the model were used to construct a receiver–operating characteristic (ROC) curve and the area under the ROC curve was calculated as an overall measure of discriminative ability. Sensitivity, specificity, positive predictive value, and negative predictive value and their 95% confidence intervals were calculated. A two-tailed p-value of <0.05 was considered statistically significant. Statistical analyses were performed with SPSS version 25.0 and R version 3.6.0.

RESULTS

Clinical characteristics of obesity patients and non-obese controls

Table 1 and Figure 2a show the characteristics of the obesity patients (n=100) and the non-obese controls (n=50). Obesity patients had significantly increased weight, BMI, systolic blood pressure, waist circumference, and heart rate. Obesity patients also had significantly more frequent comorbidities such as diabetes mellitus and hypertension and more often used medication (ACE-inhibitors/angiotensin II receptor blockers, diuretics, and oral anti-diabetics). Blood tests showed that obesity patients had significantly increased CRP, leukocytes, glucose,

HbA1C, Apo-lipoprotein B100, triglycerides, and active vitamin B12. HDL-C, albumin and vitamin D were decreased in obesity patients. Echocardiography showed an increased LV mass in obesity patients, but when corrected for the body surface area (LV mass-index), there was no significant difference between groups. Holter monitoring showed a significantly increased average and minimal heart rate in obesity patients. Obesity patients also had a significantly decreased SDNN and SDNN-index.

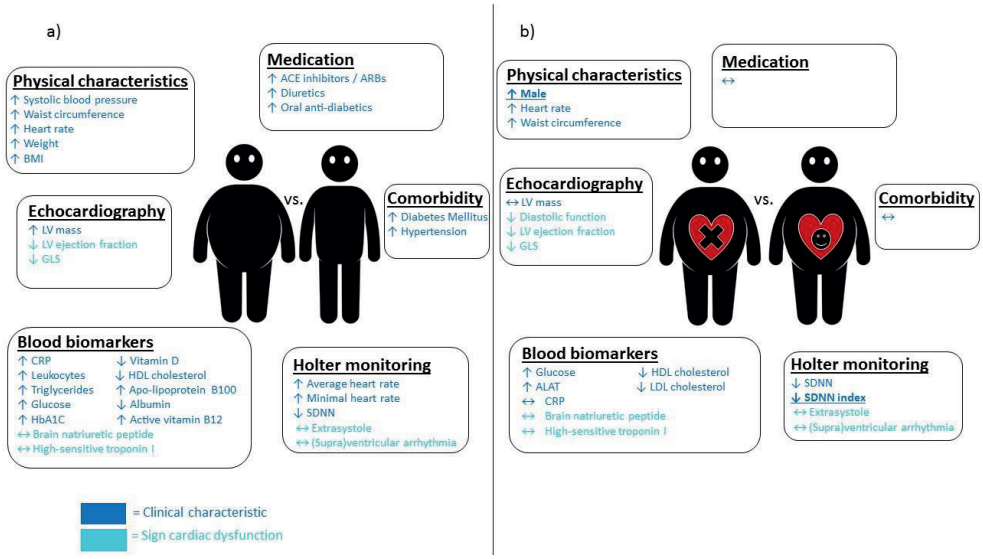

Figure 2: Difference in clinical characteristics and cardiac dysfunction parameters in
a) obesity patients vs. non-obese controls
b) obesity patients with vs. obesity patients without cardiac dysfunction
Arrows indicate whether parameters were increased or decreased in obesity patients (Figure a) or in obesity patients with cardiac dysfunction (Figure b). Bold and underlined parameters are identified as significant risk factors for cardiac dysfunction in obesity patients by multivariate analysis.

ACE= angiotensin-converting enzyme, **ALAT**= alanine transaminase, **ARBs**= angiotensin II receptor blockers, **BMI**= body mass index, **CRP**= C-reactive protein, **e'**= early diastolic mitral annular velocity, **E-wave=** early diastolic transmitralflow velocity, **GLS**= global longitudinal strain, **HbA1C**= glycated hemoglobin, **HDL**= high-density lipoprotein cholesterol, **LDL=** low-density lipoprotein cholesterol, **LV**= left ventricular, **OSAS**= obstructive sleep apnea syndrome, **SDNN**= standard deviation of NN intervals.

Parameters of cardiac function in obesity patients and non-obese controls

GLS was available in 49 non-obese controls and 94 obesity patients (unavailable in the other subjects due to insufficient echocardiographic image quality). Obesity patients had a significantly decreased GLS. Using a cut-off value of 16.9% (95th percentile of the non-obese controls), 57 (61%) obesity patients showed decreased GLS compared to none of the controls ($p<0.001$). The LV ejection fraction (57±7 vs. 65±5 %, $p<0.001$) was decreased as well, although only 24 (25% of 95 patients with available LV ejection fraction) of the obesity patients had an LV ejection fraction <52% (all with GLS <16.9%). Also, obesity patients tended to have diastolic dysfunction more frequently (11% vs. 2%, $p=0.09$). The septal e' velocity and lateral e' velocity were decreased. Levels of BNP and hs-cTnI were comparable. One obesity patient had an episode of asymptomatic atrial flutter during 5 hours recorded during Holter monitoring. In total, 60 obesity patients showed at least 1 subclinical sign of cardiac dysfunction: 57 had a decreased GLS, 1 had diastolic dysfunction without an available GLS, 1 had a normal GLS (-17.3%) but an increased BNP (49 pmol/L, normal value <30 pmol/L), and 1 had both a positive hs-cTnI and a paroxysmal atrial flutter (GLS -18.6% in this patient). The latter patient was diagnosed with acromegaly after inclusion. We, therefore, decided to exclude this patient from the following sub-analysis focusing specifically on obesity patients with cardiac dysfunction.

Table 1: Clinical characteristics of the study population and parameters of cardiac function. Differences between obesity patients and non-obese controls.

	Non-obese (n=50)	Obese (n=100)	p-value
Clinical characteristics			
General characteristics			
Age (years)	50 (40-59)	48 (42-50)	**0.02***
Female (%)	35 (70%)	70 (70%)	>0.99
Physical examination			
Length (m)	1.74 ± 0.1	1.71 ± 0.1	0.08
Weight (kg)	76 (64-82)	123 (115-135)	**<0.001***
BMI (kg/m^2)	25 (22-28)	42 (40-46)	**<0.001***
Systolic BP (mmHg)	127 (118-136)	140 (127-157)	**<0.001***
Diastolic BP (mmHg)	78 (71-82)	79 (72-88)	0.11
Waist circumference (cm)	79 (74-89)	131 (125-140)	**<0.001***
Heart rate (bpm)	64 ± 9	80 ± 13	**<0.001***
Comorbidity			
Diabetes Mellitus	0	22 (22%)	**0.007***
Hypertension	4 (8%)	32 (32%)	**0.003***
Hypercholesterolemia	5 (10%)	18 (18%)	0.21
Current smoking	7 (14%)	17 (17%)	0.63
COPD	1 (2%)	5 (5%)	0.39
OSAS	1 (2%)	12 (12%)	0.07

Medication			
Beta-blockers	0	8 (8%)	**0.03**
ACE inhibitors / ARBs	2 (4%)	24 (24%)	**0.008***
Calcium channel blockers	0	12 (12%)	**0.04**
Statins	3 (6%)	20 (20%)	**0.03**
Diuretics	1 (2%)	18 (18%)	**0.02***
Insulin	0	7 (7%)	**0.04**
Oral anti-diabetics	0	15 (15%)	**0.02***
Blood tests			
CRP (mg/L)	1 (0-2)	6 (4-10)	**<0.001***
Glucose (mmol/L)	5.1 (4.7-5.5)	5.4 (4.8-6.2)	**0.006***
HbA1c (mmol/mol)	35 (33-37)	39 (35-47)	**<0.001***
Creatinine(umol/L)	69 (65-75)	72 (65-78)	0.35
eGFR (ml/min/1.73m^2)	74 (69-79)	90 (79-90)	**<0.001***
ALAT (U/L)	22 (15-32)	28 (20-37)	0.64
Apo-lipoprotein B100 (g/L)	0.90 (0.75-1.07)	1.05 (0.91-1.30)	**0.007***
Lipoprotein (a) (mg/L)	172 (52-367)	167 (71-522)	0.80
Total cholesterol (mmol/L)	5.2 ± 1	5.3 ± 1	0.55
LDL cholesterol (mmol/L)	3.0 ± 1.0	3.2 ± 0.9	0.24
HDL cholesterol (mmol/L)	1.4 (0.94-1.80)	1.1 (1.0-1.4)	**<0.001***
Triglycerides (mmol/L)	1.25 (0.9-1.8)	1.74 (1.3-2.6)	**0.01***
Ferritin (ug/L)	79 (34-149)	90 (49-176)	0.82
Active vitamin B12 (pmol/L)	96 (71-127)	101 (70-130)	**0.002***
Folic acid (nmol/L)	17 (12-22)	12 (8-16)	**0.002***
Vitamin B1 (nmol/L)	130 (98-144)	140 (118-157)	**0.03**
Vitamin B6 (nmol/L)	84 (74-114)	69 (52-83)	0.43
Albumin (g/L)	43 ± 2	41 ± 4	**<0.001***
Magnesium (mmol/L)	0.85 ± 0.05	0.81 ± 0.07	**<0.001***
Vitamin D (nmol/L)	60 (42-75)	39 (27-61)	**<0.001***
Haemoglobin (mmol/L)	8.6 (8.3-9.1)	8.8 (8.2-9.2)	0.21
Erythrocytes (x10^12/L)	4.6 ± 0.4	4.9 ± 0.4	**<0.001***
Thrombocytes (x10^9/L)	231 ± 48	261 ± 70	**0.009***
Leukocytes (x10^9/L)	5.9 (5.0-7.4)	8.5 (6.9-9.6)	**<0.001***
TSH (mU/L)	1.60 (1.1-1.9)	1.63 (1.2-2.4)	**0.03**
Echocardiography parameters			
LVM (g)	148 (117-175)	194 (149-231)	**<0.001***
LVM-index (g/m^2)	79 (62-88)	76 (64-92)	0.16
Holter monitoring			
Average heart rate (bpm)	73 ± 10	83 ± 10	**<0.001***
Minimal heart rate (bpm)	48 (41-50)	52 (47-56)	**<0.001***
Maximum heart rate (bpm)	138 (125-155)	136 (126-150)	0.62
SDNN (ms)	160 (130-194)	101 (71-141)	**<0.001***
SDNN-index (ms)	63 (49-79)	47 (38-58)	**<0.001***
Parameters of cardiac function			
Echocardiographic Parameters			
Mitral inflow E-wave (cm/s)	73 ± 13	69 ± 14	0.06
Mitral inflow A-wave (cm/s)	64 ± 14	70 ± 14	**0.003***
E/A-ratio	1.20 (0.97-1.4)	0.98 (0.87-1.1)	**<0.001***

Septal e' velocity (cm/s)	9 (7-10)	8 (7-9)	**0.03**
Lateral e' velocity (cm/s)	13 (10-15)	10 (8-13)	**<0.001***
E/e'-ratio	8.0 (7.3-10)	8.7 (7.2-10)	0.25
Deceleration time (s)	0.18 (0.16-0.20)	0.19 (0.17-0.22)	0.25
LA volume index (ml/m^2)	26 ± 6	26 ± 8	0.88
TR velocity (cm/s)	106 (89-199)	99 (90-132)	0.16
Diastolic dysfunction (%)	1 (2%)	11 (11%)	0.09
LV ejection fraction (%)	65 ± 5	57 ± 7	**<0.001***
GLS (%)	–20 (–21 - –19)	–16 (–18 - –14)	**<0.001***
Blood tests			
BNP (pmol/L)	6 (3-9)	5 (3-8)	0.59
hs Troponin I positive (%)	0	1 (1%)	0.37
Holter monitoring			
Total PAC per 24 hours (n)	9 (3-23)	10 (2-34)	0.11
Total PVC per 24 hours (n)	4 (1-17)	3 (0-22)	0.69
Supraventricular arrhythmia (%)	0	1 (1%)	0.37
Ventricular arrhythmia (%)	1 (2%)	0	0.16

Values represent mean ± SD, median (Q1-Q3) or n (%)
p-values displayed were analyzed by using generalized linear mixed models.
* significant after Benjamini–Hochberg correction

Global longitudinal strain was available in 49 non-obese controls and in 94 obesity patients. Left ventricular ejection fraction was available in 49 non-obese controls and in 95 obesity patients.

BMI= body mass index, **BP**= blood pressure, **COPD=** chronic obstructive pulmonary disease, **OSAS**= obstructive sleep apnea syndrome, **ACE=** angiotensin-converting enzyme, **ARBs**= angiotensin II receptor blockers, **CRP**= C-reactive protein, **HbA1c**= glycated haemoglobin, **eGFR**= estimated glomerular filtration rate, **ALAT**= alanine transaminase, **LDL**= low-density lipoprotein, **HDL**= high-density lipoprotein, **TSH**= thyroid stimulating hormone, **LVM**= left ventricular mass, **LVM-index**= left ventricular mass-index, **SDNN**= standard deviation of NN intervals, **SDNN-index=** mean of the standard deviations of all the NN intervals for each 5 min segment of a 24 h heart rate variability recording, **E-wave**= early diastolic transmitralflow velocity, **A-wave**= late diastolic transmitralflow velocity, **e'**= early diastolic mitral annular velocity, **LA-volume index**= left atrial volume index, **TR velocity**= tricuspid regurgitation, **LV**= left ventricular, **GLS**= global longitudinal strain, **BNP**= brain natriuretic peptide, **PAC**= premature atrial contraction, **PVC**= premature ventricular contraction

Table 2: Clinical characteristics and parameters of cardiac function in obesity patients with and without cardiac dysfunction.

	Obese with normal cardiac function (n=40)	Obese with cardiac dysfunction (n=59)	p-value
Clinical characteristics			
General characteristics			
Age (years)	47 (42-52)	49 (42-56)	0.53
Female (%)	35 (88%)	35 (59%)	**0.004***
Physical examination			
Length (m)	1.69 ± 0.1	1.73 ± 0.1	**0.045**
Weight (kg)	123 (115-132)	124 (114-138)	0.28
BMI (kg/m^2)	43 (40-46)	42 (40-45)	0.56
Systolic blood pressure (mmHg)	139 ± 21	144 ± 20	0.08
Diastolic blood pressure (mmHg)	75 (70-84)	80 (73-89)	0.06
Waist circumference (cm)	128 (122-134)	137 (127-141)	**0.048**

Heart rate (bpm)	76 ± 11	83 ± 14	**0.019***
Comorbidity			
Diabetes Mellitus	8 (20%)	13 (22%)	0.81
Hypertension	11 (28%)	20 (34%)	0.27
Hypercholesterolemia	8 (20%)	10 (17%)	0.89
Current smoking	7 (18%)	9 (15%)	0.77
COPD	3 (8%)	2 (3%)	0.37
OSAS	3 (8%)	8 (14%)	0.35
Medication			
Beta-blockers	3 (8%)	5 (9%)	0.36
ACE inhibitors / ARBs	10 (27%)	13 (23%)	0.53
Calcium channel blockers	3 (8%)	7 (12%)	0.13
Statins	5 (13%)	14 (25%)	0.12
Diuretics	6 (16%)	11 (19%)	0.13
Insulin	2 (5%)	5 (9%)	0.51
Oral anti-diabetics	5 (13%)	9 (16%)	0.70
Blood tests			
CRP (mg/L)	7 (3-10)	6 (4-11)	0.70
Glucose (mmol/L)	5.0 (4.6-5.6)	5.6 (5.1-6.7)	**0.01***
HbA1c (mmol/mol)	37 (35-43)	40 (36-51)	0.05
Creatinine(umol/L)	68 (64-78)	73 (66-77)	0.32
eGFR (ml/min/1.73m^2)	87 (79-90)	90 (80-90)	0.43
ALAT (U/L)	23 (16-33)	31 (22-45)	**0.003***
Apo-lipoprotein B100 (g/L)	1.12 ± 0.3	1.04 ± 0.3	0.67
Lipoprotein (a) (mg/L)	190 (65-599)	149 (71-386)	0.10
Total cholesterol (mmol/L)	5.5 ± 0.8	5.1 ± 1.1	**0.025**
LDL cholesterol (mmol/L)	3.5 ± 0.8	3.0 ± 0.9	**0.003***
HDL cholesterol (mmol/L)	1.3 (1.0-1.5)	1.1 (1.0-1.3)	**0.009***
Triglycerides (mmol/L)	1.4 (1.0-2.0)	2.1 (1.5-3.0)	0.09
Ferritin (ug/L)	87 (49-136)	92 (58-189)	0.14
Active vitamin B12 (pmol/L)	93 (61-128)	108 (71-197)	0.22
Folic acid (nmol/L)	11 (8-16)	12 (9-16)	0.45
Vitamin B1 (nmol/L)	13 ± 29	145 ± 22	0.08
Vitamin B6 (nmol/L)	65 (54-91)	70 (52-80)	0.39
Albumin (g/L)	42 (40-44)	42 (39-44)	0.83
Magnesium (mmol/L)	0.81 ± 0.06	0.81 ± 0.07	0.45
Vitamin D (nmol/L)	39 (28-60)	39 (27-61)	0.95
Hemoglobin (mmol/L)	8.6 (8.0-9.0)	8.9 (8.4-9.3)	0.11
Erythrocytes (x10^12/L)	4.8 ± 0.4	5.0 ± 0.3	**0.03**
Thrombocytes (x10^9/L)	270 ± 54	255 ± 79	0.22
Leukocytes (x10^9/L)	8.4 (6.8-9.4)	8.5 (7.0-10.2)	0.48
TSH (mU/L)	1.5 (1.2-2.5)	1.7 (1.2-2.4)	0.94
Echocardiographic Parameters			
LVM (g)	169 (140-215)	203 (156-241)	0.10
LVM-index (g/m^2)	72 (59-88)	81 (67-94)	0.16
Holter monitoring			
Average heart rate (bpm)	81 ± 9	83 ± 10	0.35
Minimal heart rate (bpm)	50 (46-55)	53 (47-56)	0.66

Maximum heart rate (bpm)	142 (129-152)	132 (125-146)	0.06
SDNN (ms)	121 ± 48	99 ± 42	**0.026**
SDNN-index (ms)	54 ± 16	45 ± 14	**0.015***
Parameters of cardiac function			
Echocardiographic Parameters			
Mitral inflow E-wave (cm/s)	75 ± 15	65 ± 12	**0.007***
Mitral inflow A-wave (cm/s)	70 ± 11	70 ± 15	0.68
E/A-ratio	1.1 (0.92-1.20)	0.96 (0.80-1.10)	**0.029**
Septal e' velocity (cm/s)	8 ± 2	8 ± 2	0.22
Lateral e' velocity (cm/s)	12 ± 3	10 ± 3	**0.002***
E/e'-ratio	9.1 (7.5-10.3)	8.4 (6.9-9.7)	0.27
Deceleration time (s)	0.19 ± 0.04	0.19 ± 0.04	0.93
LA volume index (ml/m^2)	25 ± 7	26 ± 8	0.52
TR velocity (cm/s)	113 (91-140)	93 (86-125)	0.55
Diastolic dysfunction (%)	0	10 (17%)	**0.001***
LV ejection fraction (%)	62 ± 6	54 ± 7	**<0.001***
GLS	–19.2 ± 1.3	–14.4 ± 2.1	**<0.001***
Blood tests			
BNP (pmol/L)	6 (4-11)	4 (3-6)	0.29
hs Troponin I positive (%)	0	0	
Holter monitoring			
Total PAC per 24 hours	12 (3-38)	8 (2-27)	0.42
Total PVC per 24 hours	2 (0-16)	3 (0-28)	0.98
Supraventricular arrhythmia (%)	0	0	
Ventricular arrhythmia (%)	0	0	

Values represent mean ± SD, median (Q1-Q3) or n (%).
p-values displayed were analyzed by using univariable logistic regression.
* significant after Benjamini–Hochberg correction

BMI= body mass index, **BNP**= brain natriuretic peptide, **BP**= blood pressure, **COPD=** chronic obstructive pulmonary disease, **OSAS**= obstructive sleep apnea syndrome, **ACE=** angiotensin-converting enzyme, **ARBs**= angiotensin II receptor blockers, **CRP**= C-reactive protein, **HbA1c**= glycated hemoglobin, **eGFR**= estimated glomerular filtration rate, **ALAT**= alanine transaminase, **LDL**= low-density lipoprotein, **HDL**= high-density lipoprotein, **TSH**= thyroid stimulating hormone, **LVM**= left ventricular mass, **LVM-index**= left ventricular mass-index, **SDNN**= standard deviation of NN intervals, **SDNN-index=** mean of the standard deviations of all the NN intervals for each 5 min segment of a 24 h heart rate variability recording, **E-wave**= early diastolic transmitralflow velocity, **A-wave**= late diastolic transmitralflow velocity, **e'**= early diastolic mitral annular velocity, **LA-volume index**= left atrial volume index, **TR velocity**= tricuspid regurgitation, **LV**= left ventricular, **GLS**= global longitudinal strain, **BNP**= brain natriuretic peptide, **PAC**= premature atrial contractions, **PVC**= premature ventricular contractions

Characteristics of obesity patients with subclinical signs of cardiac dysfunction

Table 2 and Figure 2b display the characteristics of obesity patients with (n=59) and without (n=40) cardiac dysfunction. Obesity patients with cardiac dysfunction were more often male and had an increased heart rate. There were no significant differences regarding the prevalence of comorbidities and medication use.

Blood tests showed increased glucose and ALAT in obesity patients with cardiac dysfunction. Also, these patients had decreased levels of LDL-C and HDL-C. hs-cTnI and CRP were not significantly different.

Obesity patients with cardiac dysfunction tended to have an increased LV mass and LV mass-index. They also had more often diastolic dysfunction. Holter monitoring showed a decreased SDNN-index in obesity patients with cardiac dysfunction.

Odds ratios and predictive model of cardiac dysfunction in obesity patients

Univariable logistic regression analysis showed that cardiac dysfunction was associated with male gender, SDNN-index, SDNN, length, waist circumference, heart rate, glucose, ALAT, total cholesterol, LDL-C, HDL-C, and erythrocytes. The multivariable logistic analysis identified male gender and SDNN-index as independent significant risk factors for subclinical cardiac dysfunction in obesity patients (Table 3). The ROC-curve is shown in Figure 3. The area under the ROC-curve was: 0.81 (95% CI; 0.71-0.91, $p<0.001$). Sensitivity was 74% (95% CI; 57-86%), specificity 62% (95% CI; 45-77%), positive predictive value 67% (95% CI; 50-80%), and negative predictive value 70% (95% CI; 51-84%).

Table 3: Univariable and multivariable logistic regression analysis in obesity patients, with presence of cardiac dysfunction as the dependent variable.

Variable	Univariate p-value	Multivariable p-value
Male gender	0.004	0.001
SDNN-index	0.015	0.015
SDNN	0.026	
Waist circumference	0.048	
Heart rate	0.019	
Glucose	0.01	
ALAT	0.003	
Total cholesterol	0.025	
LDL cholesterol	0.003	
HDL cholesterol	0.009	
Erythrocytes	0.03	
Length	0.045	

Variables displayed were statistically significant different between obesity patients with and without cardiac dysfunction. Multivariable logistic regression analysis; method: backward stepwise analysis.

ALAT= alanine transaminase, **SDNN=** standard deviation of NN intervals, **SDNN-index=** mean of the standard deviations of all the NN intervals for each 5 min segment of a 24 h HRV recording

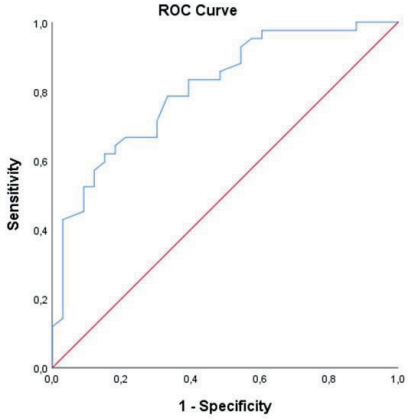

Figure 3: ROC-curve for the prediction model for cardiac dysfunction in obesity patients. Model; combination of SDNN, SDNN-index, gender, ALAT, glucose, and triglycerides. Area under the curve = 0.72 (95%CI; 0.61-0.82, p<0.001).

DISCUSSION

The main findings of the current study are 1) that there is a high prevalence (61%) of subclinical cardiac dysfunction in obesity patients (BMI ≥35 kg/m^2) without suspicion of or known cardiovascular disease, 2) in the vast majority of patients with subclinical cardiac dysfunction this was identified by abnormal GLS, clearly more than by other echocardiographic parameters, arrhythmias, increased BNP or hs-TnI, and 3) decreased heart rate variability as measured by SDNN-index and male gender are predictors of subclinical cardiac dysfunction in obesity patients.

The association between abnormalities in cardiac structure and function is known in obesity patients.[1] Because of the ongoing obesity epidemic, efficient screening for (subclinical) cardiac dysfunction in these patients is needed.[22] The current knowledge of the early signs of cardiac dysfunction in obesity patients is not optimal to develop such screening tools.

In our study, we were unable to identify subclinical cardiac dysfunction in obesity patients by Holter monitoring or assessment of hs-cTnI and BNP. The frequency of extrasystole was not increased and although obesity is a known risk factor for atrial fibrillation,[23] none of the obesity patients showed atrial fibrillation during the 24 hour Holter monitoring. There was one patient

with an atrial flutter and a positive hs-cTnI, but he was diagnosed with acromegaly after inclusion and therefore does not represent the typical obesity patients without known cardiac disease.

However, we were able to identify a high prevalence of subclinical cardiac dysfunction based on a decreased GLS by advanced echocardiography in 57 (61% of the 94 obesity patients with available GLS) of the obesity patients. GLS performed much better as compared to conventional echocardiography parameters such as LV ejection fraction (decreased in 29% of the obesity patients) and diastolic function (abnormal in only 11% of the obesity patients). Currently, GLS assessment by speckle tracking echocardiography is broadly available as echo-machines from all well-known vendors are generally equipped with speckle tracking software. Strain can be assessed in three directions (longitudinal, circumferential, and radial), with longitudinal strain known to be the most reproducible. It is therefore recommended to use GLS as a parameter of LV systolic function.[16] Recently, we demonstrated that the assessment of GLS is feasible and reproducible in obesity patients as well.[24] As said, in the current study we identified GLS as the best parameter to diagnose cardiac dysfunction in obesity patients. Therefore, when looking for subclinical cardiac abnormalities in these patients, GLS assessment by speckle tracking echocardiography seems to be the best diagnostic technique.

So far, the pathophysiology of obesity leading to cardiac dysfunction is incompletely understood and it was hypothesized that it is most likely multifactorial.[3,25] While previous studies examined the association between heart failure and obesity,[1,26] the CARDIOBESE study is the first to investigate the relation between subclinical cardiac dysfunction and obesity using a combination of techniques to simultaneously investigate different aspects that may all play a role. The transthoracic echocardiogram may identify direct local effects of obesity such as increased LV mass, systemic influences caused by secretion of adipokines by the fat tissue may be revealed by the blood tests, and the Holter monitor may identify autonomic dysfunction by assessment of HRV.

In our study, there were no differences between obesity patients with and without subclinical cardiac dysfunction regarding the presence of traditional cardiac risk factors, such as diabetes mellitus, hypertension, and hypercholesterolemia. These results are consistent with previous studies, which showed that the onset of heart failure in obesity cannot be fully explained by these risk factors.[27] Also, obesity patients are known to have a state of chronic low-grade inflammation.[28] Although increased circulating levels of CRP were observed in obesity patients compared to non-obese controls, there was no difference between obesity patients with and without subclinical cardiac dysfunction. Therefore, at least as far as CRP reflects systemic

inflammation, this was not likely to be an explanation of subclinical cardiac dysfunction in our patients. Increased cardiac filling pressures or cardiomyocyte damage have been suggested to play a role,[29] however BNP and hs-cTnI were comparable between obesity patients and non-obese controls and between obesity patients with and without cardiac dysfunction in our study. Finally, the LV mass and LV-mass index were comparable between obesity patients with and without subclinical cardiac dysfunction. Therefore, the local effect of increased LV mass does not seem to play a major role in obesity leading to subclinical cardiac dysfunction.

Nevertheless, the SDNN-index as a measure of HRV and thereby of autonomic dysfunction, was strikingly different between obesity patients with and without subclinical cardiac dysfunction, and was identified as an independent risk factor for cardiac dysfunction by multivariable analysis. The SDNN-index estimates the variability due to the factors affecting HRV within a 5 minute period.[30] Even a slight variation in the autonomic regulation of the heart changes the heart rate and rhythm.[31] The analysis of HRV thereby provides a non-invasive tool to characterize autonomic function. Depressed HRV has been confirmed to be a prognostic marker and is correlated with morbidity and mortality.[32-34] Furthermore, sympathetic nervous system dysfunction is crucial in the development of heart failure.[35] Previous studies already described a decreased HRV in obesity patients,[31,36] linking this to inflammatory processes.[37,38] However, our study not only confirmed the presence of a decreased HRV in obesity patients, it is also the first to show that decreased HRV may play a crucial role in the development of cardiac dysfunction in these patients. Therefore, the analysis of HRV may be a useful and simple non-invasive method to further investigate the effect of obesity on cardiac function.

The multivariable analysis not only identified SDNN-index but also male gender as a significant risk factor for cardiac dysfunction in obesity patients. Previous studies already described an association between obesity and more severe heart failure symptoms in male patients compared to female patients.[39] Also, overweight and obese males have higher adjusted mortality than normal-weight males, whereas a BMI in the overweight range was associated with a survival benefit in females.[40] However, the reason for these findings is not clear. It cannot be excluded that there are unidentified confounders related to gender that may explain the suggested relationship between male gender and cardiac dysfunction in obesity in our study. Further studies are needed to clarify this issue.

Limitations

GLS was missing in 7 obesity patients because of insufficient image quality. This may have affected the identified prevalence of cardiac dysfunction. In addition, cardiac magnetic

resonance could be of added value, when investigating myocardial characteristics. However, this was not available in the CARDIOBESE study. Also, the study contained a relatively large number of women (70%), which may have influenced the observed relationship between gender and subclinical cardiac dysfunction.

When studying HRV, one can select several parameters.[41] In our study, we only used SDNN and SDNN-index as markers of HRV to limit the total number of parameters studied. They were chosen because no currently recognized HRV measure provides better prognostic information than the time domain HRV measures assessing overall HRV.[41] In parallel, we only used CRP and leukocytes as inflammatory markers, also to limit the total number of parameters studied and because of limited testing that can be done in our clinical laboratory. To further investigate the role of inflammation, further studies are needed. Also, blood samples were obtained in the non-fasting state, which could have influenced our results. Finally, although obesity is usually defined as a BMI $\geq$30 kg/m^2 all patients in our study had a BMI $\geq$35kg/m^2 because they were included at the outpatient clinic for screening for bariatric surgery (BMI $\geq$35kg/m^2 is a condition to qualify for bariatric surgery). Therefore, the conclusions may only be applied to morbidly obese patients and not to obesity patients in general.

CONCLUSIONS

There was a high prevalence (61%) of subclinical cardiac dysfunction in obesity patients without known cardiovascular disease, which appeared to be best identified by GLS. Subclinical cardiac dysfunction in obesity was linked to autonomic dysfunction and male gender, and not to the presence of traditional cardiac risk factors, increased CRP, increased BNP, increased hs troponin I, or increased LV mass.

REFERENCES

1. Bui AL, Horwich TB, Fonarow GC. Epidemiology and risk profile of heart failure. Nat Rev Cardiol 2011;8:30-41.
2. Collaboration NCDRF. Trends in adult body-mass index in 200 countries from 1975 to 2014: a pooled analysis of 1698 population-based measurement studies with 19.2 million participants. Lancet 2016;387:1377-96.
3. Afshin A, Reitsma MB, Murray CJL. Health Effects of Overweight and Obesity in 195 Countries. N Engl J Med 2017;377:1496-7.
4. Global BMIMC, Di Angelantonio E, Bhupathiraju Sh N, et al. Body-mass index and all-cause mortality: individual-participant-data meta-analysis of 239 prospective studies in four continents. Lancet 2016;388:776-86.
5. Packer M. The conundrum of patients with obesity, exercise intolerance, elevated ventricular filling pressures and a measured ejection fraction in the normal range. Eur J Heart Fail 2019;21:156-62.
6. Cescau A, Van Aelst LNL, Baudet M, Cohen Solal A, Logeart D. High body mass index is a predictor of left ventricular reverse remodelling in heart failure with reduced ejection fraction. ESC Heart Fail 2017;4:686-9.
7. Gadde KM, Martin CK, Berthoud HR, Heymsfield SB. Obesity: Pathophysiology and Management. J Am Coll Cardiol 2018;71:69-84.
8. Wang YC, Liang CS, Gopal DM, et al. Preclinical Systolic and Diastolic Dysfunctions in Metabolically Healthy and Unhealthy Obese Individuals. Circ Heart Fail 2015;8:897-904.
9. Benjamin EJ, Muntner P, Alonso A, et al. Heart Disease and Stroke Statistics-2019 Update: A Report From the American Heart Association. Circulation 2019;139:e56-e528.
10. Finer N. Weight loss for patients with obesity and heart failure. Eur Heart J 2019.
11. Ersboll M, Valeur N, Mogensen UM, et al. Prediction of all-cause mortality and heart failure admissions from global left ventricular longitudinal strain in patients with acute myocardial infarction and preserved left ventricular ejection fraction. J Am Coll Cardiol 2013;61:2365-73.
12. Dalen H, Thorstensen A, Romundstad PR, Aase SA, Stoylen A, Vatten LJ. Cardiovascular risk factors and systolic and diastolic cardiac function: a tissue Doppler and speckle tracking echocardiographic study. J Am Soc Echocardiogr 2011;24:322-32 e6.
13. Manov EI, Runev NM, Shabani RA, et al. Early Left Ventricular Function Abnormalities in Obstructive Sleep Apnea. Journal of Cardiovascular Diseases & Diagnosis 2014:1-4.
14. Snelder SM, de Groot-de Laat LE, Biter LU, et al. Cross-sectional and prospective follow-up study to detect early signs of cardiac dysfunction in obesity: protocol of the CARDIOBESE study. BMJ Open 2018;8:e025585.
15. Pascual M, Pascual DA, Soria F, et al. Effects of isolated obesity on systolic and diastolic left ventricular function. Heart 2003;89:1152-6.
16. Lang RM, Badano LP, Mor-Avi V, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. Eur Heart J Cardiovasc Imaging 2015;16:233-70.
17. Nagueh SF, Smiseth OA, Appleton CP, et al. Recommendations for the Evaluation of Left Ventricular Diastolic Function by Echocardiography: An Update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. Eur Heart J Cardiovasc Imaging 2016;17:1321-60.
18. van Dalen BM, Tzikas A, Soliman OI, et al. Assessment of subendocardial contractile function in aortic stenosis: a study using speckle tracking echocardiography. Echocardiography 2013;30:293-300.
19. Grant CC, van Rensburg DC, Strydom N, Viljoen M. Importance of tachogram length and period of recording during noninvasive investigation of the autonomic nervous system. Ann Noninvasive Electrocardiol 2011;16:131-9.
20. Shaffer F, Ginsberg JP. An Overview of Heart Rate Variability Metrics and Norms. Front Public Health 2017;5:258.
21. Benjamini Y, Hochberg Y. Controlling the false discovery rate: a practical and powerful approach to multiple testing. J R Stat Soc Ser B Methodol 1995;57:289–300.
22. Weismann D, Wiedmann S, Bala M, Frantz S, Fassnacht M. [Obesity and heart failure]. Internist (Berl) 2015;56:121-6.
23. Frost L, Hune LJ, Vestergaard P. Overweight and obesity as risk factors for atrial fibrillation or flutter: the Danish Diet, Cancer, and Health Study. Am J Med 2005;118:489-95.
24. Snelder SM, Younge JO, Dereci A, et al. Feasibility and Reproducibility of Transthoracic Echocardiography in Obese Patients. J Am Soc Echocardiogr 2019.

25. Kitzman DW, Shah SJ. The HFpEF Obesity Phenotype: The Elephant in the Room. J Am Coll Cardiol 2016;68:200-3.
26. Aune D, Sen A, Norat T, et al. Body Mass Index, Abdominal Fatness, and Heart Failure Incidence and Mortality: A Systematic Review and Dose-Response Meta-Analysis of Prospective Studies. Circulation 2016;133:639-49.
27. Ndumele CE, Matsushita K, Lazo M, et al. Obesity and Subtypes of Incident Cardiovascular Disease. J Am Heart Assoc 2016;5.
28. Hotamisligil GS. Inflammation, metaflammation and immunometabolic disorders. Nature 2017;542:177-85.
29. Peterson LR, Waggoner AD, Schechtman KB, et al. Alterations in left ventricular structure and function in young healthy obese women: assessment by echocardiography and tissue Doppler imaging. J Am Coll Cardiol 2004;43:1399-404.
30. Yadav RL, Yadav PK, Yadav LK, Agrawal K, Sah SK, Islam MN. Association between obesity and heart rate variability indices: an intuition toward cardiac autonomic alteration - a risk of CVD. Diabetes Metab Syndr Obes 2017;10:57-64.
31. Lewis MJ. Heart rate variability analysis: a tool to assess cardiac autonomic function. Comput Inform Nurs 2005;23:335-41.
32. Bauer A, Kantelhardt JW, Barthel P, et al. Deceleration capacity of heart rate as a predictor of mortality after myocardial infarction: cohort study. Lancet 2006;367:1674-81.
33. Ali A, Holm H, Molvin J, et al. Autonomic dysfunction is associated with cardiac remodelling in heart failure patients. ESC Heart Fail 2018;5:46-52.
34. Forslund L, Bjorkander I, Ericson M, et al. Prognostic implications of autonomic function assessed by analyses of catecholamines and heart rate variability in stable angina pectoris. Heart 2002;87:415-22.
35. Florea VG, Cohn JN. The autonomic nervous system and heart failure. Circ Res 2014;114:1815-26.
36. Karason K, Molgaard H, Wikstrand J, Sjostrom L. Heart rate variability in obesity and the effect of weight loss. Am J Cardiol 1999;83:1242-7.
37. Williams DP, Koenig J, Carnevali L, et al. Heart rate variability and inflammation: A meta-analysis of human studies. Brain Behav Immun 2019;80:219-26.
38. Lampert R, Bremner JD, Su S, et al. Decreased heart rate variability is associated with higher levels of inflammation in middle-aged men. Am Heart J 2008;156:759 e1-7.
39. Heo S, Moser DK, Pressler SJ, et al. Association between obesity and heart failure symptoms in male and female patients. Clin Obes 2017;7:77-85.
40. Vest AR, Wu Y, Hachamovitch R, Young JB, Cho L. The Heart Failure Overweight/Obesity Survival Paradox: The Missing Sex Link. JACC Heart Fail 2015;3:917-26.
41. Heart rate variability: standards of measurement, physiological interpretation and clinical use. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. Circulation 1996;93:1043-65.

Chapter 7

Cardiac function normalizes 1 year after bariatric surgery in half of the obesity patients with Subclinical Cardiac Dysfunction

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Introduction

Obesity has reached epidemic proportions globally and the prevalence is still increasing. Subclinical cardiac dysfunction is common in obesity patients and obesity is associated with an increased risk of heart failure.[1] Clinically significant weight loss is difficult to achieve with lifestyle interventions and the results are often temporary. In contrast, bariatric surgery is an effective and safe treatment option resulting in large long-term weight loss.[2] However, little is known about potential improvement of subclinical cardiac dysfunction after bariatric surgery. The CARdiac Dysfunction In Obesity – Early Signs Evaluation (CARDIOBESE) study is a prospective study that was designed to investigate this, using a combination of (speckle tracking) echocardiography, blood tests, and Holter monitoring to simultaneously investigate different possible expressions of subclinical cardiac dysfunction. The protocol of the CARDIOBESE study has been described before.[3] In this research letter we briefly describe the main results. Additional analyses of the data will be performed in the near future to provide further insight in the pathophysiological background of the findings.

Methods

We enrolled 100 obesity patients who were referred for bariatric surgery in this longitudinal study. Inclusion criteria were age 35-65 years and BMI ≥35 kg/m^2. Patients with a suspicion of or known cardiovascular disease were excluded. Bariatric surgery was performed by either a gastric sleeve, a gastric bypass, or a mini bypass operation. Conventional and speckle tracking echocardiography, Holter monitoring, and blood tests were performed. Patients were seen pre- and one-year post-bariatric surgery. Subclinical (in other words, not previously diagnosed) cardiac dysfunction was based on the diagnostics used in CARDIOBESE and defined as either a reduced left ventricular (LV) ejection fraction,[4] decreased GLS (<17%), diastolic dysfunction,[5] (supra)ventricular arrhythmia or an increased BNP (>30 pmol/L) or hs Troponin I (≥34 ng/L for male and ≥16 ng/L for female subjects). The study protocol was approved by the ethics committee and written informed consent was obtained from all participants. Baseline characteristics of the studied population have been described before.[6] Subclinical cardiac dysfunction was present in 59 patients, mainly uncovered by decreased GLS.[6]

Statistical analysis

Patients who completed the follow-up were included in the analysis. The normality of the data was checked by the Shapiro–Wilk test. Continuous values with normal distributions were expressed as mean ± standard deviation, with skewed distributions as median and interquartile

range and categorical values as percentages. The paired Student's t-test was used for continuous variables with normal distributions, the nonparametric Wilcoxon signed-rank test for variables with skewed distributions, and the McNemar test for categorical variables was used to compare parameters pre- and post-surgery.

Results

A total of 85 patients underwent bariatric surgery and 72 patients completed the one-year follow-up. Patients did not undergo bariatric surgery because of various reasons, but mostly because of disapproval by a psychologist or because they had withdrawn themselves from surgery. There was a significant reduction in weight and BMI one year after bariatric surgery (Table 1). Prevalence of comorbidities decreased and medication use was reduced. Blood tests showed a decrease of CRP, HbA1c, ALAT, total cholesterol, LDL-C, and triglycerides. Moreover, HDL-C, folic acid, vitamin B6, and vitamin D significantly increased. The echocardiogram revealed a decrease in LV mass and Holter monitoring a decreased heart rate one year after bariatric surgery.

Regarding changes in parameters of cardiac function after bariatric surgery (Table 1), there was a mild increase in BNP. Levels of hs troponin I were comparable. Echocardiography showed an improvement of GLS. The prevalence of diastolic dysfunction and the LV ejection fraction did not change. There were no arrhythmias and the frequency of extrasystoles did not change.

Fifty of the 59 patients with subclinical cardiac dysfunction at baseline underwent bariatric surgery and 40 completed the follow-up. Of these patients, 20 (50%) had normalized cardiac function (in other words, no remaining signs of cardiac dysfunction as defined in this study) after bariatric surgery. Of the 20 patients with persistent cardiac dysfunction, 17 (43%) still had decreased GLS, one patient had an elevated hs troponin I level, and two patients had diastolic dysfunction.

Discussion

Although in previous studies changes in cardiac morphology and function after bariatric surgery have been investigated,[7] CARDIOBESE is the first study in which the focus was specifically on subclinical cardiac dysfunction, also with an innovative approach using several diagnostic modalities to concurrently investigate different possible expressions of this.

This methodology allowed us to show for the first time that bariatric surgery not only was associated with a reduction in BMI and comorbidities, but also with a decrease in LV mass and improvement of LV function, resulting in normalized cardiac function in half of the patients with subclinical cardiac dysfunction before surgery. An impressive result, bearing in mind that in large studies in which the effect of for example ACE inhibitors on LV function were studied in high-risk patient groups, results were clearly less pronounced.[8,9] However, these studies noticeably did show improvement in hard clinical endpoints that are not available in the current study and obviously focused on other patient categories. Nevertheless, our findings emphasize the relatively marked positive effect bariatric surgery may have on cardiac function.

Conclusion

Cardiac function improves significantly in obesity patients one year after bariatric surgery, resulting in normalized cardiac function in half of the patients with subclinical cardiac dysfunction before bariatric surgery.

Table 1: Clinical characteristics and parameters of cardiac function. Differences between pre- and one-year post-bariatric surgery**.**

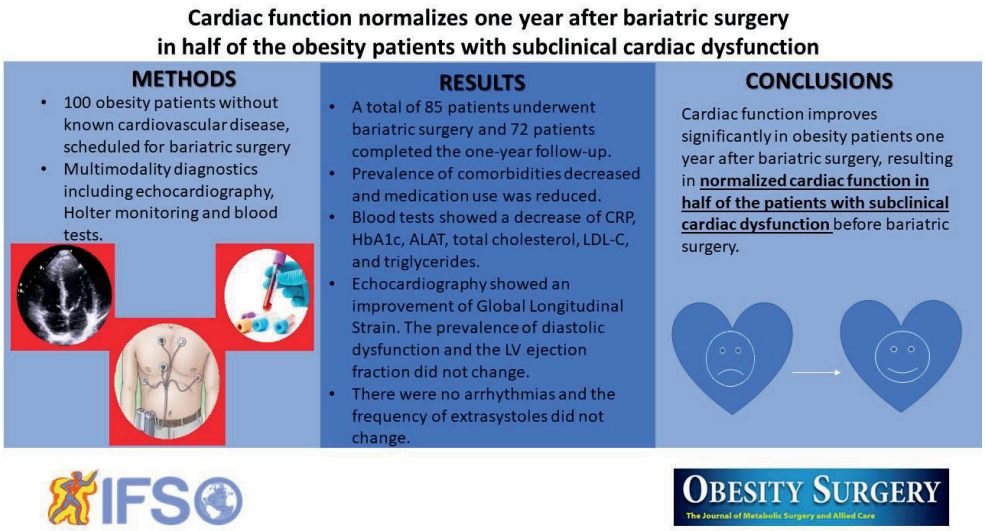
Clinical characteristics	Pre-surgery (n=72)	One-year post-surgery (n=72)	p-value
General characteristics			
Age (years)	48 [43-54]		
Female (n, %)	54 (75%)		
Physical examination			
Weight (kg)	122 [113-133]	83 [74-91]	**<0.001**
BMI (kg/m^2)	41 [39-46]	28 [25-31]	**<0.001**
Comorbidity			
Diabetes Mellitus (n,%)	16 (22%)	6 (8%)	**0.002**
Hypertension (n,%)	24 (33%)	12 (17%)	**0.035**
Medication			
ACE inhibitors / ARBs (n,%)	11 (15%)	8 (11%)	**0.012**
Statins (n,%)	16 (22%)	9 (13%)	**0.039**
Oral anti-diabetics (n,%)	10 (14%)	4 (6%)	**0.031**
Blood tests			
CRP (mg/L)	6 [3-9]	0 [0-2]	**<0.001**
HbA1c (mmol/mol)	45 ± 15	38 ± 8	**<0.001**
Creatinine(umol/L)	73 ± 10	67 ± 9	**<0.001**

ALAT (U/L)	30 [20-37]	19 [15-26]	**0.004**
Total cholesterol (mmol/L)	5.3 ± 0.9	4.6 ± 0.8	**<0.001**
LDL cholesterol (mmol/L)	3.2 ± 0.8	2.6 ± 0.7	**<0.001**
HDL cholesterol (mmol/L)	1.2 ± 0.3	1.4 ± 0.3	**<0.001**
Triglycerides (mmol/L)	2.06 ± 1.8	1.20 ± 0.8	**<0.001**
Folic acid (nmol/L)	13 [9-16]	27 [16-36]	**<0.001**
Vitamin D (nmol/L)	49 ± 25	78 ± 26	**<0.001**
Echocardiography parameters			
Left ventricular mass (g)	186 ± 72	156 ± 62	**<0.001**
Holter monitoring			
Average heart rate (bpm)	83 ± 10	73 ± 8	**<0.001**
Minimal heart rate (bpm)	53 [47-57]	46 [44-51]	**<0.001**
Maximum heart rate (bpm)	137 [128-150]	130 [120-142]	**0.005**
Parameters of cardiac function			
Blood tests			
BNP (pmol/L)	5 [3-8]	8 [6-10]	**0.029**
hs troponin I positive (n, %)	1 (1%)	5 (7%)	0.06
Echocardiography parameters			
Diastolic dysfunction (n, %)	7 (10%)	3 (4%)	0.28
LV ejection fraction (%)	58 ± 8	57 ± 7	0.25
Global longitudinal strain (%)	-15.6 ± 3.1	-18.1 ± 3.3	**0.001**
Holter monitoring			
Total PAC per 24 hours (n)	9 [2-38]	20 [8-68]	0.07
Total PVC per 24 hours (n)	3 [0-22]	5 [2-58]	0.29
Supraventricular arrhythmia (n, %)	1 (1%)	0	0.53

Values represent mean ± SD, median [Q1-Q3] or n (%)

P-values displayed were analysed by the paired Student's t-test for continuous variables with normal distributions, the nonparametric Wilcoxon signed-rank test for variables with skewed distributions, and the McNemar test for categorical variables.

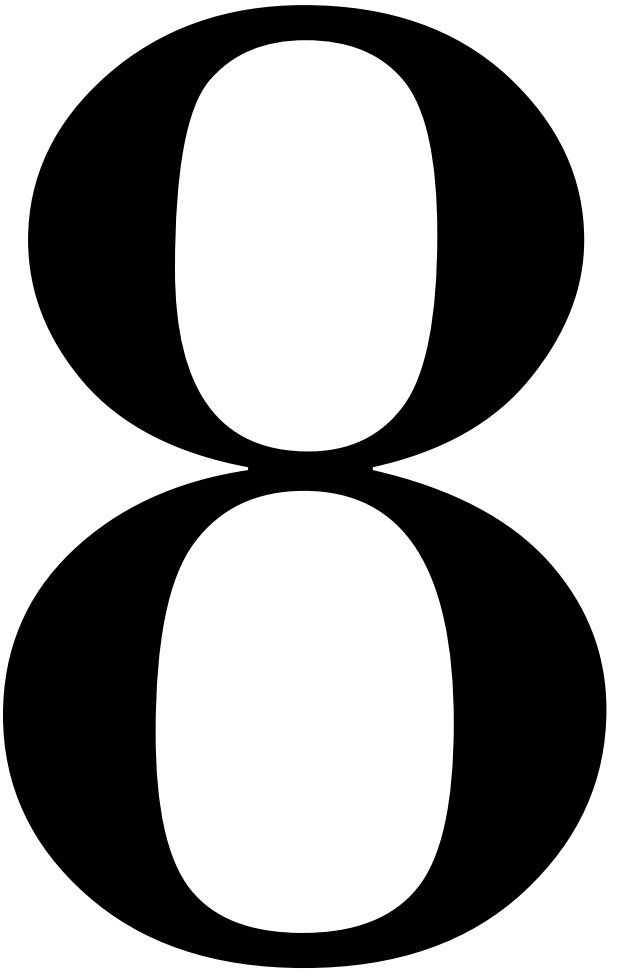
BMI= body mass index, **ACE=** angiotensin-converting enzyme, **ARBs**= angiotensin II receptor blockers, **CRP**= C-reactive protein, **HbA1c**= glycated haemoglobin, **ALAT**= alanine transaminase, **LDL**= low-density lipoprotein, **HDL**= high-density lipoprotein, **BNP**= brain natriuretic peptide, **hs troponin I**= high sensitive troponin I, **LV**= left ventricular**, PAC**= premature atrial complex, **PVC**= premature ventricular complex



Visual abstract

REFERENCES

1. M.M. Fernandes-Silva, A.M. Shah, B. Claggett, S. Cheng, H. Tanaka, O.M. Silvestre, W. Nadruz, B.A. Borlaug, S.D. Solomon, Adiposity, body composition and ventricular-arterial stiffness in the elderly: the Atherosclerosis Risk in Communities Study, Eur J Heart Fail 20(8) (2018) 1191-1201.
2. E.J. DeMaria, Bariatric surgery for morbid obesity, N Engl J Med 356(21) (2007) 2176-83.
3. S.M. Snelder, L.E. de Groot-de Laat, L.U. Biter, M. Castro Cabezas, G.J. van de Geijn, E. Birnie, B. Boxma-de Klerk, R.A. Klaassen, F. Zijlstra, B.M. van Dalen, Cross-sectional and prospective follow-up study to detect early signs of cardiac dysfunction in obesity: protocol of the CARDIOBESE study, BMJ Open 8(12) (2018) e025585.
4. R.M. Lang, L.P. Badano, V. Mor-Avi, J. Afilalo, A. Armstrong, L. Ernande, F.A. Flachskampf, E. Foster, S.A. Goldstein, T. Kuznetsova, P. Lancellotti, D. Muraru, M.H. Picard, E.R. Rietzschel, L. Rudski, K.T. Spencer, W. Tsang, J.U. Voigt, Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging, Eur Heart J Cardiovasc Imaging 16(3) (2015) 233-70.
5. S.F. Nagueh, O.A. Smiseth, C.P. Appleton, B.F. Byrd, 3rd, H. Dokainish, T. Edvardsen, F.A. Flachskampf, T.C. Gillebert, A.L. Klein, P. Lancellotti, P. Marino, J.K. Oh, B. Alexandru Popescu, A.D. Waggoner, T. Houston, N. Oslo, A. Phoenix, T. Nashville, O.C. Hamilton, S. Uppsala, Ghent, B. Liege, O. Cleveland, I. Novara, M. Rochester, R. Bucharest, M. St. Louis, Recommendations for the Evaluation of Left Ventricular Diastolic Function by Echocardiography: An Update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging, Eur Heart J Cardiovasc Imaging 17(12) (2016) 1321-1360.
6. S.M. Snelder, L.E. de Groot-de Laat, L.U. Biter, M. Castro Cabezas, N. Pouw, E. Birnie, B.M. Boxma-de Klerk, R.A. Klaassen, F. Zijlstra, B.M. van Dalen, Subclinical cardiac dysfunction in obesity patients is linked to autonomic dysfunction: findings from the CARDIOBESE study, ESC Heart Fail (2020).
7. R. Aggarwal, L. Harling, E. Efthimiou, A. Darzi, T. Athanasiou, H. Ashrafian, The Effects of Bariatric Surgery on Cardiac Structure and Function: a Systematic Review of Cardiac Imaging Outcomes, Obes Surg 26(5) (2016) 1030-40.
8. Heart Outcomes Prevention Evaluation Study, S. Yusuf, P. Sleight, J. Pogue, J. Bosch, R. Davies, G. Dagenais, Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients, N Engl J Med 342(3) (2000) 145-53.
9. K.M. Fox, E.U.t.O.r.o.c.e.w.P.i.s.c.A.d. Investigators, Efficacy of perindopril in reduction of cardiovascular events among patients with stable coronary artery disease: randomised, double-blind, placebo-controlled, multicentre trial (the EUROPA study), Lancet 362(9386) (2003) 782-8.



Chapter 8

Normalization of cardiac function after bariatric surgery is related to autonomic function and vitamin D

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Submitted

ABSTRACT

Purpose

Subclinical cardiac dysfunction is common in obesity patients. Bariatric surgery is associated with normalization of subclinical cardiac function in 50% of the obesity patients. The aim of this study was to identify predictors for a lack of improvement of subclinical cardiac dysfunction one-year post-bariatric surgery.

Methods

Patients who were referred for bariatric surgery were enrolled in a longitudinal study. Inclusion criteria were age 35-65 years and BMI ≥35 kg/m^2. Patients with a suspicion of or known cardiovascular disease were excluded. Conventional and advanced echocardiography, Holter monitoring, and blood tests were performed pre- and one-year post-bariatric surgery. Subclinical cardiac dysfunction was defined as either a reduced left ventricular ejection fraction, decreased global longitudinal strain (GLS), diastolic dysfunction, arrhythmia or an increased BNP or hs Troponin I.

Results

A total of 99 patients were included of whom 59 patients had cardiac dysfunction at baseline. Seventy-two patients completed the one year follow-up after bariatric surgery. There was a significant reduction in weight and cardiovascular risk factors. Parameters of cardiac function, such as GLS, improved. However, in 20 patients cardiac dysfunction persisted. Multivariate analysis identified a decreased heart rate variability (which is a measure of autonomic function), and a decreased vitamin D pre-surgery as predictors for subclinical cardiac dysfunction after bariatric surgery.

Conclusion

Although there was an overall improvement of cardiac function one year post-bariatric surgery, autonomic dysfunction and a decreased vitamin D pre-bariatric surgery were predictors for a lack of improvement of subclinical cardiac dysfunction.

INTRODUCTION

Obesity has reached epidemic proportions globally and the prevalence is still increasing.[1] Subclinical cardiac dysfunction is common in obesity patients,[2] and obesity is associated with an increased risk of heart failure.[3] Heart failure is characterized by an impaired quality of life, frequent hospitalizations, and poor outcome.[4] Considering that prevention and treatment of heart failure have enormous medical and socioeconomic implications, a deeper understanding of risk factors for heart failure such as obesity is imperative.

Clinically significant weight loss is difficult to achieve with lifestyle interventions and the results are often temporary. In contrast, bariatric surgery is an effective and safe treatment option resulting in large long-term weight loss.[5,6] Several studies suggest that weight loss achieved by bariatric surgery has a positive impact on heart morphology, even in obesity patients without heart failure.[7] We recently demonstrated that subclinical cardiac dysfunction normalized in half of the obesity patients one-year after bariatric surgery.[8] Also, bariatric surgery is associated with a 35% reduced incidence of new-onset heart failure during long term follow-up.[9] However, little is known about the pathophysiology of cardiac dysfunction in obesity patients and the factors determining the evolution of cardiac function after bariatric surgery are unknown. We have previously shown that subclinical cardiac dysfunction is related to autonomic dysfunction in obesity patients,[2] but it is unknown whether autonomic dysfunction may be related to a lack of recovery of cardiac dysfunction after bariatric surgery as well.

The CARdiac Dysfunction In Obesity – Early Signs Evaluation (CARDIOBESE) study was the first study in which (speckle tracking) echocardiography, blood tests, and Holter monitoring were combined to simultaneously investigate different aspects that may all play a role in the pathophysiology of subclinical cardiac dysfunction in obesity patients. The aim of this study was to identify predictors for persistent cardiac dysfunction one-year post-bariatric surgery.

METHODS

Study design and study group

The protocol of the CARDIOBESE study has been described before.[10] In short, the CARDIOBESE study is a longitudinal study in which we prospectively enrolled 100 obesity patients who were referred for bariatric surgery to the Franciscus Gasthuis & Vlietland (75 patients) and Maasstad Ziekenhuis (25 patients), both in Rotterdam, the Netherlands. Patients were included if they were between 35 and 65 years old and had a BMI of ≥35 kg/m^2. Patients with a suspicion of or known cardiovascular disease were excluded. Bariatric surgery was performed by either a gastric sleeve, a gastric bypass or a mini bypass operation. Patients were

seen pre- and one-year post-bariatric surgery to study the intra-personal impact of obesity and bariatric surgery-related changes on cardiac function. The study protocol was approved by the ethics committee and written informed consent was obtained from all participants.[10]

The presence or absence of subclinical cardiac dysfunction in the 100 obesity patients of the CARDIOBESE-study has been described in detail before.[2] In short, cardiac dysfunction was defined as either a reduced LV ejection fraction,[11] a decreased global longitudinal strain (GLS) (<17%), diastolic dysfunction,[12] ventricular arrhythmia or an increased BNP (>30 pmol/L) or hs Troponin I (≥34 ng/L for male and > 16 ng/L for female subjects). Of the predefined studied parameters, a decreased GLS (<17%) was by far the most abundant, in 57 patients; one had diastolic dysfunction without an available GLS, one had a normal GLS but an increased BNP (49 pmol/L, normal value <30 pmol/L), and one had a positive hs Troponin I. One patient with cardiac dysfunction was diagnosed with acromegaly after inclusion and was excluded from further analysis, leaving 59 obesity patients with versus 40 without subclinical cardiac dysfunction.

Transthoracic echocardiography

Two-dimensional grayscale harmonic images were obtained in the left lateral decubitus position using a commercially available ultrasound system (EPIQ 7, Philips, Best, the Netherlands), equipped with a broadband (1-5MHz) X5-1 transducer. All acquisitions and measurements were performed according to current guidelines.[11,12]

Interventricular septal thickness (IVSd), posterior wall thickness (PWd), and left ventricular dimension (LVEDD) were all measured at end-diastole. The left ventricular mass (LVM) was calculated according to the Deveraux formula using these measurements: LVM (g) = 0.80 × {1.04[(IVSd +LVEDD + PWd)^3-(LVEDD)^3]}c + 0.6. LVM-index (LVMI) was calculated by dividing LVM by body surface area.

To optimize speckle tracking echocardiography, apical images were obtained at a frame rate of 60 to 80 frames/s. Three consecutive cardiac cycles were acquired from all apical views. Subsequently, these cycles were transferred to a QLAB workstation (version 10.2, Philips, Best, the Netherlands) for off-line speckle tracking analysis. Peak regional longitudinal strain was measured in 17 myocardial regions and a weighted mean was used to derive GLS.

Blood tests

Non-fasting blood samples were taken both for the study and as part of regular care. Routine laboratory measurements included; glucose, glycosylated haemoglobin (HbA1C), creatinine,

estimated glomerular filtration rate (eGFR), alanine aminotransferase (ALAT), Apolipoprotein B, total cholesterol, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), triglycerides, ferritin, active vitamin B12, folic acid, vitamin B1, vitamin B6, albumin, magnesium, vitamin D, and haemoglobin were determined by standard clinical procedures as described.[13] In addition to the regular patient care path blood tests, high sensitive troponin I (hs troponin I), C reactive protein (CRP) and brain natriuretic peptide (BNP) were determined specifically for this study.

Holter monitoring

Heart rhythm was recorded for 24 consecutive hours using a portable digital recorder (GE HEER Light, USA). The digital recorder was connected using stickers that were placed on the chest. Average heart rate, minimal heart rate, maximum heart rate, total premature atrial contractions (PAC), total premature ventricular contractions (PVC), the standard deviation of all NN (often also referred to as RR) intervals (SDNN) and SDNN-index were measured. 24-hour recording of the SDNN reveals the sympathetic nervous system contribution to heart rate variability.[14] The SDNN-index estimates the variability due to the factors affecting heart rate variability (HRV) within a 5 minute period. It is calculated by first dividing the 24 hours record into 288 5-minute-segments and then calculating the standard deviation of all NN intervals contained within each segment.[15]

Statistical analysis

Patients who completed the follow-up were included in the analysis. The normality of the data was checked by the Shapiro–Wilk test. Continuous values with normal distributions were expressed as mean ± standard deviation, with skewed distributions as median and interquartile range and categorical values as percentages. The paired Student's t-test was used for continuous variables with normal distributions, the nonparametric Wilcoxon signed-rank test for variables with skewed distributions, and the McNemar test for categorical variables was used to compare parameters pre- and post-surgery.

The unpaired Student's t-test for continuous variables was used to compare the pre- and post-surgery values of patients with versus without cardiac dysfunction post-surgery, the non-parametric Mann-Whitney U test for continuous parameters with skewed distributions, and the χ^2 test for categorical variables. Pre-surgery parameters that significantly differed between patients with post-surgery normal cardiac function and patients with post-surgery cardiac dysfunction in the univariate analyses were added to multivariate logistic regression analysis

(method: backward stepwise analysis). The discriminative ability of the resulting model was investigated by calculating the area under the receiver operating curve (AUC). Odds ratios and 95% confidence intervals were calculated. A two-tailed p-value of <0.05 was considered statistically significant. Statistical analyses were performed with SPSS version 26.0 or higher (SPSS Inc., Chicago, USA).

RESULTS

Changes in features of obesity from pre- to one-year post-bariatric surgery

A total of 100 obesity patients were included, 85 patients underwent bariatric surgery and 72 patients completed the one-year follow-up (Figure 1). Fifteen patients did not undergo bariatric surgery because of various reasons, but mostly because of disapproval by the psychologist or because they withdrew from surgery for personal reasons.

In Table 1 it is shown that weight loss and decreased BMI were significant one-year post-bariatric surgery. Systolic blood pressure and heart rate decreased significantly as well. Also, the prevalence of comorbidities such as diabetes mellitus, hypertension, and obstructive sleep apnoea syndrome decreased significantly. Medication use was reduced post-surgery, with a significant reduction in use of ACE inhibitors/angiotensin receptor blockers, statins, and oral anti-diabetics.

Blood tests showed a significant decrease in CRP, HbA1c, creatinine, ALAT, Apolipoprotein B, total cholesterol, LDL-C, and triglycerides post-bariatric surgery. HDL-C, folic acid, vitamin B6, and vitamin D increased significantly. The echocardiogram showed a decrease in LVM, but when corrected for the body surface area (LVM-index), there was no significant decrease. Holter monitoring showed a decreased mean, minimal and maximum heart rate one-year post-surgery, whereas the SDNN and the SDNN-index increased.

Changes of parameters of cardiac dysfunction from pre- to one-year post-bariatric surgery

There was a mild but statistically significant increase in BNP one-year post-bariatric surgery (Table 2). Levels of hs troponin I were comparable. Echocardiography showed a significant improvement of GLS. The prevalence of diastolic dysfunction and the LV ejection fraction did not change. Also, the frequency of extrasystoles did not change from pre- to one-year post-bariatric surgery.

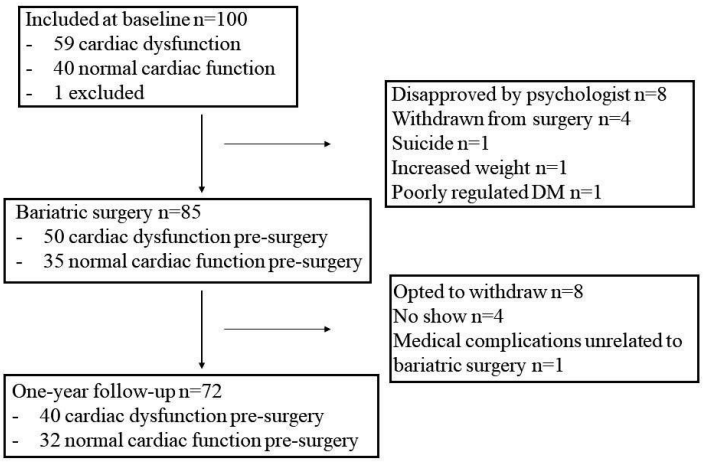

Figure 1: Flow-chart of patients with completion of or loss to follow-up

DM= diabetes mellitus

Table 1: Clinical characteristics of the study population. Differences between obesity patients from pre- to one-year post bariatric surgery.

	Pre-surgery (n=72)	One-year post-surgery (n=72)	p-value
General characteristics			
Age (years)	48 (43-54)		
Female (n, %)	54 (75%)		
Physical examination			
Weight (kg)	122 [113-133]	83 [74-91]	**<0.001**
BMI (kg/m^2)	41 [39-46]	28 [25-31]	**<0.001**
Systolic BP (mmHg)	146 ± 21	133 ± 20	**0.003**
Diastolic BP (mmHg)	79 [73-88]	80 [75-86]	0.18
Heart rate (bpm)	80 [73-86]	65 [57-71]	**<0.001**
Comorbidity			
Diabetes Mellitus (n,%)	16 (22%)	6 (8%)	**0.002**
Hypertension (n,%)	24 (33%)	12 (17%)	**0.035**
Hypercholesterolemia (n,%)	15 (21%)	8 (11%)	0.09
Current smoking (n,%)	11 (15%)	3 (6%)	0.18
COPD (n,%)	4 (6%)	0	0.13
OSAS (n,%)	8 (11%)	0	**0.008**
Medication			
Beta-blockers (n,%)	5 (7%)	3 (4%)	0.63
ACE inhibitors / ARBs (n,%)	11 (15%)	8 (11%)	**0.012**
Calcium channel blockers (n,%)	6 (8%)	5 (7%)	0.66

Statins (n,%)	16 (22%)	9 (13%)	**0.039**
Diuretics (n,%)	13 (18%)	8 (11%)	0.18
Insulin (n,%)	5 (7%)	4 (6%)	0.56
Oral anti-diabetics (n,%)	10 (14%)	4 (6%)	**0.031**
Blood tests			
CRP (mg/L)	6 [3-9]	0 [0-2]	**<0.001**
Glucose (mmol/L)	5.4 [4.8-6.4]	5.0 [4.6-5.6]	0.051
HbA1c (mmol/mol)	39 [35-48]	36 [33-39]	**<0.001**
Creatinine(umol/L)	70 [65-78]	67 [62-71]	**<0.001**
eGFR (ml/min/1.73m^2)	83 ± 9	87 ± 5	**<0.001**
ALAT (U/L)	30 [20-37]	19 [15-26]	**0.004**
Apolipoprotein B (g/L)	1.04 [0.88-1.25]	0.84 [0.73-1.05]	**<0.001**
Total cholesterol (mmol/L)	5.3 ± 0.9	4.6 ± 0.8	**<0.001**
LDL cholesterol (mmol/L)	3.2 ± 0.8	2.6 ± 0.7	**<0.001**
HDL cholesterol (mmol/L)	1.2 [1.0-1.4]	1.4 [1.2-1.6]	**<0.001**
Triglycerides (mmol/L)	1.7 [1.3-2.3]	1.0 [0.8-1.4]	**<0.001**
Ferritin (ug/L)	83 [53-177]	97 [49-171]	0.60
Active Vitamin B12 (pmol/L)	101 [71-132]	104 [66-128]	0.24
Folic acid (nmol/L)	13 [9-16]	27 [16-36]	**<0.001**
Vitamin B1 (nmol/L)	140 ± 28	131 ± 40	0.17
Vitamin B6 (nmol/L)	67 [52-81]	98 [61-128]	**0.009**
Albumin (g/L)	42 [39-44]	41 [40-43]	**0.033**
Magnesium (mmol/L)	0.82 [0.76-0.87]	0.82 [0.78-0.86]	0.38
Vitamin D (nmol/L)	39 [27-66]	75 [61-98]	**<0.001**
Haemoglobin (mmol/L)	8.8 [8.1-9.1]	8.5 [8.0-9.1]	**0.012**
Echocardiography parameters			
Left ventricular mass (g)	177 [138-214]	150 [121-182]	**<0.001**
LVM-index (g/m^2)	72 [59-87]	77 [64-87]	0.49
Holter monitoring			
Ventricular arrhythmia (n, %)	0	0	
Average heart rate (bpm)	83 ± 10	73 ± 8	**<0.001**
Minimal heart rate (bpm)	53 [47-57]	46 [44-51]	**<0.001**
Maximum heart rate (bpm)	137 [128-150]	130 [120-142]	**0.005**
SDNN (ms)	106 ± 46	124 ± 47	**<0.001**
SDNN-index (ms)	46 [38-57]	59 [49-69]	**<0.001**

Values represent mean ± SD, median (Q1-Q3) or n (%)

P-values displayed were analysed by the paired Student's t-test for continuous variables with normal distributions, the nonparametric Wilcoxon signed-rank test for variables with skewed distributions, and the McNemar test for categorical variables.

BMI= body mass index, **BP**= blood pressure, **COPD=** chronic obstructive pulmonary disease, **OSAS**= obstructive sleep apnoea syndrome, **ACE=** angiotensin-converting enzyme, **ARBs**= angiotensin II receptor blockers, **CRP**= C-reactive protein, **HbA1c**= glycated haemoglobin, **eGFR**= estimated glomerular filtration rate, **ALAT**= alanine transaminase, **LDL**= low-density lipoprotein, **HDL**= high-density lipoprotein, **LVM-index**= left ventricular mass-index, **SDNN**= standard deviation of NN intervals, **SDNN-index=** mean of the standard deviations of all the NN intervals for each 5 min segment of a 24 h heart rate variability recording.

Table 2: Parameters of cardiac function. Differences between obesity patients from pre- to one-year post bariatric surgery.

	Pre-surgery (n=72)	One year post-surgery (n=72)	p-value
Blood tests			
BNP (pmol/L)	5 [3-8]	8 [6-10]	**0.029**
hs troponin I positive (n, %)	1 (1%)	5 (7%)	0.06
Echocardiography parameters			
Mitral inflow E-wave (cm/s)	66 ± 16	69 ± 14	0.45
Mitral inflow A-wave (cm/s)	71 ± 14	65 ± 12	**<0.001**
E/A-ratio	0.98 [0.9-1.1]	1.1 [0.9-1.2]	**0.008**
Septal e' velocity (cm/s)	7.8 ± 2.1	8.3 ± 1.7	0.56
Lateral e' velocity (cm/s)	9.6 ± 3.1	12.2 ± 3.1	**<0.001**
E/e'-ratio	8.7 [7.5-9.9]	8.3 [7-.0-9.6]	0.07
Deceleration time (s)	0.18 [0.17-0.21]	0.18 [0.15-0.21]	0.51
LA volume index (ml/m^2)	24 [20-31]	27 [23-34]	0.07
TR velocity (cm/s)	106 [91-139]	191 [106-218]	**<0.001**
Diastolic dysfunction (n, %)	7 (10%)	3 (4%)	0.28
LV ejection fraction (%)	58 ± 8	57 ± 7	0.25
Global longitudinal strain (%)	-15.6 ± 3.1	-18.1 ± 3.3	**0.001**
Holter monitoring			
Total PAC per 24 hours (n)	9 [2-38]	20 [8-68]	0.07
Total PVC per 24 hours (n)	3 [0-22]	5 [2-58]	0.29
Supraventricular arrhythmia (n, %)	1 (1%)	0	0.53
Ventricular arrhythmia (n, %)	0	0	

Values represent mean ± SD, median (Q1-Q3) or n (%)

P-values displayed were analysed by the paired Student's t-test for continuous variables with normal distributions, the nonparametric Wilcoxon signed-rank test for variables with skewed distributions, and the McNemar test for categorical variables.

BNP= brain natriuretic peptide, **hs troponin I=** high sensitive troponin I, **E-wave**= early diastolic transmitralflow velocity, **A-wave**= late diastolic transmitralflow velocity, **e'**= early diastolic mitral annular velocity, **LA-volume index**= left atrial volume index, **TR velocity**= tricuspid regurgitation, **LV**= left ventricular, **PAC**= premature atrial contraction, **PVC**= premature ventricular contraction.

Comparison of patients with versus without normalization of cardiac function after bariatric surgery

Of the patients with complete follow-up, 40 (56%) had subclinical cardiac dysfunction pre-surgery. In 50% of these patients cardiac function had normalized one-year post-surgery (Table 3). In the 20 patients in whom subclinical cardiac dysfunction persisted, 17 (43%) had a decreased GLS, one patient had an elevated hs troponin I level, and two patients had diastolic dysfunction.

When comparing patients with versus without normalization of cardiac function after bariatric surgery, most pre-surgery parameters were comparable, except for albumin, vitamin D and

SDNN. Post-surgery only albumin was mildly decreased in patients without normalization. Multivariate analysis was applied including the parameters which were different pre-surgery, identifying a decreased SDNN and a decreased vitamin D pre-surgery as significant predictors for maintaining cardiac dysfunction after bariatric surgery (Table 4). The multivariate model including these two parameters to identify patients who maintained cardiac dysfunction post-surgery, had an AUC of 0.81 (95% CI: 0.67-0.95, p=0.001), with a sensitivity of 70% (95%CI: 66%-87%) and a specificity of 80% (95%CI: 56%-93%) (Figure 2).

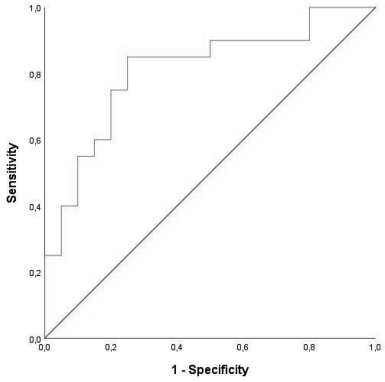

Figure 2: ROC-curve for the prediction model for cardiac dysfunction post-surgery.
Model; combination of SDNN and vitamin D pre-surgery.
Area under the curve = 0.81 (95% CI: 0.67-0.95, p=0.001), sensitivity of 70%, and a specificity of 80%.

Table 3: Comparison of characteristics of patients with pre-existent cardiac dysfunction subdivided into those who showed normalization of cardiac function after bariatric surgery compared to those with persistent cardiac dysfunction.

	Post-surgery normal cardiac function (n=20)		Post-surgery cardiac dysfunction (n=20)		p-value pre	p-value post
	Pre-surgery	Post-surgery	Pre-surgery	Post-surgery		
General characteristics						
Age (years)	48±7		51±8		0.19	
Female (n, %)	13 (65%)		12 (60%)		0.74	
Physical examination						
Weight (kg)	121 [113-132]	83 [75-90]	125 [111-144]	84 [76-98]	0.37	0.62
BMI (kg/m^2)	41 [40-46]	28 [26-31]	42 [39-46]	28 [26-30]	0.83	0.76
Systolic BP (mmHg)	140 [130-159]	138 [116-148]	147 [137-160]	128 [121-134]	0.34	0.48
Diastolic BP (mmHg)	80±13	78±10	86±14	81±7	0.23	0.54
Heart rate (bpm)	80 [78-93]	67 [59-73]	80 [77-88]	63 [53-73]	0.41	0.40
Comorbidity						
Diabetes Mellitus (n,%)	6 (30%)	2 (10%)	4 (20%)	2 (10%)	0.46	1
Hypertension (n,%)	9 (45%)	3 (15%)	7 (35%)	4 (20%)	0.52	0.62
Hypercholesterolemia (n,%)	7 (35%)	3 (15%)	3 (15%)	4 (20%)	0.14	0.62
Current smoking (n,%)	1 (5%)	2 (10%)	3 (15%)	1 (5%)	0.29	0.74
COPD (n,%)	1 (5%)	0	0	0	0.31	
OSAS (n,%)	3 (15%)	0	3 (15%)	0	1	
Medication						
Beta-blockers (n,%)	3 (15%)	2 (10%)	0	1 (5%)	0.07	0.72
ACE inhibitors / ARBs (n,%)	5 (25%)	2 (10%)	5 (25%)	3 (15%)	1	0.54
Calcium channel blockers (n,%)	3 (15%)	1 (5%)	2 (10%)	2 (10%)	0.63	0.49
Statins (n,%)	8 (40%)	3 (15%)	4 (20%)	5 (25%)	0.17	0.34
Diuretics (n,%)	5 (25%)	2 (10%)	3 (15%)	33 (15%)	0.43	0.54
Insulin (n,%)	3 (15%)	2 (10%)	1 (5%)	1 (5%)	0.29	0.62
Oral anti-diabetics (n,%)	4 (20%)	1 (5%)	2 (10%)	1 (5%)	0.38	0.94
Blood tests						
BNP (pmol/L)	5 [3-6]	7 [4-11]	3 [3-7]	8 [6-11]	0.72	0.83
hs Troponin I positive (n)	0	0	0	2 (10%)		0.15
CRP (mg/L)	5 [4-9]	1 [0-3]	6 [4-9]	0 [0-1]	0.64	0.38
Glucose (mmol/L)	6.4±2.2	5.6±1.6	7.2±3.3	6.5±2.2	0.37	0.23
HbA1c (mmol/mol)	51±18	40±9	44±12	38±3	0.13	0.41
Creatinine(umol/L)	71 [65-78]	68 [60-71]	71 [63-77]	66 [64-73]	0.94	0.74
eGFR (ml/min/1.73m^2)	85±8	87±5	85±9	89±3	0.93	0.60
ALAT (U/L)	31 [21-51]	19 [16-29]	31 [27-37]	18 [14-26]	0.91	0.39
Apolipoprotein B (g/L)	0.98±0.26	0.92±0.22	1.1±0.28	0.89±0.22	0.22	0.84
Total cholesterol (mmol/L)	5.0±1.0	4.6±0.7	5.2±0.9	4.6±0.8	0.53	0.89
LDL cholesterol (mmol/L)	2.8±0.6	2.7±0.7	3.0±0.8	2.6±0.9	0.59	0.62
HDL cholesterol (mmol/L)	1.1 [1.0-1.3]	1.3 [1.1-1.4]	1.1 [1.0-1.3]	1.4 [1.2-1.7]	0.98	0.24
Triglycerides (mmol/L)	2.2±1.4	1.3±0.7	2.3±1.1	1.5±0.9	0.74	0.56
Ferritin (ug/L)	150±142	128±90	134±70	153±139	0.66	0.53
Active Vitamin B12 (pmol/L)	82 [70-114]	95 [62-128]	97 [60-108]	128 [74-303]	0.83	0.06
Folic acid (nmol/L)	13 [11-17]	28 [16-35]	13 [9-17]	25 [10-45]	0.60	0.79
Vitamin B1 (nmol/L)	150±24	147±55	149±21	133±34	0.93	0.52
Vitamin B6 (nmol/L)	95±88	112±39	69±17	82±26	0.39	0.06
Albumin (g/L)	43±3	42±3	39±3	40±3	**0.002**	**0.008**
Magnesium (mmol/L)	0.83±0.05	0.84±0.05	0.81±0.05	0.82±0.04	0.43	0.45
Vitamin D (nmol/L)	54 [30-80]	80 [67-98]	33 [25-54]	62 [42-104]	**0.04**	0.12
Haemoglobin (mmol/L)	8.9±0.5	8.8±0.6	8.7±0.8	8.8±1.0	0.42	0.91

Values represent mean ± SD, median (Q1-Q3) or n (%).

P-value pre and p-value post represent comparison of pre- and post-surgery values respectively. p-values displayed were analysed with the unpaired Student's t-test for continuous variables, the non-parametric Mann-Whitney U test for continuous parameters with skewed distributions, and the $\chi 2$ test for categorical variables.

BMI= body mass index, **BP**= blood pressure, **COPD=** chronic obstructive pulmonary disease, **OSAS**= obstructive sleep apnoea syndrome, **ACE=** angiotensin-converting enzyme, **ARBs**= angiotensin II receptor blockers, **BNP**= brain natriuretic peptide, **hs troponin I=** high sensitive troponin I, **CRP**= C-reactive protein, **HbA1c**= glycated haemoglobin, **eGFR**= estimated glomerular filtration rate, **ALAT**= alanine transaminase, **LDL**= low-density lipoprotein, **HDL**= high-density lipoprotein, **E-wave**= early diastolic transmitralflow velocity, **A-wave**= late diastolic transmitralflow velocity, **e'**= early diastolic mitral annular velocity, **LA-volume index**= left atrial volume index, **TR velocity**= tricuspid regurgitation, **LVM-index**= left ventricular mass-index, **PAC**= premature atrial contraction, **PVC**= premature ventricular contraction, **SDNN**= standard deviation of NN intervals, **SDNN-index=** mean of the standard deviations of all the NN intervals for each 5 min segment of a 24 h heart rate variability recording

Table 4: Univariable and multivariable logistic regression analysis in obesity patients with pre-surgery cardiac dysfunction, with presence of subclinical cardiac dysfunction post-surgery as the dependent variable.

	Univariate analysis		Multivariable analysis	
Variable	**OR (95% CI)**	**p-value**	**OR (95% CI)**	**p-value**
SDNN	0.97 (0.96-1.00)	0.015	0.98 (0.96-1.00)	0.014
Vitamin D	0.97 (0.54-1.00)	0.048	0.97 (0.94-1.00)	0.043
Albumin	0.73 (0.58-0.92)	0.006		

Variables displayed were statistically significant different between obesity patients with and without cardiac dysfunction. Multivariable logistic regression analysis; method: backward stepwise analysis.

OR= odds ratio**, 95% CI=** 95% confidence interval**, SDNN**= standard deviation of NN intervals

DISCUSSION

The main finding of the current study is that persistence of cardiac dysfunction in obesity patients one year after bariatric surgery was related to autonomic dysfunction and a decreased vitamin D pre-surgery.

Although in previous studies changes of cardiac morphology and function after bariatric surgery have been investigated,[7,9,16] CARDIOBESE is the first study in which the focus was specifically on subclinical cardiac dysfunction. Furthermore, analysis with the combination of speckle tracking echocardiography, blood tests, and Holter monitoring was used for the first time to simultaneously investigate different aspects of cardiac dysfunction and the underlying pathophysiology. As expected, and in-line with previous findings,[7,9,16] many cardiovascular risk factors and parameters of cardiac function improved post-surgery. Prevalence of comorbidities decreased, lipid levels and HbA1c improved, and CRP decreased. Also, there was a mild but

statistically significant increase of BNP one-year post-surgery. BNP is known to be decreased in obesity patients, both with and without heart failure.[17] Although the reason for this remains incompletely understood, it is most likely due to lower release in obesity patients, rather than increase in their clearance.[18]

Improvement of LV function following bariatric surgery has been described before in small studies.[19-22] However, CARDIOBESE is the largest study in which speckle tracking echocardiography was used to investigate improvement of LV function after bariatric surgery. As we recently reported, there was an overall improvement of GLS one-year post-surgery, resulting in normalization of subclinical cardiac dysfunction in 50% of the obesity patients.[8]

While it was already known that autonomic dysfunction as expressed by a decreased HRV may be related to either cardiac dysfunction[23] or to obesity, [24,25] previously reported baseline data of the patients included in the CARDIOBESE study[2] for the first time showed that autonomic dysfunction appears to have a prominent role in the pathophysiology of cardiac dysfunction in obesity. However, so far it was unknown whether autonomic dysfunction may play a role in persistence of cardiac dysfunction after bariatric surgery as well. In the current study it was shown that a decreased SDNN pre-surgery was a predictor for persistent subclinical cardiac dysfunction one-year post-bariatric surgery. The SDNN represents the beat-to-beat variation during Holter monitoring by measuring the standard deviation of NN intervals.[25] The SDNN is a parameter of autonomic function through the sympathetic nervous system contribution to HRV.[14] A balanced autonomic function is crucial for normal cardiac function.[23] On the other hand, a depressed HRV is related to morbidity and mortality.[26,27] Oher studies already described a favourable effect of bariatric surgery on HRV.[28-30] Yet, by combining findings from Holter monitoring and echocardiography, our study is the first to relate the severity of autonomic dysfunction in obesity to the potential of recovery of cardiac dysfunction after bariatric surgery. In the obesity patients in our study, there was a significant increase in SDNN one-year post-surgery, indicative of improvement of autonomic function, both in patients with improvement of LV function and in patients with persistent LV dysfunction. It can therefore be hypothesized that more severe autonomic dysfunction in obesity as expressed by decreased SDNN pre-surgery, may lead to either a permanent or delayed lack of improvement of LV function after bariatric surgery. Longer follow-up of obesity patients post-bariatric surgery may elucidate whether LV function will improve after all, in-line with improvement of autonomic function.

While, as described above, a role of autonomic dysfunction was somewhat anticipated, the finding that a decreased vitamin D before bariatric surgery was also independently related to persistent subclinical cardiac dysfunction one year post-surgery was less expected. Nevertheless, vitamin D has been suggested to be involved in multiple pathophysiological pathways related to heart failure, such as inflammation, atherosclerosis, endothelial dysfunction, and thrombosis.[31] Furthermore, vitamin D deficiency is a predictor of reduced survival in patients with heart failure.[32] Also, vitamin D is known to be decreased in obesity patients,[33] and in patients with known cardiovascular disease,[34] suggesting that vitamin D may have a role in the increased risk of cardiac dysfunction in obesity. However, previous studies from our group failed to show significant effects of vitamin D supplementation on inflammatory changes in females with overweight, making this mechanism less likely.[35] Although the underlying mechanism remains to be elucidated, by combining findings from blood tests and echocardiography in our study, it was shown for the first time that a relative decreased vitamin D level pre-bariatric surgery is related to a lack of improvement of cardiac function after bariatric surgery.

Limitations

A relatively large number (32%) of the patients with cardiac dysfunction did not complete the follow-up: 15% because they did not undergo bariatric surgery, and 17% dropped out because of various other reasons. Meanwhile, 20% of the patients with a normal cardiac function was lost to follow-up. The reason for this difference is unknown, but probably it was just coincidence. Furthermore, follow-up after bariatric surgery was one year and it may be hypothesized that a longer follow-up would have shown improvement of cardiac function in a larger proportion of patients.

CONCLUSIONS

Autonomic dysfunction at baseline was related to a lack of normalization of cardiac function in obesity patients one year after bariatric surgery. This result is in-line with previous findings of our group,[2] confirming an important role of autonomic dysfunction in the pathophysiology of cardiac dysfunction in obesity. Decreased vitamin D before bariatric surgery was also independently related to persistent subclinical cardiac dysfunction one year post-surgery. Since this finding was less expected, we consider this less affirmative and more hypothesis-generating. Nevertheless, signs of either autonomic dysfunction or a decreased vitamin D pre-bariatric surgery may be indicative of a need for cardiologic follow-up after bariatric surgery.

REFERENCES

1. Global BMIMC, Di Angelantonio E, Bhupathiraju Sh N, Wormser D, Gao P, Kaptoge S, Berrington de Gonzalez A, Cairns BJ, Huxley R, Jackson Ch L, Joshy G, Lewington S, Manson JE, Murphy N, Patel AV, Samet JM, Woodward M, Zheng W, Zhou M, Bansal N, Barricarte A, Carter B, Cerhan JR, Smith GD, Fang X, Franco OH, Green J, Halsey J, Hildebrand JS, Jung KJ, Korda RJ, McLerran DF, Moore SC, O'Keeffe LM, Paige E, Ramond A, Reeves GK, Rolland B, Sacerdote C, Sattar N, Sofianopoulou E, Stevens J, Thun M, Ueshima H, Yang L, Yun YD, Willeit P, Banks E, Beral V, Chen Z, Gapstur SM, Gunter MJ, Hartge P, Jee SH, Lam TH, Peto R, Potter JD, Willett WC, Thompson SG, Danesh J, Hu FB. Body-mass index and all-cause mortality: individual-participant-data meta-analysis of 239 prospective studies in four continents. Lancet 2016;388:776-86.
2. Snelder SM, de Groot-de Laat LE, Biter LU, Castro Cabezas M, Pouw N, Birnie E, Boxma-de Klerk BM, Klaassen RA, Zijlstra F, van Dalen BM. Subclinical cardiac dysfunction in obesity patients is linked to autonomic dysfunction: findings from the CARDIOBESE study. ESC Heart Fail 2020.
3. Kenchaiah S, Evans JC, Levy D, Wilson PW, Benjamin EJ, Larson MG, Kannel WB, Vasan RS. Obesity and the risk of heart failure. N Engl J Med 2002;347:305-13.
4. Stewart S, MacIntyre K, Hole DJ, Capewell S, McMurray JJ. More 'malignant' than cancer? Five-year survival following a first admission for heart failure. Eur J Heart Fail 2001;3:315-22.
5. DeMaria EJ. Bariatric surgery for morbid obesity. N Engl J Med 2007;356:2176-83.
6. Sjostrom L, Lindroos AK, Peltonen M, Torgerson J, Bouchard C, Carlsson B, Dahlgren S, Larsson B, Narbro K, Sjostrom CD, Sullivan M, Wedel H, Swedish Obese Subjects Study Scientific G. Lifestyle, diabetes, and cardiovascular risk factors 10 years after bariatric surgery. N Engl J Med 2004;351:2683-93.
7. Vest AR, Heneghan HM, Agarwal S, Schauer PR, Young JB. Bariatric surgery and cardiovascular outcomes: a systematic review. Heart 2012;98:1763-77.
8. Snelder SM, Aga Y, Laat LEdG-d, Biter LU, Cabezas MC, Pouw N, Klerk BB-d, Klaaseen RA, Zijsltra F, Dalen BMv. Cardiac function normalizes one year after bariatric surgery in half of the obesity patients with subclinical cardiac dysfunction Obesity Surgery 2021;accepted for publication.
9. Jamaly S, Carlsson L, Peltonen M, Jacobson P, Karason K. Surgical obesity treatment and the risk of heart failure. Eur Heart J 2019.
10. Snelder SM, de Groot-de Laat LE, Biter LU, Castro Cabezas M, van de Geijn GJ, Birnie E, Boxma-de Klerk B, Klaassen RA, Zijlstra F, van Dalen BM. Cross-sectional and prospective follow-up study to detect early signs of cardiac dysfunction in obesity: protocol of the CARDIOBESE study. BMJ Open 2018;8:e025585.
11. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, Flachskampf FA, Foster E, Goldstein SA, Kuznetsova T, Lancellotti P, Muraru D, Picard MH, Rietzschel ER, Rudski L, Spencer KT, Tsang W, Voigt JU. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. Eur Heart J Cardiovasc Imaging 2015;16:233-70.
12. Nagueh SF, Smiseth OA, Appleton CP, Byrd BF, 3rd, Dokainish H, Edvardsen T, Flachskampf FA, Gillebert TC, Klein AL, Lancellotti P, Marino P, Oh JK, Alexandru Popescu B, Waggoner AD, Houston T, Oslo N, Phoenix A, Nashville T, Hamilton OC, Uppsala S, Ghent, Liege B, Cleveland O, Novara I, Rochester M, Bucharest R, St. Louis M. Recommendations for the Evaluation of Left Ventricular Diastolic Function by Echocardiography: An Update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. Eur Heart J Cardiovasc Imaging 2016;17:1321-60.
13. van Mil SR, Biter LU, van de Geijn GM, Birnie E, Dunkelgrun M, JNM IJ, van der Meulen N, Mannaerts GHH, Castro Cabezas M. Contribution of Type 2 Diabetes Mellitus to Subclinical Atherosclerosis in Subjects with Morbid Obesity. Obes Surg 2018;28:2509-16.
14. Grant CC, van Rensburg DC, Strydom N, Viljoen M. Importance of tachogram length and period of recording during noninvasive investigation of the autonomic nervous system. Ann Noninvasive Electrocardiol 2011;16:131-9.
15. Shaffer F, Ginsberg JP. An Overview of Heart Rate Variability Metrics and Norms. Front Public Health 2017;5:258.
16. Moussa O, Ardissino M, Heaton T, Tang A, Khan O, Ziprin P, Darzi A, Collins P, Purkayastha S. Effect of bariatric surgery on long-term cardiovascular outcomes: a nationwide nested cohort study. Eur Heart J 2020.
17. Mehra MR, Uber PA, Park MH, Scott RL, Ventura HO, Harris BC, Frohlich ED. Obesity and suppressed B-type natriuretic peptide levels in heart failure. J Am Coll Cardiol 2004;43:1590-5.
18. Mueller C, McDonald K, de Boer RA, Maisel A, Cleland JGF, Kozhuharov N, Coats AJS, Metra M, Mebazaa A, Ruschitzka F, Lainscak M, Filippatos G, Seferovic PM, Meijers WC, Bayes-Genis A, Mueller T, Richards

M, Januzzi JL, Jr., Heart Failure Association of the European Society of C. Heart Failure Association of the European Society of Cardiology practical guidance on the use of natriuretic peptide concentrations. Eur J Heart Fail 2019;21:715-31.
19. Leung M, Xie M, Durmush E, Leung DY, Wong VW. Weight Loss with Sleeve Gastrectomy in Obese Type 2 Diabetes Mellitus: Impact on Cardiac Function. Obes Surg 2016;26:321-6.
20. Di Bello V, Santini F, Di Cori A, Pucci A, Talini E, Palagi C, Delle Donne MG, Marsili A, Fierabracci P, Valeriano R, Scartabelli G, Giannetti M, Anselmino M, Pinchera A, Mariani M. Effects of bariatric surgery on early myocardial alterations in adult severely obese subjects. Cardiology 2008;109:241-8.
21. Koshino Y, Villarraga HR, Somers VK, Miranda WR, Garza CA, Hsiao JF, Yu Y, Saleh HK, Lopez-Jimenez F. Changes in myocardial mechanics in patients with obesity following major weight loss after bariatric surgery. Obesity (Silver Spring) 2013;21:1111-8.
22. Shin SH, Lee YJ, Heo YS, Park SD, Kwon SW, Woo SI, Kim DH, Park KS, Kwan J. Beneficial Effects of Bariatric Surgery on Cardiac Structure and Function in Obesity. Obes Surg 2017;27:620-5.
23. Florea VG, Cohn JN. The autonomic nervous system and heart failure. Circ Res 2014;114:1815-26.
24. Karason K, Molgaard H, Wikstrand J, Sjostrom L. Heart rate variability in obesity and the effect of weight loss. Am J Cardiol 1999;83:1242-7.
25. Yadav RL, Yadav PK, Yadav LK, Agrawal K, Sah SK, Islam MN. Association between obesity and heart rate variability indices: an intuition toward cardiac autonomic alteration - a risk of CVD. Diabetes Metab Syndr Obes 2017;10:57-64.
26. Forslund L, Bjorkander I, Ericson M, Held C, Kahan T, Rehnqvist N, Hjemdahl P. Prognostic implications of autonomic function assessed by analyses of catecholamines and heart rate variability in stable angina pectoris. Heart 2002;87:415-22.
27. Bauer A, Kantelhardt JW, Barthel P, Schneider R, Makikallio T, Ulm K, Hnatkova K, Schomig A, Huikuri H, Bunde A, Malik M, Schmidt G. Deceleration capacity of heart rate as a predictor of mortality after myocardial infarction: cohort study. Lancet 2006;367:1674-81.
28. Gomide Braga T, das Gracas Coelho de Souza M, Maranhao PA, Menezes M, Dellatorre-Teixeira L, Bouskela E, Le Roux CW, Kraemer-Aguiar LG. Evaluation of Heart Rate Variability and Endothelial Function 3 Months After Bariatric Surgery. Obes Surg 2020.
29. Maser RE, Lenhard MJ, Irgau I, Wynn GM. Impact of surgically induced weight loss on cardiovascular autonomic function: one-year follow-up. Obesity (Silver Spring) 2007;15:364-9.
30. Kokkinos A, Alexiadou K, Liaskos C, Argyrakopoulou G, Balla I, Tentolouris N, Moyssakis I, Katsilambros N, Vafiadis I, Alexandrou A, Diamantis T. Improvement in cardiovascular indices after Roux-en-Y gastric bypass or sleeve gastrectomy for morbid obesity. Obes Surg 2013;23:31-8.
31. Brinkley DM, Ali OM, Zalawadiya SK, Wang TJ. Vitamin D and Heart Failure. Curr Heart Fail Rep 2017;14:410-20.
32. Gotsman I, Shauer A, Zwas DR, Hellman Y, Keren A, Lotan C, Admon D. Vitamin D deficiency is a predictor of reduced survival in patients with heart failure; vitamin D supplementation improves outcome. Eur J Heart Fail 2012;14:357-66.
33. Plesner JL, Dahl M, Fonvig CE, Nielsen TRH, Kloppenborg JT, Pedersen O, Hansen T, Holm JC. Obesity is associated with vitamin D deficiency in Danish children and adolescents. J Pediatr Endocrinol Metab 2018;31:53-61.
34. Kendrick J, Targher G, Smits G, Chonchol M. 25-Hydroxyvitamin D deficiency is independently associated with cardiovascular disease in the Third National Health and Nutrition Examination Survey. Atherosclerosis 2009;205:255-60.
35. de Vries MA, van der Meulen N, van de Geijn GM, Klop B, van der Zwan EM, Prinzen L, Birnie E, Westerman EM, de Herder WW, Castro Cabezas M. Effect of a Single Dose of Vitamin D3 on Postprandial Arterial Stiffness and Inflammation in Vitamin D-Deficient Women. J Clin Endocrinol Metab 2017;102:992-1000.


IV

Part IV

Biomarker profiles related to cardiac dysfunction in obesity patients and changes after bariatric surgery

9

Chapter 9

Biomarker profiles in obesity patients and relation to cardiac dysfunction

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ABSTRACT

Background

Current knowledge on the role of obesity in causing cardiac dysfunction is insufficient. Several biomarkers reflecting biological processes that may play a role in the occurrence of cardiac dysfunction in obesity patients are available.

Purpose

To compare cardiovascular biomarker profiles between obesity patients and non-obese controls, and between obesity patients with and without cardiac dysfunction, in order to better understand the underlying pathophysiology of cardiac dysfunction in obesity patients.

Methods

Blood samples were obtained from 100 obesity patients (BMI ≥35 kg/m^2) without known cardiovascular disease, and from 50 age- and gender-matched non-obese controls (BMI ≤30 kg/m^2). The cardiovascular panel III of the Olink Multiplex platform was used for the measurement of 92 biomarkers.

Results

The majority (53%) of biomarkers were increased in obesity patients compared to non-obese controls. Only 5% of the biomarkers were elevated in obesity patients with cardiac dysfunction compared to those without. Biomarkers discriminating cardiac dysfunction from no cardiac dysfunction in obesity patients differed from those discriminating obese from non-obese patients. An elastic net model for the prediction of cardiac dysfunction in obesity patients had a high AUC of 0.87 (95% CI:0.79-0.94, $p< 0.001$). The sensitivity of this model was 84% and the specificity was 79%.

Conclusion

A multiplex immunoassay was used for the first time in obesity patients without known cardiovascular disease. These patients have cardiovascular biomarker profiles that are clearly different from non-obese controls. Comparison of obesity patients with and without cardiac dysfunction suggested an important role for inflammation, atherosclerosis, and insulin resistance in the underlying pathophysiology of cardiac dysfunction in obesity patients.

INTRODUCTION

Obesity is a growing worldwide problem. If the current trends continue, global obesity prevalence will reach 18% in men and surpass 21% in women by 2025.[1] Obesity is associated with an increased risk of all-cause mortality and cardiovascular disease.[2] A body mass index (BMI) ≥30 kg/m^2 doubles the lifetime risk of developing heart failure.[3] With the rising prevalence of obesity worldwide, cardiac dysfunction in obesity patients is a growing problem,[4,5] which warrants efficient screening to identify those at highest cardiovascular risk.[6] Current knowledge on factors contributing to cardiac dysfunction in obesity patients is insufficient to optimally develop such strategies for these patients.[2]

Nowadays, biomarkers play a major role in the diagnosis and management of heart failure.[7] Natriuretic peptides are the gold standard biomarkers for the diagnosis and prognosis of heart failure.[8] However, natriuretic peptides are decreased in obesity patients and are therefore of less use than in non-obese patients.[9] In addition, heart failure in obesity patients appears to result not only from cardiac overload or injury but also from factors specifically related to the abundant fat tissue.[10] As such, natriuretic peptides might not be the only biomarkers relevant in cardiac dysfunction in obesity patients. Currently, a variety of biomarkers are described, reflecting several biological processes that have been hypothesized to play an important role in the occurrence of cardiac dysfunction.[11,12] The hypothesized processes are inflammation (reflected by biomarkers such as SELE, SELP, and RARRES2),[13-16] insulin resistance (IGFBP-1 and IGFBP-2),[17] coagulation, oxidative stress, myocardial stretch, matrix remodelling, and atherosclerosis (CHIT1,[18] OPG,[19] and t-PA[20]). Investigating such biomarkers, using a multiplex immunoassay to determine a broad spectrum of blood biomarkers related to processes such as inflammation, atherosclerosis and insulin resistance, may help to better understand the underlying pathophysiology of cardiac dysfunction in obesity patients. Therefore, we examined cardiovascular biomarker profiles in obesity patients versus non-obese controls, and the relationship between these profiles and subclinical cardiac dysfunction in obesity.

METHODS

Study group

Blood samples from patients included in the CARdiac Dysfunction In Obesity – Early Signs Evaluation study (CARDIOBESE) were used. The protocol of the CARDIOBESE study has been described in detail.[21] CARDIOBESE is a multicentre, prospective study including 100 obesity patients referred for bariatric surgery, designed to identify novel risk factors associated

with cardiovascular disease in this cohort. Patients were included if they were between 35 and 65 years old and had a BMI of ≥35 kg/m^2. Patients with a suspicion of or known cardiovascular disease were excluded. Fifty age- and gender-matched non-obese (BMI<30 kg/m^2) controls were enrolled as controls.

The presence or absence of subclinical cardiac dysfunction in the 100 obesity patients of the CARDIOBESE study has been described in detail before.[22] In short, cardiac dysfunction was defined as either a reduced LV ejection fraction, a decreased GLS, diastolic dysfunction, ventricular arrhythmia or an increased BNP or hs Troponin I. As previously shown, cardiac dysfunction was present in 60 patients. However, one patient with cardiac dysfunction was diagnosed with acromegaly after inclusion and was excluded from further analysis, leaving 59 obesity patients with versus 40 without subclinical cardiac dysfunction.

The study protocol was approved by the medical ethics committee Toetsingscommissie Wetenschappelijk Onderzoek Rotterdam e.o. (TWOR). Written informed consent was obtained from all participants.[21] The present study was carried out in accordance with the Declaration of Helsinki. All participants underwent a transthoracic echocardiogram, Holter registration, and laboratory tests.

Laboratory procedures

Non-fasting blood samples were collected at the outpatient clinic at the moment of screening for bariatric surgery. High sensitive (hs) Troponin I and brain natriuretic peptide (BNP) were determined immediately according to local procedures of the laboratory for clinical chemistry of our hospital. The other blood samples were processed and stored at -80°C within 2 hours after collection. Serum aliquots were thawed and randomly divided over three microwell plates. Internal controls were added to each plate. Plates were frozen at -80°C and shipped on dry ice to Olink Proteomics AB, Uppsala, Sweden. The cardiovascular panel III of the Olink Multiplex platform for biomarkers was used for analysis. This panel was chosen, because it contains known human cardiovascular and inflammatory markers as well as some exploratory human proteins with potential as new cardiovascular markers. The kits are based on the proximity extension assay technology, where 92 oligonucleotide-labelled antibody probe pairs are allowed to bind to their respective target present in the sample. The proximity extension assay technique shows exceptionally high specificity and sensitivity.[23,24] The biomarkers are delivered in normalized protein expression units (NPX), which are relative units. Therefore, NPX values for 2 different analyses/proteins are not directly comparable. They are expressed on a log2 scale where 1 unit higher NPX value represents a doubling of the measured protein

concentration. For statistical analysis, NPX were converted back to a linear scale: 2NPX= linear NPX. All biomarkers and abbreviations are shown in Supplementary Table 1.

Transthoracic echocardiography

Two-dimensional grayscale harmonic images were obtained in the left lateral decubitus position using a commercially available ultrasound system (EPIQ 7, Philips, the Netherlands), equipped with a broadband (1-5MHz) X5-1 transducer. All acquisitions and measurements were performed according to the current guidelines.[25,26] Off-line speckle tracking was performed using a QLAB workstation (version 10.2, Philips, the Netherlands). Peak regional longitudinal strain was measured in 17 myocardial regions and a weighted mean was used to derive Global Longitudinal Strain (GLS).[25]

Sample size calculation

A conservative estimate would be that cardiac dysfunction based on conventional echocardiography is present in 20% of obesity patients and 2.5% of age-matched and gender-matched non-obese controls.[27] Given these estimates, to be able to reject the null hypothesis of the CARDIOBESE study that cardiac dysfunction rates are equal between patients and controls, at least 97 obesity patients and 49 non-obese controls have to be included in the analysis (alpha: 0.05 (two sided), power: 0.80, 2:1 ratio of patients:controls). The use of more sensitive techniques may increase the proportion of non-obese controls with an early sign of cardiac dysfunction. Nevertheless, the proportion of obesity patients with an early sign of cardiac dysfunction is expected to increase even more, assuring that the previous sample size calculation will still suffice.

Statistical analysis

The normality of the data was checked by the Shapiro–Wilk test. Normally distributed data are presented as means and standard deviations, skewed data as medians and interquartile ranges, and categorical variables as counts and percentages.

Differences in clinical characteristics, parameters of cardiac function, and biomarkers between obesity patients and matched non-obese controls were estimated by using generalized linear mixed models with obesity as the independent variable, and the aforementioned variables entered consecutively as the dependent variable. Random intercepts were used to account for the matched pairs. Missing variables were omitted. For dependent variables with complete

separation, Bayesian generalized linear mixed models were used. The Benjamini–Hochberg procedure, with a 5% false discovery rate, was used to correct for the multiple testing.[28]

Linear regression was used to compare biomarker levels between obesity patients with cardiac dysfunction to those without. For the biomarkers, results were displayed as the beta-coefficients of each biomarker from the generalized linear mixed model and the linear regression, which signifies the difference in biomarker level (in NPX units) according to the presence of obesity or cardiac dysfunction. Again, the Benjamini-Hochberg procedure was used to correct for multiple testing.

Subsequently, a multiple biomarker model was constructed to optimally identify patients with cardiac dysfunction. In order to select the subset of biomarkers that carries the best predictive value for cardiac dysfunction and, at the same time, to reduce the risk of overfitting (which is especially important in the setting where the number of events is low relative to the number of predictors), elastic net logistic regression was used. This method combines two established shrinkage-methods: Ridge regression and Lasso regression.[29] Patient characteristics and all available biomarkers were used as input for this model. The discriminative ability of the resulting model was investigated by calculating the area under the receiver operating curve (AUC). Odd's ratios of the Z-scores were reported. All statistical tests were 2-sided and a p-value of 0.05 was considered statistically significant unless otherwise stated. The analyses were performed with R 3.0.3 (glmnet and nlme packages were used) and SPSS version 25.

RESULTS

Patient characteristics

A total of 100 obesity patients and 50 non-obese controls were studied, both without a suspicion of or known cardiovascular disease. The characteristics of the participants are shown in Table 1. Physical examination showed an increased weight, BMI, systolic blood pressure, waist circumference and heart rate in obesity patients. Obesity patients had more often comorbidities such as diabetes mellitus and hypertension and used more often medication than non-obese controls. Echocardiography showed that obesity patients had an increased left ventricular mass (LVM), a higher prevalence of diastolic dysfunction, and a decreased GLS and LV ejection fraction.

Comparison between obesity patients with and without cardiac dysfunction revealed that patients with cardiac dysfunction were more often male and had an increased heart rate. The prevalence of comorbidities and medication use were comparable between these two groups.

Cardiovascular biomarkers in obesity patients compared to non-obese controls

The differences in biomarker levels between the obesity patients and the non-obese controls are presented in Figure 1a, where the bars represent the beta coefficients of the biomarkers (difference in NPX units between those with and without obesity). The majority (49 out of 92, 53%) of biomarkers were significantly increased in obesity patients. The most strongly increased biomarkers in obesity patients were: E-selectin (SELE) with beta=1581 (95% CI:592 – 2571), p=0.002 (SELE was 1581 NPX higher in the obesity patients than in the non-obese controls), Retinoic acid receptor responder protein 2 (RARRES2), beta=976 (95%CI: 695 – 1257), p<0.001, and P-selectin (SELP), beta=687 (95%CI: 224 – 1149), p=0.004. The most strongly decreased biomarkers in obesity patients were: Insulin-like growth factor-binding protein 2 (IGFBP-2) with a beta= –109 (95%CI: –147, –71), p<0.001, Paraoxonase (PON3), beta= –77 (95%CI: –95, –59), p<0.001, and Insulin-like growth factor-binding protein 1 (IGFBP-1), beta= –27 (95%CI: –39, –15), p<0.001.

Table 1: Characteristics of the obesity patients compared to non-obese controls, and comparison between obesity patients with or without cardiac dysfunction

	Non-obese controls (n=50)	Obesity patients (n=100)	p-value	Obesity patient without cardiac dysfunction (n=59)	Obesity patient with cardiac dysfunction (n=40)	p-value
General characteristics						
Age (years)	50 (40-59)	48 (42-50)	**0.02***	47 (42-52)	49 (42-56)	0.53
Female (%)	35 (70%)	70 (70%)	>0.99	35 (87.5%)	35 (59.3%)	**0.004***
Physical examination						
Length (m)	1.74 ± 0.1	1.71 ± 0.1	0.08	1.69 ± 0.1	1.73 ± 0.1	**0.045**
Weight (kg)	76 (64-82)	123 (115-135)	**<0.001***	123 (115-132)	124 (114-138)	0.28
BMI (kg/m^2)	25 (22-28)	42 (40-46)	**<0.001***	43 (40-46)	42 (40-45)	0.56
Systolic BP (mmHg)	127 (118-136)	140 (127-157)	**<0.001***	139 ± 21	144 ± 20	0.08
Diastolic BP (mmHg)	78 (71-82)	79 (72-88)	0.11	75 (70-84)	80 (73-89)	0.06
Waist (cm)	79 (74-89)	131 (125-140)	**<0.001***	128 (122-134)	137 (127-141)	**0.048**
Heart rate (bpm)	64 ± 9	80 ± 13	**<0.001***	76 ± 11	83 ± 14	**0.019***
Comorbidity						
Diabetes Mellitus	0	22 (22%)	**0.007***	8 (20%)	13 (22%)	0.81
Hypertension	4 (8%)	32 (32%)	**0.003***	11 (27.5%)	20 (33.9%)	0.27
Hypercholesterolemia	5 (10%)	18 (18%)	0.21	8 (20%)	10 (16.9%)	0.89
Current smoking	7 (14%)	17 (17%)	0.63	7 (17.5%)	9 (15.3%)	0.77
COPD	1 (2%)	5 (5%)	0.39	3 (7.5%)	2 (3.4%)	0.37
OSAS	1 (2%)	12 (12%)	0.07	3 (7.5%)	8 (13.5%)	0.35
Medication						
Beta-blockers	0	8 (8%)	**0.03**	3 (8.1%)	5 (8.8%)	0.36
ACE / ARBs	2 (4%)	24 (24%)	**0.008***	10 (27%)	13 (22.8%)	0.53
CCB	0	12 (12%)	**0.04**	3 (8.1%)	7 (12.3%)	0.13

Statins	3 (6%)	20 (20%)	**0.03**	5 (13.5%)	14 (24.6%)	0.12
Diuretics	1 (2%)	18 (18%)	**0.02***	6 (16.2%)	11 (19.3%)	0.13
Insulin	0	7 (7%)	**0.04**	2 (5.4%)	5 (8.8%)	0.51
Oral anti-diabetics	0	15 (15%)	**0.02***	5 (13.5%)	9 (15.8%)	0.70
Blood tests						
BNP	6 (3-9)	5 (3-8)	0.59	6 (4-11)	4 (3-6)	0.29
hs Troponin I	0	1 (1%)	0.37	0	0	
Echocardiography						
LVM (g)	148 (117-175)	194 (149-231)	**<0.001***	169 (140-215)	203 (156-241)	0.10
LVM-index (g/m^2)	79 (62-88)	76 (64-92)	0.16	72 (59-88)	81 (67-94)	0.16
Diastolic dysfunction	1 (2%)	11 (11%)	0.09	0	10 (17%)	**<0.001***
GLS (%)	-20 (-21 - -19)	-16 (-18 - -14)	**<0.001***	-19.2 ± 1.3	-14.4 ± 2.1	**<0.001***
LVEF (%)	65 ± 5	57 ± 7	**<0.001***	62 ± 6	54 ± 7	**<0.001***

Values represent mean ± SD, median (Q1-Q3) or n (%).

P-values displayed for obesity patients versus matched non-obese controls were analyzed by using generalized linear mixed models, and p-values for obesity patients with cardiac dysfunction versus normal cardiac function were analyzed by univariable logistic regression.

* significant after Benjamini–Hochberg correction

BMI= body mass index, **BP**=blood pressure, **CCB**= calcium channel blockers, **COPD**= chronic obstructive pulmonary disease, **OSAS**= obstructive sleep apnea syndrome, **ACE**= angiotensin-converting enzyme, **ARBs**= angiotensin II receptor blockers, **BNP**= brain natriuretic peptide, **GLS**= global longitudinal strain, hs **Troponin I**= high sensitive Troponin I, **LVEF**= left ventricular ejection fraction**, LVM**= left ventricular mass

Cardiovascular biomarkers in obesity patients with cardiac dysfunction compared to those without

Figure 1b shows that 5 out of 92 (5%) biomarkers were significantly increased in obesity patients with cardiac dysfunction compared to those without cardiac dysfunction. The most strongly increased biomarkers in the obesity patients with cardiac dysfunction were: SELE with a beta=2492 (95%CI: 1228 – 3755), p<0.001, and Tumor necrosis factor receptor superfamily member 6 (FAS), beta=13 (95%CI: 5 – 21), p=0.002. None of the biomarkers were significantly decreased in patients with cardiac dysfunction.

The biomarkers discriminating cardiac dysfunction from no cardiac dysfunction in obesity patients differed from those discriminating obesity patients from non-obese controls (as shown by Figure 1b compared to 1a).

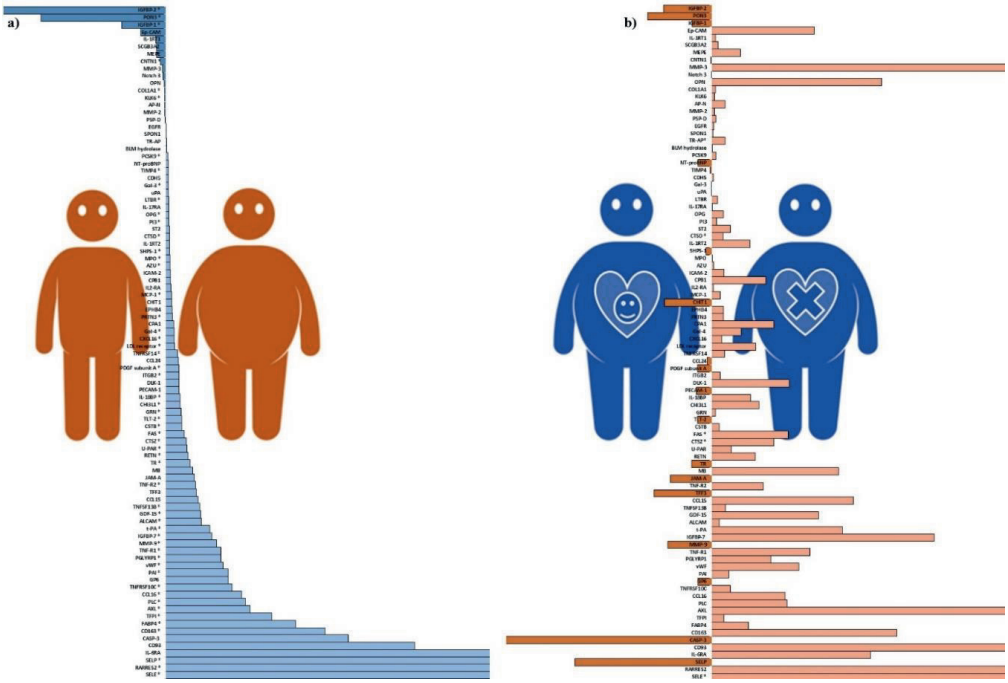

Figure 1: Graphical representation of the betas from the generalized linear mixed model for all 92 biomarkers in obesity patients (n=100) versus non-obese controls (n=50) (a) and the linear regression for the obesity patients with cardiac dysfunction (n=59) versus obesity patients with normal cardiac function (n=40) (b).
* Significant by p<0.05 by generalized linear mixed model (a) or linear regression (b)

Model for identification of cardiac dysfunction in obesity patients

The elastic net regression analysis selected the following biomarkers for inclusion in the multivariable model for identification of cardiac dysfunction in obesity patients: the biomarkers Cathepsin D (CTSD), Chitotriosidase-1 (CHIT1), SELE, Osteopontin (OPN), Osteoprotegerin (OPG), Tartrate-resistant acid phosphatase type 5 (TR-AP), Tissue-type plasminogen activator (t-PA), and FAS. Patient characteristics that were selected by this model were male gender, waist circumference, systolic blood pressure, heart rate, and LVM. Table 2 shows the odd's ratios of Z-scores of the variables selected by the elastic net regression. Figure 2 shows the ROC-curve for this model. The ability of this model to discriminate between obesity patients with and without cardiac dysfunction had an AUC of 0.87 (95% CI;0.79-0.94, p<0.001). The sensitivity of this model was 84%, the specificity was 79%, the positive predictive value 82%, and the negative predictive value 81%.

Table 2: Odd's ratios of the Z-scores of the variables selected by the elastic net regression

Variable	Odd's ratio
CTSD	1.43
CHIT1	0.34
SELE	2.05
OPN	1.19
OPG	1.41
TR-AP	1.37
t-PA	1.27
FAS	1.16
Male gender	1.58
Waist circumference	0.84
Systolic blood pressure	1.66
Heart rate	1.48
Left ventricular mass	1.41

CTSD= Cathepsin D, **CHIT1=** Chitotriosidase-1, **SELE=** E-selectin, **OPN=** Osteopontin, **OPG=** Osteoprotegrin, **TR-AP=** Tartrate-resistant acid phosphatase type 5, **t-PA=** Tissue-type plasminogen activator, **FAS=** Tumor necrosis factor receptor superfamily member 6

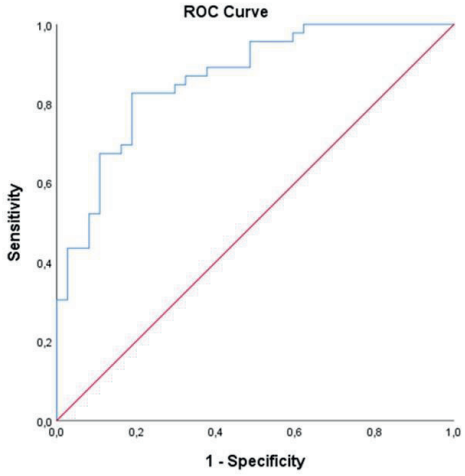

Figure 2: ROC-curve for the elastic net model (n=99). Variables included were CTSD, CHIT1, SELE, OPN, OPG, TR-AP, t-PA, FAS, male gender, waist circumference, systolic blood pressure, heart rate, and left ventricular mass.
AUC= 0.87 (95% CI: 0.79-0.94), p<0.001

DISCUSSION

The main findings of the current study are that the cardiovascular biomarker profile of obesity patients without known cardiovascular disease is overtly different from that of non-obese controls, and that obesity patients with subclinical cardiac dysfunction have a different cardiovascular biomarker profile than obesity patients with normal cardiac function. To our knowledge, this is the first publication describing cardiovascular biomarkers in relation to subclinical cardiovascular dysfunction in obesity patients.

While there is strong evidence from epidemiological studies on the detrimental effects of obesity on health outcomes, the underlying biological mechanisms are not completely understood.[30] The use of multiplex immunoassays that determine a broad spectrum of blood biomarkers to increase insights in pathophysiological aspects of diseases is gaining interest in medical science.[11] In our study, such a multiplex immunoassay was used for the first time to compare obesity patients and non-obese controls. Even in obesity patients without known cardiovascular disease, the cardiovascular biomarker profile was very different from non-obese controls. Since the studied biomarkers covered several processes potentially involved in the pathophysiology of cardiovascular disease in obesity, such as inflammation, insulin resistance, coagulation, oxidative stress, myocardial stretch, matrix remodeling, and atherosclerosis, our findings support the hypothesis of a multifactorial origin of cardiovascular disease in obesity patients. Nevertheless, there remains uncertainty on the precise extent of the mechanisms involved. In our analysis, the most strongly elevated biomarkers in obesity patients (SELE, SELP, and RARRES2) were biomarkers known to be linked to inflammation.[13-16] It has been hypothesized before, that inflammation has an important role in the increased risk of cardiovascular disease in obesity.[31] However, the most strongly decreased biomarkers in obesity patients (IGFBP-1, IGFBP-2, and PON-3), are not related to inflammation. Both IGFBP-1 and IGFBP-2 levels are known to be decreased in obesity patients,[32] which mainly has been related to insulin resistance.[17] PON-3 has been suggested to play an important role in protection against the detrimental effects of obesity,[33] and is involved in the metabolism of lipids as well as protection against atherosclerosis.[34]

In a recent paper, we described a high prevalence (61%) of subclinical cardiac dysfunction in obesity patients.[22] In the current study, we compared cardiovascular biomarkers between obesity patients with and without cardiac dysfunction to further investigate the underlying pathophysiology. While one may expect that the dissimilarities in cardiovascular biomarker

profile between obesity patients and non-obese controls may be comparable and even exaggerated between obesity patients with and without cardiac dysfunction, the opposite was found (as shown by Figure 1a compared to 1b). Herewith, these findings suggest that obesity patients with cardiac dysfunction do not just have a more extensive presence of abnormal underlying pathophysiological processes that play a role in obesity patients in general. On the contrary, our results suggest that processes reflected by the 5 biomarkers that were increased in obesity patients with versus without cardiac dysfunction may be relatively important factors.

Characteristics of these 5 biomarkers are mainly related to inflammation, atherosclerosis and insulin resistance. SELE[13,35] and TR-AP[36,37] are related to all three processes, while FAS[38,39] and CTSD[40,41] are linked to both inflammation and atherosclerosis. CTSZ is only related to inflammation. Of these 5 biomarkers increased in obesity patients with cardiac dysfunction, TR-AP stood out because, contrary to the other 4, it did not differ between the obesity patients and the non-obese controls. In other words, while our findings suggest that processes reflected by SELE, FAS, CTSD and CTSZ play a role in obesity patients in general and also in obesity patients with cardiac dysfunction, TR-AP appeared to be linked most specifically to obesity patients with cardiac dysfunction. TR-AP has been proposed before as a useful marker for screening and assessment of cardiovascular disease risk.[43] Our findings suggest that there may be such a role for this biomarker in obesity patients as well. Nevertheless, further research would be required to confirm this notion.

Finally, a multivariable model was developed to predict the presence of subclinical cardiac dysfunction in obesity patients. This elastic net model selected several biomarkers and clinical characteristics as the optimal set of predictors and had a very good AUC of 0.87 (95% CI:0.79-0.94, $p< 0.001$). While there was overlap with findings from the univariate analysis discussed above (SELE, FAS, TR-AP, and CTSD were identified by the univariate analysis too), other biomarkers were selected by the model as well. This selection of biomarkers further supported the hypothesis of an important role for the combination of inflammation, atherosclerosis and insulin resistance in the pathophysiology of cardiac dysfunction in obesity patients. OPN is a biomarker related to inflammation and insulin resistance,[44] whereas the other biomarkers have been associated with atherosclerosis (CHIT1,[18] OPG,[19] and t-PA[20]). Assessment of a well-chosen combination of biomarkers may be used to identify obese patients at relatively high risk of having subclinical cardiac dysfunction.

A broad range of processes potentially involved in the pathophysiology of cardiovascular disease in obesity has been described before,[45,46] a relatively important role for the combination of inflammation, atherosclerosis and insulin resistance therefore seems plausible. Previous studies already have shown a relation between these three processes and cardiac dysfunction in general patient populations (not specifically obese). The pivotal role of inflammation in the initiation and progression of cardiovascular disease has been extensively studied and is widely accepted,[47] Endothelial inflammation may cause coronary dysfunction and thereby myocardial fibrosis.[48] Atherosclerosis can lead to ischemia, which in its turn can lead to heart failure.[49] Insulin resistance is an independent risk factor for the development of cardiac dysfunction.[50] On the other hand, next to being linked to cardiac dysfunction, these three processes are also known to be independently related to obesity.[51,52] However, our study is the first in which the importance of inflammation, atherosclerosis and insulin resistance was shown in obesity patients with subclinical cardiac dysfunction.

Limitations

The assay we used to determine the biomarkers is designed as a biomarker discovery tool rather than being an approved clinical test. The clinical significance of the biomarker profiles needs to be elucidated. Our cohort predominantly consisted of female patients (70%). Moreover, although obesity is usually defined as a BMI ≥30 kg/m^2 all patients in our study had a BMI ≥35kg/m^2 because they were included at the outpatient clinic for screening for bariatric surgery (BMI ≥35kg/m^2 is a condition to qualify for bariatric surgery). Therefore, the conclusions may only be applied to morbidly obese patients and not to obesity patients in general. Also, although we selected patients without known cardiovascular disease, a relatively large proportion of patients did have cardiovascular risk factors such as diabetes and hypertension, which may also partly explain some of the biomarker differences between obesity patients and non-obese controls. Nevertheless, these risk factors were not different between the obesity patients with and without cardiac dysfunction, limiting the influence on differences in biomarker profiles between these patients. Finally, the sample size was relatively small. However, as mentioned before, the current study was the first to create a risk model for cardiac dysfunction in obesity patients without known cardiovascular disease with this cardiovascular biomarker panel consisting of 92 biomarkers, and we accounted for potential overfitting by applying the elastic net model.

CONCLUSIONS

In the current study, a multiplex immunoassay was used for the first time in obesity patients without known cardiovascular disease. This multiplex allowed assessment of 92 biomarkers covering a broad spectrum of processes potentially involved in cardiac dysfunction in obesity patients. Obesity patients without known cardiovascular disease have cardiovascular biomarker profiles that are clearly different from non-obese controls. Comparison of obesity patients with and without cardiac dysfunction suggested an important role for inflammation, atherosclerosis and insulin resistance in the underlying pathophysiology of cardiac dysfunction in obesity patients.

REFERENCES

1. Collaboration NCDRF. Trends in adult body-mass index in 200 countries from 1975 to 2014: a pooled analysis of 1698 population-based measurement studies with 19.2 million participants. Lancet 387(10026), 1377-1396 (2016).
2. Poirier P, Giles TD, Bray GA et al. Obesity and cardiovascular disease: pathophysiology, evaluation, and effect of weight loss: an update of the 1997 American Heart Association Scientific Statement on Obesity and Heart Disease from the Obesity Committee of the Council on Nutrition, Physical Activity, and Metabolism. Circulation 113(6), 898-918 (2006).
3. Bui AL, Horwich TB, Fonarow GC. Epidemiology and risk profile of heart failure. Nat Rev Cardiol 8(1), 30-41 (2011).
4. Webber L, Divajeva D, Marsh T et al. The future burden of obesity-related diseases in the 53 WHO European-Region countries and the impact of effective interventions: a modelling study. BMJ Open 4(7), e004787 (2014).
5. Ndumele CE, Coresh J, Lazo M et al. Obesity, subclinical myocardial injury, and incident heart failure. JACC Heart Fail 2(6), 600-607 (2014).
6. Benjamin EJ, Muntner P, Alonso A et al. Heart Disease and Stroke Statistics-2019 Update: A Report From the American Heart Association. Circulation 139(10), e56-e528 (2019).
7. Brouwers FP, Van Gilst WH, Damman K et al. Clinical risk stratification optimizes value of biomarkers to predict new-onset heart failure in a community-based cohort. Circ Heart Fail 7(5), 723-731 (2014).
8. Mueller C, Mcdonald K, De Boer RA et al. Heart Failure Association of the European Society of Cardiology practical guidance on the use of natriuretic peptide concentrations. Eur J Heart Fail 21(6), 715-731 (2019).
9. Mehra MR, Uber PA, Park MH et al. Obesity and suppressed B-type natriuretic peptide levels in heart failure. J Am Coll Cardiol 43(9), 1590-1595 (2004).
10. Alpert MA, Lavie CJ, Agrawal H, Kumar A, Kumar SA. Cardiac Effects of Obesity: PATHOPHYSIOLOGIC, CLINICAL, AND PROGNOSTIC CONSEQUENCES-A REVIEW. J Cardiopulm Rehabil Prev 36(1), 1-11 (2016).
11. Braunwald E. Biomarkers in heart failure. N Engl J Med 358(20), 2148-2159 (2008).
12. Dalzell JR, Cannon JA, Jackson CE, Lang NN, Gardner RS. Emerging biomarkers for heart failure: an update. Biomark Med 8(6), 833-840 (2014).
13. Ley K. The role of selectins in inflammation and disease. Trends Mol Med 9(6), 263-268 (2003).
14. Collaboration IRGCERF, Sarwar N, Butterworth AS et al. Interleukin-6 receptor pathways in coronary heart disease: a collaborative meta-analysis of 82 studies. Lancet 379(9822), 1205-1213 (2012).
15. Perkins LA, Anderson CJ, Novelli EM. Targeting P-selectin Adhesion Molecule in Molecular Imaging: P-selectin Expression as Valuable Imaging Biomarker of Inflammation in Cardiovascular Disease. J Nucl Med doi:10.2967/jnumed.118.225169 (2019).
16. Er LK, Wu S, Hsu LA, Teng MS, Sun YC, Ko YL. Pleiotropic Associations of RARRES2 Gene Variants and Circulating Chemerin Levels: Potential Roles of Chemerin Involved in the Metabolic and Inflammation-Related Diseases. Mediators Inflamm 2018 4670521 (2018).
17. Heald AH, Cruickshank JK, Riste LK et al. Close relation of fasting insulin-like growth factor binding protein-1 (IGFBP-1) with glucose tolerance and cardiovascular risk in two populations. Diabetologia 44(3), 333-339 (2001).
18. Guclu A, Yilmaz MI, Tokmak TT et al. Chitotriosidase as a novel biomarker of early atherosclerosis in hemodialysis patients. Hemodial Int 21(1), 41-46 (2017).
19. Venuraju SM, Yerramasu A, Corder R, Lahiri A. Osteoprotegerin as a predictor of coronary artery disease and cardiovascular mortality and morbidity. J Am Coll Cardiol 55(19), 2049-2061 (2010).
20. Ridker PM, Vaughan DE, Stampfer MJ, Manson JE, Hennekens CH. Endogenous tissue-type plasminogen activator and risk of myocardial infarction. Lancet 341(8854), 1165-1168 (1993).
21. Snelder SM, De Groot-De Laat LE, Biter LU et al. Cross-sectional and prospective follow-up study to detect early signs of cardiac dysfunction in obesity: protocol of the CARDIOBESE study. BMJ Open 8(12), e025585 (2018).
22. Snelder SM, De Groot-De Laat LE, Biter LU et al. Subclinical cardiac dysfunction in obesity patients is linked to autonomic dysfunction: findings from the CARDIOBESE study. ESC Heart Fail doi:10.1002/ehf2.12942 (2020).
23. Assarsson E, Lundberg M, Holmquist G et al. Homogenous 96-plex PEA immunoassay exhibiting high sensitivity, specificity, and excellent scalability. PLoS One 9(4), e95192 (2014).

24. Lundberg M, Eriksson A, Tran B, Assarsson E, Fredriksson S. Homogeneous antibody-based proximity extension assays provide sensitive and specific detection of low-abundant proteins in human blood. Nucleic Acids Res 39(15), e102 (2011).
25. Lang RM, Badano LP, Mor-Avi V et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. Eur Heart J Cardiovasc Imaging 16(3), 233-270 (2015).
26. Nagueh SF, Smiseth OA, Appleton CP et al. Recommendations for the Evaluation of Left Ventricular Diastolic Function by Echocardiography: An Update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. Eur Heart J Cardiovasc Imaging 17(12), 1321-1360 (2016).
27. Pascual M, Pascual DA, Soria F et al. Effects of isolated obesity on systolic and diastolic left ventricular function. Heart 89(10), 1152-1156 (2003).
28. Benjamini Y, Hochberg Y. Controlling the false discovery rate: a practical and powerful approach to multiple testing. J R Stat Soc Ser B Methodol 57 289–300 (1995).
29. Friedman J, Hastie T, Tibshirani R. Regularization Paths for Generalized Linear Models via Coordinate Descent. J Stat Softw 33(1), 1-22 (2010).
30. Nimptsch K, Konigorski S, Pischon T. Diagnosis of obesity and use of obesity biomarkers in science and clinical medicine. Metabolism 92 61-70 (2019).
31. Golia E, Limongelli G, Natale F et al. Inflammation and cardiovascular disease: from pathogenesis to therapeutic target. Curr Atheroscler Rep 16(9), 435 (2014).
32. Conover CA, Lee PD, Kanaley JA, Clarkson JT, Jensen MD. Insulin regulation of insulin-like growth factor binding protein-1 in obese and nonobese humans. J Clin Endocrinol Metab 74(6), 1355-1360 (1992).
33. Shih DM, Xia YR, Wang XP et al. Decreased obesity and atherosclerosis in human paraoxonase 3 transgenic mice. Circ Res 100(8), 1200-1207 (2007).
34. Shih DM, Yu JM, Vergnes L et al. PON3 knockout mice are susceptible to obesity, gallstone formation, and atherosclerosis. FASEB J 29(4), 1185-1197 (2015).
35. Lee CH, Kuo FC, Tang WH et al. Serum E-selectin concentration is associated with risk of metabolic syndrome in females. PLoS One 14(9), e0222815 (2019).
36. Huang YJ, Huang TW, Chao TY et al. Elevated serum tartrate-resistant acid phosphatase isoform 5a levels in metabolic syndrome. Oncotarget 8(44), 78144-78152 (2017).
37. Morisawa T, Nakagomi A, Kohashi K, Kusama Y, Shimizu W. Serum Tartrate-resistant Acid Phosphatase-5b Levels are Associated with the Severity and Extent of Coronary Atherosclerosis in Patients with Coronary Artery Disease. J Atheroscler Thromb 24(10), 1058-1068 (2017).
38. Nelson DP, Setser E, Hall DG et al. Proinflammatory consequences of transgenic fas ligand expression in the heart. J Clin Invest 105(9), 1199-1208 (2000).
39. Shimizu M, Fukuo K, Nagata S et al. Increased plasma levels of the soluble form of Fas ligand in patients with acute myocardial infarction and unstable angina pectoris. J Am Coll Cardiol 39(4), 585-590 (2002).
40. Hausmann M, Obermeier F, Schreiter K et al. Cathepsin D is up-regulated in inflammatory bowel disease macrophages. Clin Exp Immunol 136(1), 157-167 (2004).
41. Goncalves I, Hultman K, Duner P et al. High levels of cathepsin D and cystatin B are associated with increased risk of coronary events. Open Heart 3(1), e000353 (2016).
42. Nagler DK, Lechner AM, Oettl A et al. An enzyme-linked immunosorbent assay for human cathepsin X, a potential new inflammatory marker. J Immunol Methods 308(1-2), 241-250 (2006).
43. Janckila AJ, Lin HF, Wu YY et al. Serum tartrate-resistant acid phosphatase isoform 5a (TRACP5a) as a potential risk marker in cardiovascular disease. Clin Chim Acta 412(11-12), 963-969 (2011).
44. Nomiyama T, Perez-Tilve D, Ogawa D et al. Osteopontin mediates obesity-induced adipose tissue macrophage infiltration and insulin resistance in mice. J Clin Invest 117(10), 2877-2888 (2007).
45. Ebong IA, Goff DC, Jr., Rodriguez CJ et al. The relationship between measures of obesity and incident heart failure: the multi-ethnic study of atherosclerosis. Obesity (Silver Spring) 21(9), 1915-1922 (2013).
46. Aurigemma GP, De Simone G, Fitzgibbons TP. Cardiac remodeling in obesity. Circ Cardiovasc Imaging 6(1), 142-152 (2013).
47. Awan Z, Genest J. Inflammation modulation and cardiovascular disease prevention. Eur J Prev Cardiol 22(6), 719-733 (2015).
48. Paulus WJ, Tschope C. A novel paradigm for heart failure with preserved ejection fraction: comorbidities drive myocardial dysfunction and remodeling through coronary microvascular endothelial inflammation. J Am Coll Cardiol 62(4), 263-271 (2013).
49. Gheorghiade M, Sopko G, De Luca L et al. Navigating the crossroads of coronary artery disease and heart failure. Circulation 114(11), 1202-1213 (2006).

50. Jia G, Whaley-Connell A, Sowers JR. Diabetic cardiomyopathy: a hyperglycaemia- and insulin-resistance-induced heart disease. Diabetologia 61(1), 21-28 (2018).
51. Lumeng CN, Saltiel AR. Inflammatory links between obesity and metabolic disease. J Clin Invest 121(6), 2111-2117 (2011).
52. Packer M. Do most patients with obesity or type 2 diabetes, and atrial fibrillation, also have undiagnosed heart failure? A critical conceptual framework for understanding mechanisms and improving diagnosis and treatment. Eur J Heart Fail 22(2), 214-227 (2020).

Supplementary Table 1: List of abbreviations of all 92 biomarkers

Abbreviation	Full name
AP-N	Aminopeptidase N
AZU	Azurocidin
BLM hydrolase	Bleomycin hydrolase
CCL15	C-C motif chemokine 15
CCL16	C-C motif chemokine 16
CCL24	C-C motif chemokine 24
CXCL16	C-X-C motif chemokine 16
CDH5	Cadherin-5
CPA1	Carboxypeptidase A1
CPB1	Carboxypeptidase B
CASP-3	Caspase-3
CTSD	Cathepsin D
CTSZ	Cathepsin Z
ALCAM	CD166 antigen
CHI3L1	Chitinase-3-like protein 1
CHIT1	Chitotriosidase-1
COL1A1	Collagen alpha-1(I) chain
CD93	Complement component C1q receptor
CNTN1	Contactin-1
CSTB	Cystatin-B
SELE	E-selectin
PI3	Elafin
EPHB4	Ephrin type-B receptor 4
EGFR	Epidermal growth factor receptor
Ep-CAM	Epithelial cell adhesion molecule
FABP4	Fatty acid-binding protein, adipocyte
Gal-3	Galectin-3
Gal-4	Galectin-4
GRN	Granulins
GDF-15	Growth/differentiation factor 15
IGFBP-1	Insulin-like growth factor-binding protein 1
IGFBP-2	Insulin-like growth factor-binding protein 2
IGFBP-7	Insulin-like growth factor-binding protein 7
ITGB2	Integrin beta-2
ICAM-2	Intercellular adhesion molecule 2
IL-1RT1	Interleukin-1 receptor type 1
IL-1RT2	Interleukin-1 receptor type 2
IL-17RA	Interleukin-17 receptor A
IL-18BP	Interleukin-18-binding protein
IL2-RA	Interleukin-2 receptor subunit alpha
IL-6RA	Interleukin-6 receptor subunit alpha
JAM-A	Junctional adhesion molecule A
KLK6	Kallikrein-6
LDL receptor	Low-density lipoprotein receptor
LTBR	Lymphotoxin-beta receptor
MEPE	Matrix extracellular phosphoglycoprotein
MMP-2	Matrix metalloproteinase-2
MMP-3	Matrix metalloproteinase-3
MMP-9	Matrix metalloproteinase-9
TIMP4	Metalloproteinase inhibitor 4
MCP-1	Monocyte chemotactic protein 1
PRTN3	Myeloblastin

MPO	Myeloperoxidase
MB	Myoglobin
NT-proBNP	N-terminal prohormone brain natriuretic peptide
Notch 3	Neurogenic locus notch homolog protein 3
OPN	Osteopontin
OPG	Osteoprotegerin
SELP	P-selectin
PON3	Paraoxonase
PGLYRP1	Peptidoglycan recognition protein 1
PLC	Perlecan
PAI	Plasminogen activator inhibitor 1
PECAM-1	Platelet endothelial cell adhesion molecule
GP6	Platelet glycoprotein VI
PDGF subunit A	Platelet-derived growth factor subunit A
PCSK9	Proprotein convertase subtilisin/kexin type 9
DLK-1	Protein delta homolog 1
PSP-D	Pulmonary surfactant-associated protein D
RETN	Resistin
RARRES2	Retinoic acid receptor responder protein 2
CD163	Scavenger receptor cysteine-rich type 1 protein M130
SCGB3A2	Secretoglobin family 3A member 2
SPON1	Spondin-1
ST2	ST2 protein
TR-AP	Tartrate-resistant acid phosphatase type 5
TFPI	Tissue factor pathway inhibitor
t-PA	Tissue-type plasminogen activator
TR	Transferrin receptor protein 1
TFF3	Trefoil factor 3
TLT-2	Trem-like transcript 2 protein
TNFSF13B	Tumor necrosis factor ligand superfamily member 13B
TNF-R1	Tumor necrosis factor receptor 1
TNF-R2	Tumor necrosis factor receptor 2
TNFRSF10C	Tumor necrosis factor receptor superfamily member 10C
TNFRSF14	Tumor necrosis factor receptor superfamily member 14
FAS	Tumor necrosis factor receptor superfamily member 6
AXL	Tyrosine-protein kinase receptor UFO
SHPS-1	Tyrosine-protein phosphatase non-receptor type substrate 1
U-PAR	Urokinase plasminogen activator surface receptor
uPA	Urokinase-type plasminogen activator
vWF	von Willebrand factor

10

Chapter 10

Cardiovascular biomarker profiles in obesity and relation with normalization of subclinical cardiac dysfunction after bariatric surgery

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Submitted

ABSTRACT

Aims

Weight loss and associated metabolic improvement achieved by bariatric surgery have a positive impact on heart morphology and function. However, little is known about the physiology behind this improvement, and it remains unknown why in some patients cardiac function does not normalize after bariatric surgery. Therefore, we aimed to gain insight into the underlying pathophysiology of cardiac dysfunction in obesity patients and the improvement of cardiac function after weight loss.

Methods

This is a longitudinal study in which 92 cardiovascular biomarkers were measured by multiplex immunoassays in obesity patients without known cardiovascular disease before, and one year after bariatric surgery.

Results

Out of 100 eligible patients, 72 patients completed the one year follow-up. A total of 72 (78%) biomarkers changed significantly after bariatric surgery. The biomarkers with the highest relative changes represented mainly processes linked to insulin resistance and inflammation. Subclinical cardiac dysfunction persisted in 50% of the patients. In these patients, baseline values of 10 biomarkers were different from values in patients with normalization of cardiac function. Most of these biomarkers were linked to inflammation or atherosclerosis. Finally, a model was developed to investigate the relation between changes of the biomarkers and persistent subclinical cardiac dysfunction. Seven biomarkers, were retained in this model, mainly linked to inflammation, atherosclerosis, and hypercoagulability.

Conclusion

One year after bariatric surgery, the majority (78%) of cardiovascular biomarkers changed, pointing at modulation of insulin resistance and inflammation. Baseline levels of 10 biomarkers, as well as change in 7 biomarkers, were related to persistent subclinical cardiac dysfunction post-surgery. Thus, circulating biomarkers may help to identify patients at elevated cardiovascular risk due to lack of improvement of cardiac function after bariatric surgery.

INTRODUCTION

Obesity has reached epidemic proportions globally and the prevalence will continue to increase.[1,2] The risk of heart failure is known to be increased in obesity patients,[3] and subclinical cardiac dysfunction is even present in 60% of obesity patients without known cardiovascular disease.[4] Bariatric surgery has proven to be an effective and safe treatment option resulting in large long-term weight loss.[5,6] Weight loss and associated metabolic improvement achieved by bariatric surgery have a positive impact on heart morphology even in obesity patients without heart failure,[7] and subclinical cardiac dysfunction improves in 50% of the patients one-year post-bariatric surgery.[8] However, little is known about the physiology behind this improvement, and it remains unknown why in some patients cardiac function does not normalize.

Currently, extensive body of evidence is available on the role of circulating proteins in cardiovascular disease. These proteins reflect several biological processes that also have been hypothesized to play an important role in cardiac dysfunction in obesity patients.[9] Moreover, the use of multiplex immunoassays that determine a broad spectrum of biomarkers is gaining momentum in medical science.[10] In the current study, we investigate changes in cardiovascular biomarker profiles one year after bariatric surgery. Herewith we aim to gain insight into the underlying pathophysiology of cardiac dysfunction in obesity patients and the improvement of cardiac function after weight loss.

METHODS

Study design and study group

The protocol of the CARDIOBESE study has been described before.[11] In short, this study is a multicentre, prospective study in which 100 obesity patients who were referred for bariatric surgery were enrolled. Patients were included if they were between 35 and 65 years old with a body mass index (BMI) of ≥35 kg/m^2. Patients with a suspicion of or known cardiovascular disease were excluded. Bariatric surgery included either a gastric sleeve, gastric bypass, or a mini-gastric bypass. Patients were seen before and one year after bariatric-surgery. The study protocol was approved by the ethics committee and written informed consent was obtained from all participants.[11] All participants underwent a transthoracic echocardiogram and laboratory tests.

The presence or absence of subclinical cardiac dysfunction in the 100 obesity patients of the CARDIOBESE-study has been described in detail before.[4] In short, cardiac dysfunction was defined as either a reduced left ventricular (LV) ejection fraction,[12] a decreased global longitudinal strain (GLS), diastolic dysfunction,[13] ventricular arrhythmia or an increased BNP

or hs Troponin I. Of the predefined studied parameters, a decreased GLS (<17%) was by far the most abundant, in 57 patients; one had diastolic dysfunction without an available GLS, one had a normal GLS but an increased BNP (49 pmol/L, normal value <30 pmol/L), and one had a positive hs Troponin I. One patient with cardiac dysfunction was diagnosed with acromegaly after inclusion and was excluded from further analysis, leaving 59 obesity patients with versus 40 without subclinical cardiac dysfunction.

Laboratory procedures

Non-fasting blood samples were collected before- and one-year after bariatric-surgery. Blood samples were processed and stored at -80°C within two hours after collection. Biomarker measurements were subsequently performed in one batch. Serum aliquots were thawed and randomly divided over three microwell plates. Internal controls were added to each plate. Plates were frozen at -80°C and shipped on dry ice to Olink Proteomics AB, Uppsala, Sweden. The cardiovascular panel III of the Olink Multiplex platform for biomarkers was used for analysis. The kits are based on the proximity extension assay technology, where 92 oligonucleotide-labelled antibody probe pairs are allowed to bind to their respective target in the sample. The proximity extension assay technique shows exceptionally high specificity and sensitivity.[14,15] The biomarkers are delivered in normalized protein expression units (NPX), which are relative units. Therefore, NPX values for 2 different analyses/proteins are not directly comparable. They are expressed on a log2 scale where 1 unit higher NPX value represents a doubling of the measured protein concentrations. NPX were converted into a linear scale: 2NPX= linear NPX. Abbreviations of all 92 biomarkers are listed in Supplementary Table 1.

Transthoracic echocardiography

Two-dimensional grayscale harmonic images were obtained in the left lateral decubitus position using a commercially available ultrasound system (EPIQ 7, Philips, Best, the Netherlands), equipped with a broadband (1-5MHz) X5-1 transducer. All acquisitions and measurements were performed according to current guidelines.[12,13]

To optimize speckle tracking echocardiography, apical images were obtained at a frame rate of 60 to 80 frames/s. Three consecutive cardiac cycles were acquired from all apical views. Subsequently, these cycles were transferred to a QLAB workstation (version 10.2, Philips, Best, the Netherlands) for off-line speckle tracking analysis. Peak regional longitudinal strain was measured in 17 myocardial regions and a weighted mean was used to derive global longitudinal strain (GLS).

Statistical analysis

Patients who completed the one year follow-up were included in the analysis. The distributions of the variables were tested for normality by the Shapiro–Wilk test. Continuous variables with normal distributions were expressed as mean ± standard deviation, those with skewed distributions as median and interquartile range, and categorical variables as counts and percentages. Missing values were omitted (between 0-2%, none of the biomarkers were missing). To compare variables pre- and one-year post-surgery, paired t-tests were used for continuous variables with normal distributions, the nonparametric Wilcoxon signed-rank test for variables with non-normal distributions, and the McNemar test for categorical variables.

Relative changes of all biomarkers from pre- to one year post-bariatric surgery were calculated by subtracting the median value of biomarkers pre-surgery from the value of the biomarkers post-surgery, and dividing the obtained difference by the median value of the biomarkers pre-surgery. In addition to aforementioned exploration, change between pre- and post-surgery was analysed by univariable linear mixed modelling for each of the biomarkers, with moment of measurement (baseline and follow-up) as the independent variable, and all of the biomarkers entered consecutively as the dependent variable. Random intercepts and slopes were used to account for presence of two biomarker measurements per patient. The Benjamini–Hochberg procedure, with a 5% false discovery rate, was used to correct for multiple testing.[16]

In the subset of obesity patients with pre-surgery cardiac dysfunction, baseline biomarker levels in those with normalization of cardiac function were compared to levels in those with persisting cardiac dysfunction post-surgery with the Mann-Whitney U test. Again, the Benjamini-Hochberg procedure was used to correct for multiple testing. A multiple biomarker model was than constructed to investigate the relation between changes in biomarkers and persistent cardiac dysfunction post-surgery. In order to select the subset of biomarkers that carries the best predictive value for cardiac dysfunction and, at the same time, to reduce the risk of overfitting (which is especially important in the setting where the number of events is low relative to the number of predictors), elastic net logistic regression was used. This method combines two established shrinkage-methods: Ridge regression and Lasso regression.[17] Delta's (value post-surgery minus value pre-surgery) of all individual biomarkers were used simultaneously as input for this model. The discriminative ability of the resulting model was investigated by calculating the area under the receiver operating curve (AUC). Odds ratios of the Z-scores were reported. A two-tailed p-value of <0.05 was considered statistically significant unless otherwise reported. Statistical analyses were performed with SPSS version 25.0 or higher (SPSS Inc., Chicago, USA) or R 3.0.3 (glmnet R package).

RESULTS

Changes in clinical characteristics from before to one year after bariatric-surgery

A total of 85 patients underwent bariatric surgery and 72 patients completed the one-year follow-up (Figure 1). Fifteen patients did not undergo bariatric surgery because of various reasons, but mostly because of disapproval by the psychologist or because they withdrew themselves from surgery. Incomplete follow-up was mainly because of withdrawal from follow-up. There was a significant decrease in weight, BMI, systolic blood pressure, and heart rate post-bariatric surgery (Table 1). Also, the prevalence of comorbidities such as diabetes mellitus, hypertension, obstructive sleep apnoea syndrome, and use of medication decreased.

Changes in cardiovascular biomarkers levels from before to one year after bariatric surgery

The relative changes of all 92 biomarkers from before to one year after bariatric surgery are displayed in Figure 2 and Supplementary Table 2. A total of 72 (78%) biomarkers were significantly different: 52 (56%) biomarkers decreased, and 20 (22%) increased after bariatric surgery. The biomarkers with the highest relative changes were Insulin-like growth factor-binding protein 1 (IGFBP-1) (increase of 175%, $p<0.001$), Integrin beta-2 (ITGBP2) (increase

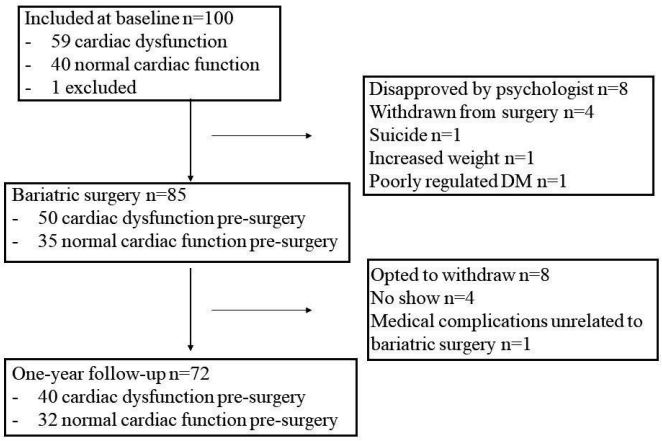

Figure 1: Flow-chart of follow-up
DM= diabetes mellitus

of 139%, p<0.001), Epithelial cell adhesion molecule (Ep-CAM) (increase of 90%, p<0.001), Osteopontin (OPN) (increase of 59%, p<0.001), N-terminal prohormone brain natriuretic peptide (NT-proBNP) (increase of 58%, p=0.01), and Insulin-like growth factor-binding protein 2 (IGFBP-2) (decrease of -58%, p<0.001).

Table 1: Clinical characteristics of the study population. Changes in obesity patients from pre- to 1 year post-bariatric surgery.

	Pre-surgery (n=72)	**Post-surgery (n=72)**	**p-value**
General characteristics			
Age (years)	48 (43-54)		
Female (%)	54 (75%)		
Physical examination			
Weight (kg)	122 [113-133]	83 [74-91]	**<0.001**
BMI (kg/m^2)	41 [39-46]	28 [25-31]	**<0.001**
Systolic BP (mmHg)	146 ± 21	133 ± 20	**0.003**
Diastolic BP (mmHg)	79 [73-88]	80 [75-86]	0.18
Heart rate (bpm)	80 [73-86]	65 [57-71]	**<0.001**
Comorbidity			
Diabetes Mellitus (%)	16 (22%)	6 (8%)	**0.002**
Hypertension (%)	24 (33%)	12 (17%)	**0.035**
Hypercholesterolemia (%)	15 (21%)	8 (11%)	0.09
Current smoking (%)	11 (15%)	3 (6%)	0.18
COPD (%)	4 (6%)	0	0.13
OSAS (%)	8 (11%)	0	**0.008**
Medication			
Beta-blockers (%)	5 (7%)	3 (4%)	0.63
ACE inhibitors / ARBs (%)	11 (15%)	8 (11%)	**0.012**
Calcium channel blockers (%)	6 (8%)	5 (7%)	0.66
Statins (%)	16 (22%)	9 (13%)	**0.039**
Diuretics (%)	13 (18%)	8 (11%)	0.18
Insulin (%)	5 (7%)	4 (6%)	0.56
Oral anti-diabetics (%)	10 (14%)	4 (6%)	**0.031**

Values represent mean ± SD, median [Q1-Q3] or n (%).

P-values displayed were analysed by the paired Student's t-test for continuous variables with normal distributions, the Wilcoxon signed-rank test for variables with non-normal distributions, and the McNemar test for categorical variables.

BMI= body mass index, **BP**= blood pressure, **COPD**= chronic obstructive pulmonary disease, **OSAS**= obstructive sleep apnoea syndrome**, ACE=** angiotensin-converting enzyme, **ARBs**= angiotensin II receptor blockers

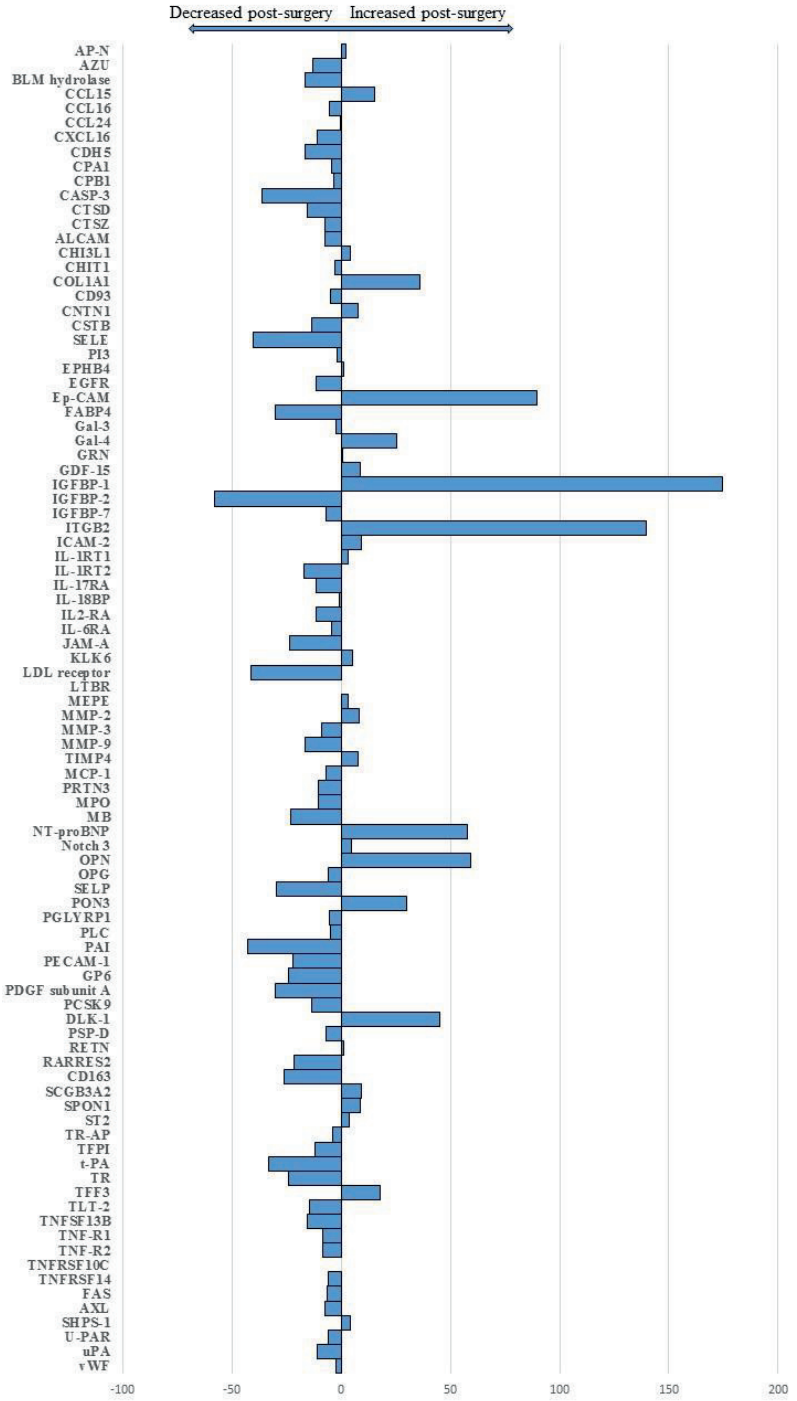

Figure 2: Graphical representation of the relative changes of all 92 biomarkers, pre- and post-bariatric surgery.

* significant after Benjamini–Hochberg correction

Comparison of changes in biomarkers levels in patients with versus without normalization of cardiac function after bariatric surgery

59 obesity patients (60%) showed subclinical cardiac dysfunction pre-surgery, 50 of these patients underwent bariatric surgery, and 40 completed the one year follow-up. Of these patients, 20 (50%) had a normal cardiac function, and 20 (50%) still had cardiac dysfunction one year after surgery. Table 2 shows that baseline values of 10 biomarkers were significantly decreased in patients with persisting cardiac dysfunction post-bariatric surgery as compared to patients with normalization of cardiac function: Bleomycin hydrolase (BLM hydrolase), Caspase-3 (CASP-3), Junctional adhesion molecule A (JAM-A), P-selectin (SELP), Platelet endothelial cell adhesion molecule (PECAM-1), Platelet glycoprotein VI (GP6), Platelet-derived growth factor subunit A (PDGF subunit A), Retinoic acid receptor responder protein 2 (RARRES2), Trem-like transcript 2 protein (TLT-2), and Tumor necrosis factor receptor superfamily member 14 (TNFRSF14).

Table 2: Comparison of baseline biomarker values in obesity patients with cardiac dysfunction pre-surgery and normalization of cardiac function one-year post-bariatric surgery vs. persisting cardiac dysfunction.

Abbreviation	Post-surgery normal cardiac function (n=20)	Post-surgery cardiac dysfunction (n=20)	p-value
AP-N	37.6 [34.2-41.5]	36.5 [32.6-40.1]	0.81
AZU	7.8 [6.4-10.4]	6.4 [5.3-7.8]	0.61
BLM hydrolase	9.9 [8.2-10.8]	7.4 [6.3-8.6]	**0.004***
CCL15	126 [108-178]	126 [110-183]	0.37
CCL16	155 [114-163]	150 [104-172]	0.97
CCL24	41 [28-68]	43 [23-60]	0.90
CXCL16	51 [40-59]	51 [48-61]	0.15
CDH5	26 [23-28]	26 [19-32]	0.95
CPA1	67 [52-99]	70 [49-98]	0.30
CPB1	61 [46-85]	67 [44-95]	0.31
CASP-3	750 [564-903]	295 [155-551]	**<0.001***
CTSD	8.3 [6.4-11.6]	7.9 [5.9-10.5]	0.67
CTSZ	59.5 [54.5-68.5]	60.1 [43.2-70.6]	0.67
ALCAM	232 [209-284]	222 [197-244]	0.91
CHI3L1	21.1 [17.6-30.0]	18.9 [13.5-27.2]	0.96
CHIT1	26.2 [20.0-38.1]	36.2 [14.9-48.5]	0.84
COL1A1	8.2 [7.3-9.7]	9.1 [8.0-10.8]	0.42
CD93	2200 [2002-2592]	2572 [2058-2955]	0.22
CNTN1	29.1 [24.3-33.5]	27.0 [24.7-32.0]	0.95
CSTB	26.8 [19.9-33.3]	21.5 [17.5-26.5]	**0.012**
SELE	7543 [5486-9772]	7098 [5587-10785]	0.38
PI3	5.7 [5.0-7.8]	5.8 [5.0-7.5]	0.41
EPHB4	49.6 [44.8-58.5]	51.4 [46.3-60.4]	0.57
EGFR	11.9 [11.1-13.3]	11.1 [10.1-12.7]	0.22
Ep-CAM	49.6 [33.5-75.1]	51.8 [26.3-126.9]	0.91
FABP4	109.2 [88.9-169.3]	104.2 [85.1-142.8]	0.59
Gal-3	11.5 [10.6-13.1]	11.0 [10.4-12.4]	0.96

Gal-4	19.7 [13.7-23.8]	18.0 [14.8-21.5]	0.72
GRN	60.1 [46.6-75.5]	59.8 [53.6-70.0]	0.42
GDF-15	72.0 [46.6-96.8]	54.4 [48.1-59.4]	0.85
IGFBP-1	10.6 [6.4-18.8]	9.5 [6.2-13.3]	0.63
IGFBP-2	159 [127-200]	170 [133-226]	0.22
IGFBP-7	296 [243-323]	275 [247-322]	0.22
ITGB2	58.4 [49.1-66.6]	54.6 [46.3-65.3]	0.37
ICAM-2	57.3 [48.3-66.9]	53.1 [44.0-69.8]	0.96
IL-1RT1	91.3 [78.1-104.4]	81.9 [74.8-101.4]	0.64
IL-1RT2	57.2 [45.5-62.8]	50.9 [40.9-54.3]	0.91
IL-17RA	24.2 [19.3-33.6]	20.4 [15.8-26.1]	0.06
IL-18BP	72.2 [65.5-80.9]	68.0 [64.6-86.3]	0.65
IL2-RA	15.3 [14.1-17.8]	12.4 [10.2-17.8]	**0.033**
IL-6RA	5523 [4150-6345]	4812 [3881-6379]	0.96
JAM-A	160 [116-205]	64 [29-103]	**<0.001***
KLK6	5.8 [5.1-7.3]	5.4 [4.6-6.0]	0.26
LDL receptor	27.4 [19.9-40.3]	25.2 [21.6-31.2]	0.82
LTBR	17.9 [15.5-19.4]	17.3 [14.5-19.0]	0.31
MEPE	74.8 [64.0-89.3]	65.7 [62.4-80.6]	0.58
MMP-2	16.6 [14.8-19.6]	18.8 [15.4-20.2]	**0.014**
MMP-3	183 [137-241]	210 [168-266]	**0.018**
MMP-9	68.7 [50.8-123.1]	60.5 [36.9-86.8]	0.06
TIMP4	12.3 [11.4-14.7]	14.2 [11.8-15.5]	0.62
MCP-1	20.2 [17.8-24.6]	17.5 [13.9-19.9]	0.33
PRTN3	19.6 [15.7-25.4]	17.4 [14.2-24.9]	0.92
MPO	12.0 [9.8-14.9]	12.0 [9.3-15.0]	0.57
MB	205 [170-267]	226 [193-286]	**0.014**
NT-proBNP	11.6 [7.2-15.2]	7.7 [4.4-16.6]	0.41
Notch 3	50.2 [41.6-54.4]	53.3 [42.0-63.4]	**0.018**
OPN	224 [196-271]	218 [165-275]	0.71
OPG	18.0 [14.4-22.6]	16.7 [14.0-19.7]	0.66
SELP	3845 [2941-4907]	2152 [1093-2368]	**<0.001***
PON3	70.7 [61.2-105.7]	91.4 [75.1-106.8]	0.10
PGLYRP1	205 [175-255]	177 [159-211]	0.23
PLC	308 [284-336]	315 [290-348]	0.40
PAI	95 [74-202]	73 [52-97]	0.05
PECAM-1	89 [77-116]	56 [31-63]	**<0.001***
GP6	23 [18-27]	12 [7-16]	**<0.001***
PDGF subunit A	36 [26-48]	19 [13-28]	**<0.001***
PCSK9	9.1 [7.5-11.8]	9.5 [7.7-10.4]	0.57
DLK-1	79 [60-105]	94 [70-105]	0.65
PSP-D	6.4 [5.4-9.9]	8.6 [5.6-10.8]	0.52
RETN	87 [76-108]	81 [71-98]	0.73
RARRES2	4849 [4614-5629]	4256 [4044-4862]	**0.003***
CD163	381 [305-455]	367 [251-407]	0.45
SCGB3A2	5.1 [4.3-6.5]	3.8[3.0-5.2]	0.08
SPON1	4.9 [4.4-5.3]	4.4 [4.0-5.9]	0.73
ST2	33.3 [22.3-40.1]	23.3 [15.3-27.8]	**0.047**
TR-AP	15.8 [14.4-22.0]	15.8 [13.5-18.3]	0.93
TFPI	792 [688-850]	742 [646-877]	0.50
t-PA	134 [97-167]	144 [96-170]	0.58
TR	65 [39-87]	62 [42-75]	0.70
TFF3	39 [33-46]	38 [28-45]	0.73
TLT-2	73 [64-88]	51 [42-62]	**<0.001***
TNFSF13B	170 [152-184]	174 [143-205]	0.54
TNF-R1	139 [128-155]	141 [128-174]	0.37
TNF-R2	68 [62-78]	65 [61-79]	0.67
TNFRSF10C	192 [132-253]	161 [98-199]	0.45
TNFRSF14	40 [37-46]	33 [29-36]	**0.004***
FAS	79 [73-94]	83 [75-89]	0.17

AXL	650 [547-763]	623 [544-809]	0.29
SHPS-1	16.3 [13.6-20.4]	13.6 [11.5-17.5]	0.62
U-PAR	54.4 [45.6-63.7]	48.8 [39.5-60.7]	0.53
uPA	31.0 [25.9-38.3]	30.7 [25.0-34.3]	0.36
vWF	211 [151-313]	176 [108-239]	0.85

Values represent median [Q1-Q3] of pre-surgery biomarker levels, all units are NPX.
P-values displayed were obtained with the Mann-Whitney U test.
* Significant after Benjamini–Hochberg correction

Association of changes in biomarker levels with presence of cardiac dysfunction post-bariatric surgery

The elastic net regression model selected the delta of the following set of biomarkers to optimally predict the presence of cardiac dysfunction post-surgery: Carboxypeptidase B (CPB1), CASP-3, SELP, GP6, PDGF subunit A, TLT-2, and von Willebrand factor (vWF) (Table 3). Figure 3 shows the ROC-curve for this model. The ability of this model to identify patients with cardiac dysfunction post-surgery was high, as shown by the AUC of 0.91 (95% CI: 0.82-0.99, $p<0.001$). The sensitivity of this model was 90%, specificity 80%, positive predictive value 82%, and negative predictive value 89%.

Table 3: Odds ratios of the Z-scores of the biomarkers selected by the elastic net regression

Biomarker	Odds ratio
CPB1	0.94
CASP3	1.06
SELP	1.01
GP6	1.12
PDGFsubunitA	1.03
TLT-2	1.22
vWF	1.03

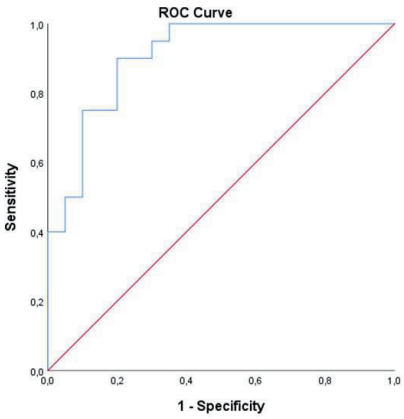

Figure 3: ROC-curve for the elastic net model. Biomarkers included are CPB1, CASP3, SELP, GP6, PDGF-subunit A, TLT2, and vWF.
AUC 0.91 (95% CI: 0.82-0.99, p<0.001)

DISCUSSION

A multiplex immunoassay was used for the first time to investigate changes of a broad spectrum of cardiovascular biomarkers in obesity patients from pre- to one-year post-bariatric surgery. The main findings are that the majority (78%) of the cardiovascular biomarkers changed, and reduced levels of 10 biomarkers pre-surgery were related to persistent subclinical cardiac dysfunction post-surgery. Furthermore, a multivariable model showed that changes in 7 biomarkers were associated with a lack of improvement of cardiac function.

A total of 72 biomarkers significantly changed from pre- to post-surgery, indicating alterations in a wide range of processes related to metabolic status and cardiovascular function. However, the biomarkers with the highest relative changes mainly represented processes linked to insulin resistance and inflammation. For example, IGFBP-1 is known to be lower in patients with impaired glucose tolerance.[18] IGFBP-1 increased after bariatric surgery, suggesting improved glucose tolerance. Also, circulating IGFBP-2 levels are associated with reduced insulin sensitivity in obesity patients,[19] and the decrease in IGFBP-2 post-surgery indicates an increase in insulin sensitivity. ITGBP2 is of crucial importance for leukocyte trafficking and immune cell activation, but interestingly plays a role in immune suppression as well. Consequently, dysfunctional or absent ITGPB-2 is linked not only to immune deficiency disease but also to

inflammatory disease, thereby contributing to both ends of the spectrum of immune-related diseases.[20] The increase of ITGBP2 post-bariatric surgery may indicate a change of balance towards a decrease of inflammation, however further research is needed to explore this finding. OPN showed a relatively large increase post-bariatric surgery. At first sight, a surprising finding since OPN has been suggested to play a key role in linking obesity to the development of insulin resistance by promoting inflammation.[21,22] Nevertheless, our result is in line with findings from other studies.[23,24] Changes in bone metabolism has been suggested as a potential source of enhanced OPN concentrations post-bariatric surgery, and not inflammation or insulin resistance.[23] Again, further research will be needed to explore this relation.
NT-proBNP also strongly increased post-bariatric surgery. NT-proBNP is known to be decreased in obesity patients, both with and without heart failure.[25] Although the reason for this remains incompletely understood, it is most likely due to lower release in obesity patients, rather than an increase in clearance.[26]

A distinctive aspect of the CARDIOBESE study is that different diagnostic techniques were used in parallel to simultaneously investigate a variety of cardiac and metabolic changes after bariatric surgery. This design allowed the correlation of changes in cardiovascular biomarkers with a (lack of) improvement of cardiac function.
Baseline values of 10 biomarkers were related to persistent cardiac dysfunction post-surgery. Most of these biomarkers are known to be linked to inflammation and/or atherosclerosis. JAM-A plays an important role in leukocyte transmigration and is upregulated on the early atherosclerotic endothelium.[27] PECAM-1 is upregulated in inflammatory conditions,[28] and is particularly evident in atherosclerotic lesions.[29] TNFRSF14 is a mediator of atherosclerosis by inducing inflammation.[30] TLT-2 is known to regulate inflammation through the integration of inflammatory signals.[31] RARRES2 has been associated with inflammation, obesity, and the metabolic syndrome.[32] SELP is expressed at the surface of platelets in activated endothelium and mediates atherosclerotic plaque progression.[33] Also, GP6 has been described to mediate platelet adhesion on atherosclerotic plaque tissues,[34] and PDGF subunit A is expressed by macrophages within atherosclerotic lesions.[35] The remaining 2 biomarkers do not have a clear relationship with either inflammation or atherosclerosis. CASP-3 is activated in the apoptotic cell and is known to be elevated after myocyte injury.[36] The normal physiological role of BLM hydrolase is unknown,[37] however, it has been suggested to play a part in inflammation by regulating the secretion of chemokines.[38]

Afterward a model was developed to investigate the relation between changes of the biomarkers from pre- to one-year post-surgery and the presence of subclinical cardiac dysfunction post-surgery. The change in 7 biomarkers selected by the multivariable model for the persistence of cardiac dysfunction post-surgery suggests that there is an important role for the combination of inflammatory status (reflected by CPB1,[39] TLT-2,[40] and vWF[41]), markers of atherosclerosis (reflected by SELP,[33] PDGF subunit A[35], GP6[34], CASP-3[36]) and hypercoagulability (reflected by CPB1[39], SELP[33], GP6[34], and vWF[41]).

The lack of improvement of inflammatory status is in line with other findings of our study. As mentioned before, it was shown that the highest relative changes from pre- to post-bariatric surgery were in biomarkers related to inflammation. Also, pre-bariatric surgery values of biomarkers related to inflammation were associated with persistence of cardiac dysfunction. Inflammation is known to be increased in obesity patients, and is has been suggested that heart failure with preserved ejection fraction in these patients is typically the result of systemic inflammation.[42] The increased size of adipocytes plays a decisive role in inflammation, because, to the extent that it increases in the adipose tissue, the production of adipocytokines increases, and this triggers a series of inflammation-related pathophysiological processes.[43]

Our study suggests that both increased baseline levels of markers of atherosclerosis and an increase of these levels over time may play a part in the persistence of cardiac dysfunction post-surgery. Obesity is a well-known major risk factor for atherosclerotic vascular disease. The exact mechanism behind this remains to be elucidated, but probably there is an important role for increased inflammation.[44] When atherosclerosis causes myocardial ischemia, it can lead to cardiac dysfunction.[45]

Hypercoagulability was related to the persistence of cardiac dysfunction in obesity patients after bariatric surgery as well. Hypercoagulability has previously been described in obese patients.46 Possible explanations for this are the actions of adipocytokines from adipose tissue, increased activity of the coagulation factors, decreased activity of the fibrinolytic system, increased inflammation, increased oxidative stress, endothelial dysfunction, and disturbances of lipids and glucose tolerance in association with the metabolic syndrome.[46] Also, the presence of platelet activation and hypercoagulability in heart failure has been well documented,[47] suggesting that indeed there may be a relation between hypercoagulability and cardiac dysfunction in obesity patients as found in our study.

Limitations

Because known cardiovascular disease was an exclusion criterion, only a minority of the patients had subclinical cardiac dysfunction. Also, the assay that was used to determine the biomarkers is designed as a biomarker discovery tool rather than being an approved clinical test. Finally for some of the investigated biomarkers more extensive evidence is available on their involvement in biological processes than for others.

CONCLUSIONS

The present study provides novel data on 92 cardiovascular biomarkers measured in obesity patients before and one year after bariatric surgery. The vast majority of these biomarkers changed one-year after bariatric-surgery, indicating alterations in a wide range of processes related to metabolic status and cardiovascular function. However, the biomarkers with the highest relative changes mainly represent processes linked to insulin resistance and inflammation.

This design of the study allowed correlation of changes in cardiovascular biomarkers with a (lack of) improvement of cardiac function after bariatric surgery. Most of the biomarkers whose baseline levels were associated with persistence of cardiac dysfunction are known to be linked to inflammation, while there also appeared to be a relatively important role for subclinical atherosclerosis. The relation between certain biomarkers and the persistence of subclinical cardiac dysfunction post-surgery again highlighted the importance of inflammation and atherosclerosis, with a potential role for hypercoagulability as well. This is in line with the knowledge that increased inflammatory status is known to have an important role in the induction of both atherosclerosis and hypercoagulability. Thus, although cardiac dysfunction in obesity seems to be a heterogeneous disorder, inflammation plays a central part.

REFERENCES

1. Global BMIMC, Di Angelantonio E, Bhupathiraju Sh N, et al. Body-mass index and all-cause mortality: individual-participant-data meta-analysis of 239 prospective studies in four continents. Lancet 2016;388:776-86.
2. Ward ZJ, Bleich SN, Cradock AL, et al. Projected U.S. State-Level Prevalence of Adult Obesity and Severe Obesity. N Engl J Med 2019;381:2440-50.
3. Kenchaiah S, Evans JC, Levy D, et al. Obesity and the risk of heart failure. N Engl J Med 2002;347:305-13.
4. Snelder SM, De Groot-de Laat LE, Biter LU, et al. Subclinical cardiac dysfunction in obesity patients is linked to autonomic dysfunction: findings from the CARDIOBESE study. ESC Heart Failure 2020.
5. DeMaria EJ. Bariatric surgery for morbid obesity. N Engl J Med 2007;356:2176-83.
6. Sjostrom L, Lindroos AK, Peltonen M, et al. Lifestyle, diabetes, and cardiovascular risk factors 10 years after bariatric surgery. N Engl J Med 2004;351:2683-93.
7. Vest AR, Heneghan HM, Agarwal S, Schauer PR, Young JB. Bariatric surgery and cardiovascular outcomes: a systematic review. Heart 2012;98:1763-77.
8. Snelder SM, Aga Y, de Groot-de Laat LE, et al. Cardiac Function Normalizes 1 Year After Bariatric Surgery in Half of the Obesity Patients with Subclinical Cardiac Dysfunction. Obesity Surgery 2021
9. Braunwald E. Biomarkers in heart failure. N Engl J Med 2008;358:2148-59.
10. Santema BT, Kloosterman M, Van Gelder IC, et al. Comparing biomarker profiles of patients with heart failure: atrial fibrillation vs. sinus rhythm and reduced vs. preserved ejection fraction. Eur Heart J 2018;39:3867-75.
11. Snelder SM, de Groot-de Laat LE, Biter LU, et al. Cross-sectional and prospective follow-up study to detect early signs of cardiac dysfunction in obesity: protocol of the CARDIOBESE study. BMJ Open 2018;8:e025585.
12. Lang RM, Badano LP, Mor-Avi V, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. Eur Heart J Cardiovasc Imaging 2015;16:233-70.
13. Nagueh SF, Smiseth OA, Appleton CP, et al. Recommendations for the Evaluation of Left Ventricular Diastolic Function by Echocardiography: An Update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. Eur Heart J Cardiovasc Imaging 2016;17:1321-60.
14. Assarsson E, Lundberg M, Holmquist G, et al. Homogenous 96-plex PEA immunoassay exhibiting high sensitivity, specificity, and excellent scalability. PLoS One 2014;9:e95192.
15. Lundberg M, Eriksson A, Tran B, Assarsson E, Fredriksson S. Homogeneous antibody-based proximity extension assays provide sensitive and specific detection of low-abundant proteins in human blood. Nucleic Acids Res 2011;39:e102.
16. Benjamini Y, Hochberg Y. Controlling the false discovery rate: a practical and powerful approach to multiple testing. J R Stat Soc Ser B Methodol 1995;57:289–300.
17. Friedman J, Hastie T, Tibshirani R. Regularization Paths for Generalized Linear Models via Coordinate Descent. J Stat Softw 2010;33:1-22.
18. Heald AH, Cruickshank JK, Riste LK, et al. Close relation of fasting insulin-like growth factor binding protein-1 (IGFBP-1) with glucose tolerance and cardiovascular risk in two populations. Diabetologia 2001;44:333-9.
19. Yau SW, Harcourt BE, Kao KT, et al. Serum IGFBP-2 levels are associated with reduced insulin sensitivity in obese children. Clin Obes 2018;8:184-90.
20. Fagerholm SC, Guenther C, Llort Asens M, Savinko T, Uotila LM. Beta2-Integrins and Interacting Proteins in Leukocyte Trafficking, Immune Suppression, and Immunodeficiency Disease. Front Immunol 2019;10:254.
21. Nomiyama T, Perez-Tilve D, Ogawa D, et al. Osteopontin mediates obesity-induced adipose tissue macrophage infiltration and insulin resistance in mice. J Clin Invest 2007;117:2877-88.
22. Kiefer FW, Zeyda M, Gollinger K, et al. Neutralization of osteopontin inhibits obesity-induced inflammation and insulin resistance. Diabetes 2010;59:935-46.
23. Riedl M, Vila G, Maier C, et al. Plasma osteopontin increases after bariatric surgery and correlates with markers of bone turnover but not with insulin resistance. J Clin Endocrinol Metab 2008;93:2307-12.

24. Schaller G, Aso Y, Schernthaner GH, et al. Increase of osteopontin plasma concentrations after bariatric surgery independent from inflammation and insulin resistance. Obes Surg 2009;19:351-6.
25. Mehra MR, Uber PA, Park MH, et al. Obesity and suppressed B-type natriuretic peptide levels in heart failure. J Am Coll Cardiol 2004;43:1590-5.
26. Mueller C, McDonald K, de Boer RA, et al. Heart Failure Association of the European Society of Cardiology practical guidance on the use of natriuretic peptide concentrations. Eur J Heart Fail 2019;21:715-31.
27. Tokat B, Kurt O, Bugra Z, Ozturk O, Yilmaz-Aydogan H. Investigation of the monocyte diapedesis-related LFA-1 and JAM-A gene variants in Turkish coronary heart disease patients. Meta Gene 2014;2:1-10.
28. Caligiuri G. Mechanotransduction, immunoregulation, and metabolic functions of CD31 in cardiovascular pathophysiology. Cardiovasc Res 2019;115:1425-34.
29. Tzima E, Irani-Tehrani M, Kiosses WB, et al. A mechanosensory complex that mediates the endothelial cell response to fluid shear stress. Nature 2005;437:426-31.
30. Lee WH, Kim SH, Lee Y, et al. Tumor necrosis factor receptor superfamily 14 is involved in atherogenesis by inducing proinflammatory cytokines and matrix metalloproteinases. Arterioscler Thromb Vasc Biol 2001;21:2004-10.
31. Ford JW, McVicar DW. TREM and TREM-like receptors in inflammation and disease. Curr Opin Immunol 2009;21:38-46.
32. Er LK, Wu S, Hsu LA, Teng MS, Sun YC, Ko YL. Pleiotropic Associations of RARRES2 Gene Variants and Circulating Chemerin Levels: Potential Roles of Chemerin Involved in the Metabolic and Inflammation-Related Diseases. Mediators Inflamm 2018;2018:4670521.
33. Bertrand MJ, Tardif JC. Inflammation and beyond: new directions and emerging drugs for treating atherosclerosis. Expert Opin Emerg Drugs 2017;22:1-26.
34. Bigalke B, Langer H, Geisler T, Lindemann S, Gawaz M. Platelet glycoprotein VI: a novel marker for acute coronary syndrome. Semin Thromb Hemost 2007;33:179-84.
35. Ricci C, Ferri N. Naturally occurring PDGF receptor inhibitors with potential anti-atherosclerotic properties. Vascul Pharmacol 2015;70:1-7.
36. Kim M, Lorinsky MK, Gold CA, et al. Usefulness of Circulating Caspase-3 p17 and Caspase-1 p20 Peptides and Cardiac Troponin 1 During Cardioplegia to Gauge Myocardial Preservation. Am J Cardiol 2019;123:899-904.
37. Crnovcic I, Gan F, Yang D, Dong LB, Schultz PG, Shen B. Activities of recombinant human bleomycin hydrolase on bleomycins and engineered analogues revealing new opportunities to overcome bleomycin-induced pulmonary toxicity. Bioorg Med Chem Lett 2018;28:2670-4.
38. Riise R, Odqvist L, Mattsson J, et al. Bleomycin hydrolase regulates the release of chemokines important for inflammation and wound healing by keratinocytes. Sci Rep 2019;9:20407.
39. Edginton S, Hitchon C, Froese W, El-Gabalawy H. Effects of Rituximab and Infliximab Treatment on Carboxypeptidase B and Its Substrates in RA Synovium. J Rheumatol 2016;43:846-54.
40. Hashiguchi M, Kobori H, Ritprajak P, Kamimura Y, Kozono H, Azuma M. Triggering receptor expressed on myeloid cell-like transcript 2 (TLT-2) is a counter-receptor for B7-H3 and enhances T cell responses. Proc Natl Acad Sci U S A 2008;105:10495-500.
41. Kawecki C, Lenting PJ, Denis CV. von Willebrand factor and inflammation. J Thromb Haemost 2017;15:1285-94.
42. Packer M. Do most patients with obesity or type 2 diabetes, and atrial fibrillation, also have undiagnosed heart failure? A critical conceptual framework for understanding mechanisms and improving diagnosis and treatment. Eur J Heart Fail 2020;22:214-27.
43. Van Gaal LF, Mertens IL, De Block CE. Mechanisms linking obesity with cardiovascular disease. Nature 2006;444:875-80.
44. Lovren F, Teoh H, Verma S. Obesity and atherosclerosis: mechanistic insights. Can J Cardiol 2015;31:177-83.
45. Heusch G, Libby P, Gersh B, et al. Cardiovascular remodelling in coronary artery disease and heart failure. Lancet 2014;383:1933-43.
46. Campello E, Zabeo E, Radu CM, et al. Hypercoagulability in overweight and obese subjects who are asymptomatic for thrombotic events. Thromb Haemost 2015;113:85-96.
47. Kim JH, Shah P, Tantry US, Gurbel PA. Coagulation Abnormalities in Heart Failure: Pathophysiology and Therapeutic Implications. Curr Heart Fail Rep 2016;13:319-28.

Supplementary Table 1: List of abbreviations of all 92 biomarkers

Abbreviation	Full name
AP-N	Aminopeptidase N
AZU	Azurocidin
BLM hydrolase	Bleomycin hydrolase
CCL15	C-C motif chemokine 15
CCL16	C-C motif chemokine 16
CCL24	C-C motif chemokine 24
CXCL16	C-X-C motif chemokine 16
CDH5	Cadherin-5
CPA1	Carboxypeptidase A1
CPB1	Carboxypeptidase B
CASP-3	Caspase-3
CTSD	Cathepsin D
CTSZ	Cathepsin Z
ALCAM	CD166 antigen
CHI3L1	Chitinase-3-like protein 1
CHIT1	Chitotriosidase-1
COL1A1	Collagen alpha-1(I) chain
CD93	Complement component C1q receptor
CNTN1	Contactin-1
CSTB	Cystatin-B
SELE	E-selectin
PI3	Elafin
EPHB4	Ephrin type-B receptor 4
EGFR	Epidermal growth factor receptor
Ep-CAM	Epithelial cell adhesion molecule
FABP4	Fatty acid-binding protein, adipocyte
Gal-3	Galectin-3
Gal-4	Galectin-4
GRN	Granulins
GDF-15	Growth/differentiation factor 15
IGFBP-1	Insulin-like growth factor-binding protein 1
IGFBP-2	Insulin-like growth factor-binding protein 2
IGFBP-7	Insulin-like growth factor-binding protein 7
ITGB2	Integrin beta-2
ICAM-2	Intercellular adhesion molecule 2
IL-1RT1	Interleukin-1 receptor type 1
IL-1RT2	Interleukin-1 receptor type 2
IL-17RA	Interleukin-17 receptor A
IL-18BP	Interleukin-18-binding protein
IL2-RA	Interleukin-2 receptor subunit alpha
IL-6RA	Interleukin-6 receptor subunit alpha
JAM-A	Junctional adhesion molecule A
KLK6	Kallikrein-6
LDL receptor	Low-density lipoprotein receptor
LTBR	Lymphotoxin-beta receptor
MEPE	Matrix extracellular phosphoglycoprotein
MMP-2	Matrix metalloproteinase-2
MMP-3	Matrix metalloproteinase-3
MMP-9	Matrix metalloproteinase-9
TIMP4	Metalloproteinase inhibitor 4
MCP-1	Monocyte chemotactic protein 1
PRTN3	Myeloblastin

MPO	Myeloperoxidase
MB	Myoglobin
NT-proBNP	N-terminal prohormone brain natriuretic peptide
Notch 3	Neurogenic locus notch homolog protein 3
OPN	Osteopontin
OPG	Osteoprotegerin
SELP	P-selectin
PON3	Paraoxonase
PGLYRP1	Peptidoglycan recognition protein 1
PLC	Perlecan
PAI	Plasminogen activator inhibitor 1
PECAM-1	Platelet endothelial cell adhesion molecule
GP6	Platelet glycoprotein VI
PDGF subunit A	Platelet-derived growth factor subunit A
PCSK9	Proprotein convertase subtilisin/kexin type 9
DLK-1	Protein delta homolog 1
PSP-D	Pulmonary surfactant-associated protein D
RETN	Resistin
RARRES2	Retinoic acid receptor responder protein 2
CD163	Scavenger receptor cysteine-rich type 1 protein M130
SCGB3A2	Secretoglobin family 3A member 2
SPON1	Spondin-1
ST2	ST2 protein
TR-AP	Tartrate-resistant acid phosphatase type 5
TFPI	Tissue factor pathway inhibitor
t-PA	Tissue-type plasminogen activator
TR	Transferrin receptor protein 1
TFF3	Trefoil factor 3
TLT-2	Trem-like transcript 2 protein
TNFSF13B	Tumor necrosis factor ligand superfamily member 13B
TNF-R1	Tumor necrosis factor receptor 1
TNF-R2	Tumor necrosis factor receptor 2
TNFRSF10C	Tumor necrosis factor receptor superfamily member 10C
TNFRSF14	Tumor necrosis factor receptor superfamily member 14
FAS	Tumor necrosis factor receptor superfamily member 6
AXL	Tyrosine-protein kinase receptor UFO
SHPS-1	Tyrosine-protein phosphatase non-receptor type substrate 1
U-PAR	Urokinase plasminogen activator surface receptor
uPA	Urokinase-type plasminogen activator
vWF	von Willebrand factor

Supplementary Table 2: Comparison of all biomarkers pre- and post-bariatric surgery

Abbreviation	Pre-surgery (n=72)	Post-surgery (n=72)	Relative changes	p-value
AP-N	36.6 [33.1-41.8]	37.4 [33.3-42.3]	2.2%	0.27
AZU	6.1 [5.0-8.0]	5.3 [4.6-6.5]	-13.1%	**<0.001***
BLM hydrolase	8.0 [6.7-9.5]	6.7 [5.4-7.8]	-16.3%	**<0.001***
CCL15	117 [103-154]	135 [115-172]	15.3%	0.75
CCL16	126 [91-158]	119 [92-147]	-5.6%	**<0.001***
CCL24	40.9 [24.4-67.5]	40.8 [26.4-69.0]	-0.2%	0.75
CXCL16	48.2 [43.2-55.9]	43.0 [38.8-49.9]	-10.8%	**<0.001***
CDH5	26.1 [22.0-29.7]	21.8 [18.9-25.9]	-16.5%	**<0.001***
CPA1	74.1 [51.3-96.8]	70.7 [53.3-102.6]	-4.6%	0.92
CPB1	65.5 [45.4-87.2]	63.2 [49.0-89.8]	-3.5%	0.26
CASP-3	529 [335-751]	336 [198-532]	-36.5%	**<0.001***
CTSD	6.5 [5.5-8.4]	5.5 [4.7-6.7]	-15.4%	**<0.001***
CTSZ	50.9 [42.6-63.5]	47.2 [42.6-53.5]	-7.3%	**<0.001***
ALCAM	224 [205-251]	207 [181-228]	-7.6%	**<0.001***
CHI3L1	17.3 [11.9-26.1]	18.0 [11.3-26.9]	4.0%	0.49
CHIT1	29.7 [19.4-40.3]	28.8 [19.3-44.8]	-3.0%	0.15
COL1A1	8.6 [7.2-10.1]	11.7 [9.8-13.3]	36.0%	**<0.001***
CD93	2349 [2074-2722]	2239 [1842-2415]	-4.7%	**0.001***
CNTN1	29.3 [24.9-34.3]	31.6 [26.1-36.1]	7.8%	**<0.001***
CSTB	21.1 [16.1-28.6]	18.3 [14.1-21.2]	-13.3%	**<0.001***
SELE	6035 [4054-7535]	3604 [2477-4478]	-40.3%	**<0.001***
PI3	5.4 [4.5-7.3]	5.3 [4.2-7.0]	-1.9%	**0.019***
EPHB4	51.9 [47.4-59.9]	52.5 [47.2-59.8]	1.2%	0.22
EGFR	11.3 [10.5-12.5]	10.0 [9.1-10.7]	-11.5%	**<0.001***
Ep-CAM	56.6 [28.4-94.1]	107.3 [58.5-204.4]	89.6%	**<0.001***
FABP4	98.3 [60.9-135.9]	68.8 [47.9-85.2]	-30.0%	**<0.001***
Gal-3	11.5 [10.4-12.9]	11.2 [10.1-12.6]	-2.6%	0.35
Gal-4	15.6 [12.7-19.8]	19.6 [14.9-25.9]	25.6%	**0.002***
GRN	57.1 [49.8-66.1]	57.2 [47.5-63.8]	0.2%	**0.003***
GDF-15	47.6 [38.5-59.7]	51.8 [40.1-63.1]	8.8%	**0.048**
IGFBP-1	13.4 [6.6-23.9]	36.8 [20.8-52.4]	174.6%	**<0.001***
IGFBP-2	450 [338-641]	188 [136-286]	-58.2%	**<0.001***
IGFBP-7	270 [236-304]	252 [222-294]	-6.7%	0.09
ITGB2	188 [136-286]	450 [337-641]	139.4%	**<0.001***
ICAM-2	53.8 [44.8-61.3]	58.1 [48.3-68.4]	9.0%	**<0.001***
IL-1RT1	93.2 [79.8-105.7]	96.3 [88.7-109.8]	3.3%	**<0.001***
IL-1RT2	48.6 [40.8-54.5]	40.3 [33.3-46.6]	-17.1%	**<0.001***
IL-17RA	22.1 [18.1-28.9]	19.6 [16.3-25.2]	-11.3%	**<0.001***
IL-18BP	71.1 [63.9-81.4]	70.4 [60.5-79.9]	-1.0%	**0.007***
IL2-RA	15.0 [11.9-17.7]	13.3 [11.8-17.2]	-11.3%	**<0.001***
IL-6RA	5075 [4208-6023]	4850 [4003-5553]	-4.4%	**<0.001***
JAM-A	110.2 [74.7-161.9]	84.0 [51.3-127.5]	-23.8%	**<0.001***
KLK6	5.9 [5.1-6.8]	6.2 [5.2-6.9]	5.1%	**<0.001***
LDL receptor	25.4 [19.5-32.9]	14.9 [11.6-19.8]	-41.3%	**<0.001***
LTBR	17.0 [15.3-19.2]	17.0 [14.8-18.8]	0%	0.35
MEPE	71.2 [60.3-88.7]	73.4 [62.3-90.2]	3.1%	**0.025***
MMP-2	17.4 [14.9-19.5]	18.8 [16.3-22.4]	8.0%	**<0.001***
MMP-3	194 [154-278]	177 [132-234]	-8.8%	0.22
MMP-9	58.8 [40.7-89.8]	49.2 [33.2-61.6	-16.3%	**<0.001***

TIMP4	13.2 [11.4-15.2]	14.2 [11.8-17.0]	7.6%	**0.047**
MCP-1	17.4 [14.8-21.1]	16.2 [13.3-18.9]	-6.9%	**<0.001***
PRTN3	18.2 [14.5-21.6]	16.3 [13.8-18.9]	-10.4%	**<0.001***
MPO	11.2 [9.5-13.5]	10.0 [8.6-12.4]	-10.7%	**<0.001***
MB	212 [170-292]	163 [130-213]	-23.1%	**0.003***
NT-proBNP	11.1 [6.6-16.6]	17.5 [11.2-24.6]	57.7%	**0.010***
Notch 3	50.2 [41.2-59.1]	52.6 [42.5-63.3]	4.9%	**0.021***
OPN	198 [157-248]	315 [257-400]	59.1%	**<0.001***
OPG	16.7 [13.6-18.35]	15.7 [14.1-18.3]	-6.0%	0.12
SELP	2615 [1877-3616]	1841 [1210-2617]	-29.6%	**<0.001***
PON3	107 [77-156]	139 [106-159]	29.9%	**<0.001***
PGLYRP1	188 [154-228]	178 [148-204]	-5.3%	**<0.001***
PLC	299 [266-337]	284 [249-309]	-5.0%	**<0.001***
PAI	77.6 [53.7-109.1]	44.5 [31.0-64.9]	-42.7%	**<0.001***
PECAM-1	70.4 [52.6-92.3]	54.8 [39.6-75.0]	-22.2%	**<0.001***
GP6	17.4 [11.5-23.2]	13.2 [8.7-18.4]	-24.1%	**<0.001***
PDGF subunit A	25.2 [18.7-36.1]	17.6 [13.2-25.9]	-30.2%	**<0.001***
PCSK9	8.9 [7.4-10.5]	7.7 [7.0-8.8]	-13.5%	**<0.001***
DLK-1	53.8 [36.5-66.9]	78.7 [57.7-97.1]	45.3%	**<0.001***
PSP-D	7.0 [5.4-10.3]	6.5 [4.5-8.1]	-7.1%	**0.007***
RETN	82.0 [68.5-100.8]	83.0 [62.6-97.2]	1.2%	**0.037***
RARRES2	4461 [3888-4950]	3489 [3100-4032]	-21.8%	**<0.001***
CD163	299.4 [249.6-389.6]	220.5 [175.9-301.6]	-26.4%	**<0.001***
SCGB3A2	5.4 [4.1-7.8]	5.9 [4.8-8.7]	9.3%	**0.009***
SPON1	4.5 [4.1-5.1]	4.9 [4.2-5.5]	8.9%	**0.024***
ST2	23.3 [18.3-29.3]	24.2 [18.1-30.3]	3.9%	0.45
TR-AP	15.3 [13.2-17.7]	14.7 [12.8-16.8]	-3.9%	**0.009***
TFPI	736 [654-847]	674 [578-780]	-12.1%	**<0.001***
t-PA	111 [84-155]	74 [61-100]	-33.3%	**<0.001***
TR	59.5 [44.1-83.9]	45.2 [37.8-56.6]	-24.0%	**<0.001***
TFF3	36.9 [31.7-46.0]	43.5 [38.0-55.0]	17.9%	0.67
TLT-2	61.9 [52.7-73.6]	52.8 [43.8-62.3]	-14.7%	**<0.001***
TNFSF13B	168 [142-189]	142 [121-159]	-15.5%	**<0.001***
TNF-R1	133 [115-150]	122 [101-138]	-8.3%	**<0.001***
TNF-R2	66.7 [55.3-77.8]	61.0 [52.1-70.4]	-8.5%	**<0.001***
TNFRSF10C	155 [122-202]	155 [103-203]	0%	**<0.001***
TNFRSF14	36.1 [30.7-42.1]	34.0 [29.8-39.4]	-5.8%	**<0.001***
FAS	76.4 [67.4-87.2]	71.5 [62.0-81.7]	-6.4%	**0.0013***
AXL	637 [553-726]	588 [507-676]	-7.7%	**0.012***
SHPS-1	15.0 [12.9-18.4]	15.6 [12.9-18.0]	4.0%	0.51
U-PAR	48.8 [40.9-60.1]	45.8 [40.5-52.7]	-6.1%	**<0.001***
uPA	29.9 [26.2-34.7]	26.6 [21.8-31.0]	-11.0%	**<0.001***
vWF	153 [108-216]	149 [122-196]	-2.6%	0.07

Values represent median [Q1-Q3], all units are NPX.

Relative changes of all biomarkers from pre- to one year post-bariatric surgery were calculated by subtracting the median value of biomarkers pre-surgery from the value of the biomarkers post-surgery, and dividing the obtained difference by the median value of the biomarkers pre-surgery.

P-values displayed for changes in biomarker levels between pre- and post-surgery were obtained by univariable linear mixed modeling.

* Significant after Benjamini–Hochberg correction.

Part V

Cardiac rehabilitation in obesity patients

11

Chapter 11

Echocardiographic follow-up in obesity patients after tailor-made cardiac rehabilitation

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Submitted

ABSTRACT

Aim

We hypothesize that a novel tailor-made cardiac rehabilitation (CR) program for obesity patients (OPTICARE XL) has better outcomes as compared to usual CR regarding parameters of cardiac function as measured by conventional and advanced transthoracic echocardiography.

Methods

This is an open-label, randomized controlled trial. Inclusion criteria were: patients referred to CR with a body mass index (BMI) ≥30 kg/m^2, and age ≥18 years with either coronary artery disease or nonvalvular atrial fibrillation. The experimental group participated in OPTICARE XL and the controls received the usual CR. Subjects randomized to OPTICARE XL received on top of usual CR behavioural therapy for a healthy diet and an active lifestyle for the first 12 weeks. Also, the exercise program was more tailored. Furthermore, a behavioural after-care program was organized with 6 meetings between weeks 13-52. Transthoracic (speckle tracking) echocardiography was performed at baseline and one-year follow-up.

Results

A total of 42 patients completed the follow-up, 21 in both groups. There was a mild but statistically significant reduction in weight over time, however, this was comparable between groups. There was no improvement observed in any of the echocardiographic parameters.

Conclusion

Cardiac function in obesity patients was not improved one-year after a novel tailor-made CR program (OPTICARE XL) as compared to usual CR.

INTRODUCTION

Cardiac rehabilitation (CR) is a valuable treatment for patients with a broad spectrum of cardiac disease. Currently, CR is a class 1 recommendation (evidence and/or general agreement that a given treatment or procedure is beneficial, useful, effective) in several European society of cardiology (ESC) and American college of cardiology (ACC) guidelines.[1-3] Throughout the years, CR has evolved from exercise only into a comprehensive program that also addresses other cardiovascular disease risk factors and provides education, social support and focusses on lifestyle.[4-6] By implementing these progresses, sustained improvements were made not only in social and physical functioning but also in hospitalization and mortality rates at 5-years.[7-10]

Currently, at entry into CR over 80% of the patients are overweight (body mass index (BMI) ≥25 kg/m^2), and over 40% are even obese (BMI≥30 kg/m^2).[11] However, usual CR programs are far from optimal in patients with obesity, because they have a higher cardio-metabolic risk and poorer fitness.[5,12] There is growing evidence that effects achieved during usual CR in obesity patients are substantially smaller than in non-obese patients.[13] Nevertheless, intentional weight loss, accomplished through behavioural weight loss and exercise, improves insulin sensitivity and associated cardio-metabolic risk factors such as lipid measures, blood pressure, inflammation, and vascular function.[14] However, CR programs are not specifically designed to obtain weight loss.[11]

Recently, we have shown that weight loss achieved by bariatric surgery improves many echocardiographic parameters of cardiac function and dimension at one-year follow-up.[15] Besides the benefits of weight reduction, exercise itself could reverse parameters of cardiac function measured with (advanced) echocardiography.[16] Therefore, we hypothesized that a novel tailor-made CR program for obesity patients (OPTICARE XL) with a focus on exercise and weight loss has better outcomes as compared to usual CR regarding conventional and advanced transthoracic echocardiography parameters of cardiac function.

METHODS

Study population and design

The OPTICARE XL (OPTImal CArdiac Rehabilitation XL) study is an open-label, randomized controlled trial. Inclusion criteria were: patients with a BMI≥30 kg/m^2 and age≥18 years with either coronary artery disease (myocardial infarction, angina pectoris) or nonvalvular atrial fibrillation, who were referred for CR. Exclusion criteria were: heart failure, left ventricle (LV) ejection fraction <40%, implantable cardioverter defibrillator, psychological or cognitive impairments, renal failure or other severe co-morbidity (e.g. severe chronic obstructive

pulmonary disease, active malignancy, poorly controlled diabetes, intermittent claudication, and musculoskeletal impairments) which could impair participation in CR. After inclusion in OPTICARE XL, consecutive patients were asked to participate in this echocardiography substudy.

The experimental group participated in OPTICARE XL, and the controls received usual CR as recommended by the guidelines.[17] Subjects randomized to OPTICARE XL received on top of usual CR behavioural therapy for a healthy diet (once a week program of 60 minutes during 12 weeks) and an active lifestyle (once every 3 weeks a program of 45 minutes during 12 weeks). The exercise program (part of usual CR) during the first 12 weeks was more tailored than the usual CR and was a combination of aerobic training and muscle strength training. This combination is considered to be the preferred training in obesity patients.[18] Furthermore, a behavioural after-care program was organized with 6 meetings (one hour each) between weeks 13-52 for the OPTICARE XL patients. This was done in small groups with a maximum of 8 participants instead of the standard groups with a maximum of 25 participants.

Weight loss was defined as any decrease in weight and measured with a calibrated weight scale. Clinically significant weight loss was defined as a loss of 5% of body weight at baseline.[19] Transthoracic echocardiography was performed at baseline and one-year follow-up. The study protocol was approved by the 'Medisch Ethische Toetsings Commissie Erasmus MC' and written informed consent was obtained from all participants.

Sample size calculation

Although there is some uncertainty regarding the standard deviations (SD) of the "delta's" (changes from before to after the intervention) of the parameters that were studied (because these have not been reported in previous studies), these were expected to be smaller than the SD's at either baseline or after the intervention reported in previous studies,[20,21] supporting the notion that this study will have sufficient power to detect changes in cardiac function caused by the intervention. The total sample size for the optional echocardiography substudy was aimed to be 50 patients, randomized to either the intervention or control group. When using a two-sided test in two groups of 25 patients, the study was powered to determine an effect size of 0.8 times the SD, regardless of the parameter studied (alpha 0.05 [two-sided], power 0.80).

Transthoracic echocardiography

Two-dimensional grayscale harmonic images were obtained in the left lateral decubitus position using a commercially available ultrasound system (EPIQ 7, Philips, the Netherlands), equipped

with a broadband (1-5MHz) X5-1 transducer. Diastolic dysfunction and reduced ejection fraction (≤54% in females, and ≤52% in males) were defined according to the current guidelines.[22,23]

Interventricular septal thickness (IVSd), posterior wall thickness (PWd), and LV dimension (LVEDD) were all measured at end-diastole. The LV mass (LVM) was calculated according to the Deveraux formula using these measurements: LVM (g) = 0.80 × {1.04[(IVSd +LVEDD + PWd)^3-(LVEDD)^3]} + 0.6. LVM-index (LVMI) was calculated by dividing LVM by body surface area (BSA). BSA was calculated with the Mosteller formula.[24] LV hypertrophy (LVH) was defined as LVMI ≥102 g/m^2 for males and ≥88 g/m^2 for females.[23]

To optimize speckle tracking echocardiography, apical images were obtained at a frame rate of 60 to 80 frames/s. Three consecutive cardiac cycles were acquired from all apical views (4-chamber, 2-chamber, and 3-chamber). Subsequently, these cycles were transferred to a QLAB workstation (version 10.2, Philips, the Netherlands) for off-line speckle tracking analysis. Peak regional longitudinal strain was measured in 17 myocardial regions and a weighted mean was used to derive global longitudinal strain (GLS).[23] GLS of lower than -16% was considered abnormal.[25]

Statistical analysis

The normality of the data was checked by the Shapiro–Wilk test. The unpaired Student's t-test for continuous variables was used to compare parameters with normal distributions, the non-parametric Mann-Whitney U test for continuous parameters with skewed distributions, and the χ^2 test/Fisher's exact test for categorical variables. Continuous values were expressed as mean ± SD and categorical values as percentages.

Patients who completed follow-up were added to the following analyses. Repeated-measure analyses of variance (ANOVA) was used for continuous variables, to assess the relationship of changes in follow-up between groups. Generalized linear mixed models were used to compare categorical data between start and follow-up. The categorical parameters were entered subsequently as the dependent variable, and group (usual CR vs. OPTICARE XL) and follow-up as the independent variables. Random intercepts were used to account for the patient ID.

All statistical tests were 2-sided and a p-value of 0.05 was considered statistically significant. The analyses were performed with SPSS version 25 and R version 3.6.0 (glm package).

RESULTS

Clinical characteristics and echocardiographic parameters of both groups at baseline

A total of 48 obesity patients were included and randomized to both groups (usual CR n=23, and OPTICARE XL n=25). The inclusion of 50 patients was not achieved because the inclusion of the main study was completed at the time of the inclusion of 48 patients in the echocardiography substudy. The clinical characteristics of both groups are summarized in Table 1. The mean BMI was 34.8 kg/m^2 in the usual CR group and 35.3 kg/m^2 in the OPTICARE XL group (p=0.69). Also, all other parameters of physical examination were comparable. Most comorbidities were comparable between groups, except that more patients in the usual CR group had hypercholesterolemia (p=0.014). There were no differences in medication use between groups.

Almost all echocardiographic parameters were comparable between groups, except for the LVM-index, which was increased in the OPTICARE-XL group (99[86-125]g/m^2 vs. 90[70-11]g/m^2, p=0.029). However, the percentage of patients with LVH was not significantly different between groups (56% vs 30%, p=0.07).

Table 1: Clinical characteristics and echocardiographic parameters of obesity patients in both groups at baseline.

	Usual CR (n=23)	OPTICARE-XL (n=25)	p-value
General characteristics			
Age (years)	56 ± 8	58 ± 10	0.61
Male (n, %)	20 (87%)	19 (76%)	0.46
Indication for rehabilitation			
Coronary artery disease (n, %)	21 (91%)	19 (76%)	0.25
Atrial fibrillation (n, %)	2 (9%)	6 (24%)	0.25
Physical examination			
Length (m)	1.80 ± 0.11	1.77 ± 0.10	0.28
Weight (kg)	113 ± 15	111 ± 21	0.70
BMI (kg/m^2)	34.8 ± 3	35.3 ± 5	0.69
BSA (m$^{2)}$	2.38 ± 0.2	2.33 ± 0.3	0.50
Systolic BP (mmHg)	139 ± 19	135 ± 14	0.35
Diastolic BP (mmHg)	80 [75-90]	80 [75-89]	0.53
Waist circumference (cm)	119 ± 9	116 ± 12	0.30
Heart rate (bpm)	66 ± 10	67 ± 10	0.58

Comorbidity			
Diabetes Mellitus (n, %)	5 (22%)	5 (20%)	0.88
Hypertension (n, %)	11 (48%)	9 (36%)	0.41
Hypercholesterolemia (n, %)	10 (44%)	3 (12%)	**0.014**
History of smoking (n, %)	19 (86%)	18 (72%)	0.23
COPD (n, %)	1 (4%)	2 (8%)	0.60
OSAS (n, %)	1 (4%)	3 (12%)	0.34
Medication			
Beta-blockers (n, %)	12 (57%)	19 (79%)	0.11
ACE inhibitors (n, %)	14 (61%)	21 (84%)	0.09
Statins (n, %)	17 (74%)	18 (72%)	0.63
Antiarrhythmic drugs (n, %)	4 (17%)	1 (4%)	0.11
Insulin (n, %)	3 (13%)	1 (4%)	0.23
Oral anti-diabetics (n, %)	10 (43%)	7 (28%)	0.20
Echocardiography parameters			
LVM (g)	207 [173-255]	242 [183-334]	0.11
LVM-index (g/m^2)	90 [70-111]	99 [86-125]	**0.029**
Left ventricular hypertrophy (n,%)	7 (30%)	14 (56%)	0.07
Mitral inflow E-wave (cm/s)	68 ± 12	62 ± 17	0.14
Mitral inflow A-wave (cm/s)	69 ± 15	67 ± 16	0.68
E/A-ratio	0.94 [0.86-1.20]	0.90 [0.75-1.10]	0.29
Septal e' velocity (cm/s)	8 ± 2	7 ± 2	0.05
Lateral e' velocity (cm/s)	10 ± 2	9 ± 2	0.19
E/e'-ratio	9 ± 2	9 ± 3	0.62
Deceleration time (s)	0.19 [0.18-0.23]	0.19 [0.15-0.22]	0.43
LA volume index (ml/m^2)	28 [24-35]	26 [23-35]	0.67
TR velocity (cm/s)	93 [77-131]	94 [81-179]	0.69
Diastolic dysfunction (n, %)	10 (43%)	16 (64%)	0.15
TAPSE (cm)	2.4 ± 0.4	2.4 ± 0.5	0.97
LV ejection fraction (%)	55 ± 8	53 ± 9	0.57
Reduced LV ejection fraction (n,%)	8 (35%)	12 (48%)	0.35
GLS (%)	-17 ± 3	-16 ± 3	0.27
Reduced GLS (n,%)	8 (35%)	11 (46%)	0.44

Values represent mean ± standard deviation, median (Q1-Q3) or n (%)

BMI= body mass index, *BSA*= body surface area, *COPD*= chronic obstructive pulmonary disease, *CR*= cardiac rehabilitation, *OSAS*= obstructive sleep apnea syndrome, *ACE*= angiotensin converting enzyme, *LVM*= left ventricular mass, *E-wave*= early diastolic transmitralflow velocity, *A-wave*= late diastolic transmitralflow velocity, *e'*=early diastolic mitral annular velocity, *LA-volume index*= left atrial volume index, *TR*= tricuspid regurgitation, *TAPSE*= tricuspid annular plane systolic excursion, *GLS*= global longitudinal strain

One-year follow-up; all patients

Four patients did not complete the follow-up and two patients had a new cardiac event. A total of 42 patients completed the one-year follow-up (Figure 1). Table 2 shows that there was significant weight loss at follow-up ($p<0.001$). Also, the heart rate increased ($p=0.032$). None of the echocardiographic parameters changed from before to one year either form of rehabilitation.

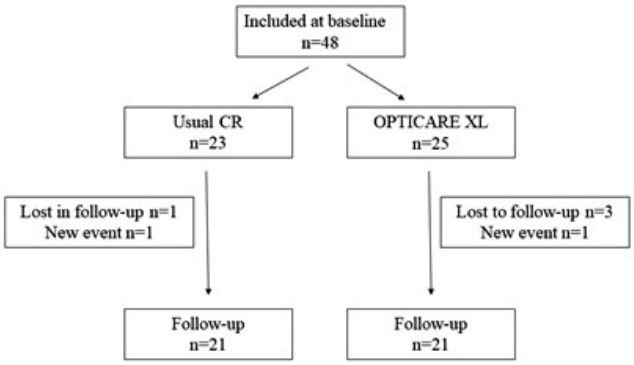

Figure 1: Flow chart.
Usual CR = usual cardiac rehabilitation

One-year follow-up; comparison between groups

Weight loss was comparable between groups (Table 2, Figure 2). A total of 13 patients in the usual CR group lost weight, as compared to 16 of the patients in the OPTICARE XL group ($p=0.43$). Clinical significant weight loss was achieved in 5 patients in the usual CR, and in 7 in the OPTICARE XL group ($p=0.50$). Also, the increase in heart rate that was present in the total group was comparable between groups ($p=0.41$). The vast majority of changes in echocardiographic parameters were comparable as well. Only the proportion of patients with LVH was more decreased in the OPTICARE XL group after one-year follow-up ($p=0.019$) (Figure 3).

Table 2: Physical examination and echocardiographic parameters at baseline and at one-year follow-up

	Usual CR (n=21)		OPTICARE-XL (n=21)			
	Baseline	Follow-up	Baseline	Follow-up	p-value baseline vs follow-up	p-value* usual CR vs OPTICARE-XL
Physical examination						
Weight (kg)	113 ± 15	110 ± 17	111 ± 21	105 ± 22	**0.001**	0.43
BMI (kg/m^2)	34.8 ± 3	33.9 ± 4	35.3 ± 5	33.5 ± 5	**<0.001**	0.45
Heart rate (bpm)	65 ± 9	67 ± 11	68 ± 13	72 ± 17	**0.032**	0.41
Echocardiographic parameters						
LVM (g)	219 ± 60	207 ± 67	257 ± 80	237 ± 75	0.17	0.49
LVM-index (g/m^2)	92 ± 22	88 ± 27	110 ± 30	117 ± 66	0.80	0.25
Left ventricular hypertrophy (n,%)	7 (33%)	5 (24%)	14 (67%)	10 (48%)	0.63	**0.019**
Mitral inflow E-wave (cm/s)	68 ± 12	65 ± 14	69 ± 14	64 ± 17	0.82	0.77
Mitral inflow A-wave (cm/s)	69 ± 16	63 ± 13	66 ± 14	65 ± 14	0.78	0.27
E/A-ratio	1.03 ± 0.32	1.01 ± 0.19	1.01 ± 0.34	0.95 ± 0.26	0.27	0.66
Septal e' velocity (cm/s)	8 ± 2	7 ± 2	8 ± 2	8 ± 3	0.27	0.12
Lateral e' velocity (cm/s)	10 ± 2	10 ± 2	11 ± 2	9 ± 3	0.67	0.57
E/e'-ratio	8.8 ± 2	9.7 ± 2	8.8 ± 2	8.4 ± 2	0.11	0.13
Deceleration time (s)	0.20 ± 0.04	0.19 ± 0.06	0.20 ± 0.04	0.19 ± 0.06	0.70	0.79
LA volume index (ml/m^2)	30 ± 8	30 ± 9	30 ± 8	32 ± 8	0.44	0.36
TR velocity (cm/s)	110 ± 58	138 ± 72	113 ± 61	155 ± 81	0.37	0.52
TAPSE (cm)	2.4 ± 0.4	2.4 ± 0.6	2.3 ± 0.4	2.4 ± 0.6	0.40	0.19
Diastolic dysfunction (n, %)	9 (43%)	8 (38%)	14 (67%)	13 (62%)	0.56	0.07
LV ejection fraction (%)	55 ± 9	54 ± 8	54 ± 8	53 ± 10	0.49	0.88
Reduced LV ejection fraction (n,%)	7 (33%)	7 (33%)	10 (48%)	9 (43%)	0.75	0.28
GLS (%)	-17 ± 3	-16 ± 3	-16 ± 3	-16 ± 5	0.38	0.66
Reduced GLS (n,%)	7 (33%)	9 (43%)	9 (43%)	11 (52%)	0.44	0.38

Values represent mean ± standard deviation or n (%)
* p-value of the changes over time, comparison between groups
p-values displayed of continuous variables were calculated with repeated measures ANOVA, and for the categorical variables with generalized linear mixed models.
BMI= body mass index, *CR*= cardiac rehabilitation, *GLS*= global longitudinal strain, *LV*= left ventricular, *LVM*= left ventricular mass, *LVM-index*= left ventricular mass index, *TAPSE*= tricuspid annular plane systolic excursion, *TR velocity*= tricuspid regurgitation velocity

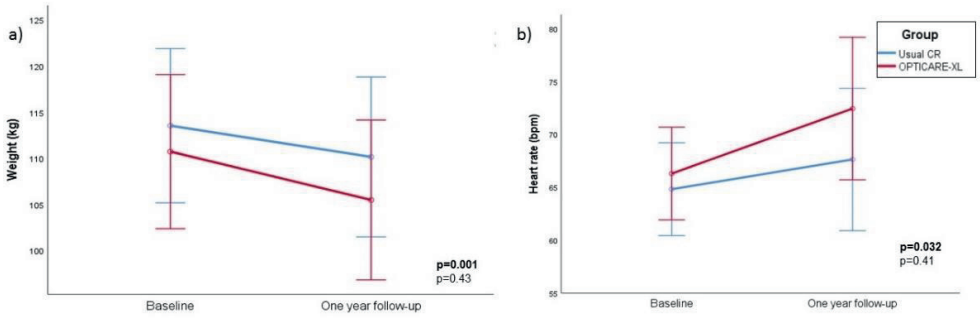

Figure 2: Changes in mean weight (a), heart rate (b), global longitudinal strain (c), and ejection fraction (d) between baseline and one-year follow-up.
Error bars represent 95% CI

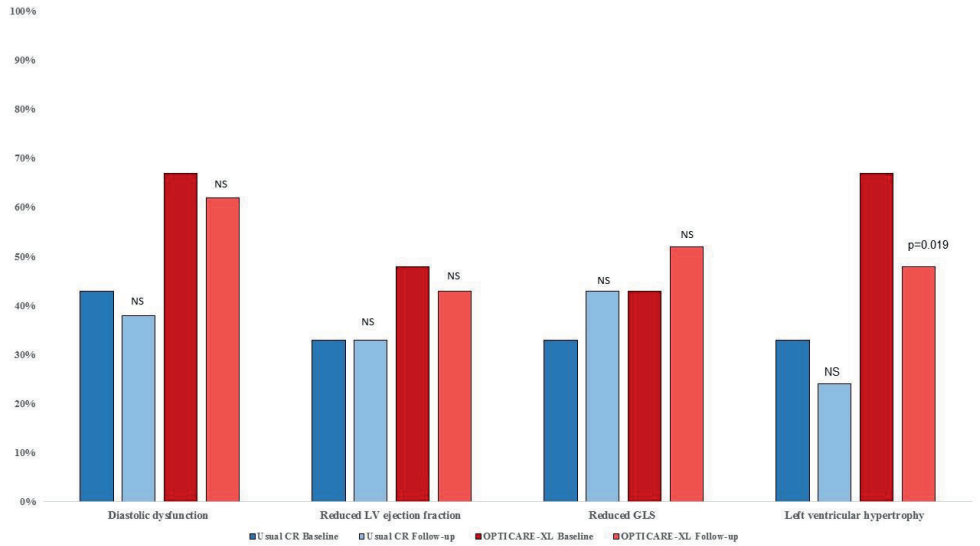

Figure 3: Comparison of percentage of diastolic dysfunction, reduced ejection fraction, reduces global longitudinal strain, and left ventricular hypertrophy between both usual cardiac rehabilitation, OPTICARE-XL, and baseline and follow-up.

DISCUSSION

The main finding of the current study is that cardiac function in obesity patients as measured with echocardiography did not improve one-year after a novel tailor-made CR program (OPTICARE XL) as compared to usual CR.

Although there was a significant reduction in weight and thereby BMI in both groups, this reduction was relatively small and does not meet the definition of clinically significant weight loss.[19] This finding of mild weight reduction one year after CR is consistent with the results of other studies.[26,27] In a study of 73 obesity patients with coronary artery disease also a statistically significant but small decrease in weight was observed after completing CR.[27] In another study it was concluded that the prevalence of obesity did not change significantly after the CR program (37% to 33%), and the prevalence of severe obesity (BMI>35 kg/m^2) improved only slightly (3.5% to 2.5%).[26] A clinical significant weight reduction through CR, therefore, seems difficult to achieve. The OPTICARE XL program was developed to achieve better results than previous studies regarding CR in obesity patients. It is, therefore, disappointing that the goal of clinically important weight loss was only achieved in a minority of patients.

The current study is the first in which echocardiographic parameters of cardiac function were investigated in obesity patients who participated in usual CR or a more tailor-made CR program. However, a few small studies have been performed in obesity patients in which the impact of exercise on cardiac function as measured by speckle tracking echocardiography was evaluated. Schuster et al.[20] described a GLS of -15.9±0.8% in 10 obesity patients at baseline, significantly improving to -17.4±0.9% after 8 weeks of training. The training program consisted of three 45-min sessions of walking and/or cycling at home, without any dietary intervention. The body fat mass decreased without significant weight or BMI change by this intervention. In another study, Obert et al.[21] evaluated the impact of both diet and exercise training in 28 obese adolescents. The training consisted of nine sessions of 5-min each, three times per week. Additionally, moderate physical activities were performed twice a week during the first two months and then five times per week during the following 7 months. Moreover, the total daily calorie intake was controlled at about 2300-2500 kcal. Both body weight (99±15kg vs 84±115kg) and BMI (36±5kg/m^2 vs 31±5kg/m^2) decreased significantly. The GLS in these patients was -14.2±3.6% at baseline, and improved significantly to -16.9±3.5% at 9 months follow-up. In contrast, in our study, GLS did not improve in obesity patients after one year of either program. An explanation for this could be the more intense exercise training in the mentioned other studies. Also, follow-up in our study was one year, which is considerably longer than the follow-up in the aforementioned studies. Therefore, it may be hypothesized that weight loss and concurring improved GLS at the beginning of CR was more in our patients as well, but that the effect was lost later due to failure to maintain weight loss.

There are several studies in which echocardiographic parameters of LV function, such as GLS, were assessed in patients who participated in usual CR. However, the focus of none of the studies was on obesity patients. First, Malfatto et al.[28] studied GLS is a small group who entered CR after a first uncomplicated myocardial infarction. They concluded that a short period of intensive CR induces rapid recovery of GLS (-17.0±3.7% vs -20.1±3.2%) and diastolic function. Also, Acar et al.[29] found a significant increase in LV ejection fraction (49±7.9% vs 54±9.1%) and GLS (-13±2.3% vs -17±3.0%) after three months of usual CR in a group of 27 patients with acute myocardial infarction. We found no changes in GLS and LV ejection fraction. Our study was different as compared to these other studies regarding the focus specifically on obesity patients and the longer follow-up. As mentioned earlier, obesity patients have a higher cardiometabolic risk and poorer fitness,[13] which could also have a negative impact on GLS recovery. In a recent study, it was shown that decreased baseline fitness, such as may be present in obesity patients, may moderate weight loss achieved by weight loss programs.[30] However, despite this, we did expect that echocardiographic parameters of cardiac function, such as GLS would improve after the tailor-made CR of the patients in the OPTICARE XL group, which unfortunately did not happen.

Finally, both groups showed a mild but non-significant decrease of LVH after rehabilitation. Nevertheless, the proportion of patients with LVH was significantly more decreased in the OPTICARE XL group. This finding suggests that the more intensive program of the OPTICARE XL may have a positive contribution to the reduction of LVH.

Limitations

Although echocardiographic parameters of cardiac function did not improve in the patients undergoing CR in our study, one may hypothesize such parameters may even have worsened without any CR. However, because a control group of obesity patients not undergoing any CR is lacking in the current study, this remains to be investigated. The number of subjects in this study was small. Studies with a larger sample size would be necessary for further evaluation of some of the trends that have been observed. Also, a more intensified echocardiographic follow-up with measurements for example also at six months would have allowed better comparison with the other studies with shorter follow-up described before.

CONCLUSIONS

Both in obesity patients undergoing usual CR or a novel tailor-made CR program, echocardiographic parameters of cardiac function did not improve at one-year follow-up. This

finding suggests that obesity patients may participate in usual CR programs without the need to implement more tailor-made programs for these patients. To our knowledge, this is the first publication describing findings of extensive echocardiographic evaluation before and after tailor-made cardiac rehabilitation for obesity patients.

REFERENCES

1. Knuuti J, Wijns W, Saraste A, et al. 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes. Eur Heart J 2020;41:407-77.
2. Ibanez B, James S, Agewall S, et al. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: The Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). Eur Heart J 2018;39:119-77.
3. American Association of C, Pulmonary R, American College of Cardiology F, et al. AACVPR/ACCF/AHA 2010 Update: Performance Measures on Cardiac Rehabilitation for Referral to Cardiac Rehabilitation/Secondary Prevention Services Endorsed by the American College of Chest Physicians, the American College of Sports Medicine, the American Physical Therapy Association, the Canadian Association of Cardiac Rehabilitation, the Clinical Exercise Physiology Association, the European Association for Cardiovascular Prevention and Rehabilitation, the Inter-American Heart Foundation, the National Association of Clinical Nurse Specialists, the Preventive Cardiovascular Nurses Association, and the Society of Thoracic Surgeons. J Am Coll Cardiol 2010;56:1159-67.
4. McMahon SR, Ades PA, Thompson PD. The role of cardiac rehabilitation in patients with heart disease. Trends Cardiovasc Med 2017;27:420-5.
5. Martin BJ, Aggarwal SG, Stone JA, et al. Obesity negatively impacts aerobic capacity improvements both acutely and 1-year following cardiac rehabilitation. Obesity (Silver Spring) 2012;20:2377-83.
6. Anderson L, Thompson DR, Oldridge N, et al. Exercise-based cardiac rehabilitation for coronary heart disease. Cochrane Database Syst Rev 2016:CD001800.
7. Doimo S, Fabris E, Piepoli M, et al. Impact of ambulatory cardiac rehabilitation on cardiovascular outcomes: a long-term follow-up study. Eur Heart J 2019;40:678-85.
8. Candelaria D, Randall S, Ladak L, Gallagher R. Health-related quality of life and exercise-based cardiac rehabilitation in contemporary acute coronary syndrome patients: a systematic review and meta-analysis. Qual Life Res 2019.
9. Sunamura M, Ter Hoeve N, van den Berg-Emons RJG, et al. Randomised controlled trial of two advanced and extended cardiac rehabilitation programmes. Heart 2018;104:430-7.
10. de Vries H, Kemps HM, van Engen-Verheul MM, Kraaijenhagen RA, Peek N. Cardiac rehabilitation and survival in a large representative community cohort of Dutch patients. Eur Heart J 2015;36:1519-28.
11. Ades PA, Savage PD, Harvey-Berino J. The treatment of obesity in cardiac rehabilitation. J Cardiopulm Rehabil Prev 2010;30:289-98.
12. Gunstad J, Luyster F, Hughes J, Waechter D, Rosneck J, Josephson R. The effects of obesity on functional work capacity and quality of life in phase II cardiac rehabilitation. Prev Cardiol 2007;10:64-7.
13. Savage PD, Ades PA. The obesity epidemic in the United States: role of cardiac rehabilitation. Coron Artery Dis 2006;17:227-31.
14. Ades PA, Savage PD. Potential benefits of weight loss in coronary heart disease. Prog Cardiovasc Dis 2014;56:448-56.
15. Sanne M Snelder, Yaar Aga, Lotte E de Groot-de Laat, L Ulas Biter, Manuel Castro Cabezas, Nadine Pouw, Bianca M Boxma-de Klerk, René A Klaassen, Felix Zijlstra, Bas M van Dalen. Cardiac Function Normalizes 1 Year After Bariatric Surgery in Half of the Obesity Patients with Subclinical Cardiac Dysfunction. Obesity Surgery 2021
16. Baynard T, Carhart RL, Jr., Ploutz-Snyder LL, Weinstock RS, Kanaley JA. Short-term training effects on diastolic function in obese persons with the metabolic syndrome. Obesity (Silver Spring) 2008;16:1277-83.
17. Hartstichting RvdNVVCedN. Multidisciplinaire Richtlijn Hartrevalidatie 2011. 2011.
18. Ades PA, Savage PD, Toth MJ, et al. High-calorie-expenditure exercise: a new approach to cardiac rehabilitation for overweight coronary patients. Circulation 2009;119:2671-8.
19. Jensen MD, Ryan DH, Apovian CM, et al. 2013 AHA/ACC/TOS guideline for the management of overweight and obesity in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and The Obesity Society. J Am Coll Cardiol 2014;63:2985-3023.
20. Schuster I, Vinet A, Karpoff L, et al. Diastolic dysfunction and intraventricular dyssynchrony are restored by low intensity exercise training in obese men. Obesity (Silver Spring) 2012;20:134-40.

21. Obert P, Gueugnon C, Nottin S, et al. Impact of diet and exercise training-induced weight loss on myocardial mechanics in severely obese adolescents. Obesity (Silver Spring) 2013;21:2091-8.
22. Nagueh SF, Smiseth OA, Appleton CP, et al. Recommendations for the Evaluation of Left Ventricular Diastolic Function by Echocardiography: An Update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. Eur Heart J Cardiovasc Imaging 2016;17:1321-60.
23. Lang RM, Badano LP, Mor-Avi V, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. Eur Heart J Cardiovasc Imaging 2015;16:233-70.
24. Mosteller RD. Simplified calculation of body-surface area. N Engl J Med 1987;317:1098.
25. Yang H, Wright L, Negishi T, Negishi K, Liu J, Marwick TH. Research to Practice: Assessment of Left Ventricular Global Longitudinal Strain for Surveillance of Cancer Chemotherapeutic-Related Cardiac Dysfunction. JACC Cardiovasc Imaging 2018;11:1196-201.
26. Lavie CJ, Milani RV, Ventura HO, Messerli FH, Murgo JP. Cardiac rehabilitation, exercise training, and preventive cardiology research at Ochsner Heart and Vascular Institute. Tex Heart Inst J 1995;22:44-52.
27. Lavie CJ, Morshedi-Meibodi A, Milani RV. Impact of cardiac rehabilitation on coronary risk factors, inflammation, and the metabolic syndrome in obese coronary patients. J Cardiometab Syndr 2008;3:136-40.
28. Malfatto G, Revera M, Branzi G, et al. A brief period of intensive cardiac rehabilitation improves global longitudinal strain and diastolic function after a first uncomplicated myocardial infarction. Acta Cardiol 2017;72:284-91.
29. Acar RD, Bulut M, Ergun S, Yesin M, Akcakoyun M. Evaluation of the effect of cardiac rehabilitation on left atrial and left ventricular function and its relationship with changes in arterial stiffness in patients with acute myocardial infarction. Echocardiography 2015;32:443-7.
30. Catenacci AZDMOZPSACBLSDHBHRWELMVA. SAT-575 Association Between Baseline Fitness and Changes in Physical Activity and Weight Loss in an 18-Month Behavioral Weight Loss Program. Journal of the endocrine society 2020.


VI

Part VI

Discussion and summary

12

Chapter 12

General discussion

GENERAL DISCUSSION

This thesis covers different aspects of cardiac function in obesity patients. The focus is mainly on diagnostics in this specific group of patients, the early signs of cardiac dysfunction, changes after weight loss, and the possible pathophysiology. In this chapter, the relevance of the performed studies will be discussed and future perspectives will be described.

Diagnostics in obesity patients

Prevalence of obesity is increasing rapidly and obesity is becoming a global public health crisis.[1] Due to the increase in the number of obesity patients, there will also be an increase in the use of various diagnostics used in daily clinical practice in this specific patient group.[2] Unfortunately, it is not always well known how well different diagnostics, such as an electrocardiogram (ECG) and transthoracic echocardiography can be used in these patients.[3,4]

Obesity patients are often considered technically difficult to evaluate by transthoracic echocardiography. However, we demonstrated for the first time that although non-obese controls on average had better echocardiographic image quality than obesity patients, the feasibility of assessment of a broad variety of parameters of cardiac function and dimension was excellent in obesity patients and that there were no important differences regarding the variability of measurements.[5] This implies that the widespread idea of echocardiography usually being non-diagnostic in obesity patients can be rejected.

Also, nowadays, global longitudinal strain (GLS) is recommended to use as a parameter of LV systolic function.[6] Until now it has been unclear how well this method would perform in obesity patients. We demonstrated that GLS had good feasibility and reproducibility in these patients. Therefore, we suggest that this parameter may be used in daily practice in obesity patients as well.

Left ventricular hypertrophy (LVH) occurs frequently in obesity patients, even in the absence of comorbidities such as hypertension.[7] Although echocardiography is a more sensitive tool to identify LVH, the standard ECG remains widely used.[8] However, despite a generally high specificity, ECG criteria for the detection of LVH lack sensitivity, particularly in obesity patients.[9] The reason for this is probably that the ECG voltages at the skin level are attenuated by the subcutaneous adipose tissue.[10] Therefore, we evaluated the accuracy of the most commonly used ECG-criteria for the detection of LVH (Cornell voltage and the Sokolow-Lyon index) and the recently introduced more sensitive Peguero – Lo Presti criteria. We concluded that established ECG criteria indeed lack sufficient sensitivity, most of them did not even reach

20%.[11] From this, we can conclude that these criteria are not usable in obesity patients in daily clinical practice. Therefore, we proposed and prospectively tested adjusted ECG criteria with a correction for body mass index (BMI), namely: Cornell voltage*BMI ≥ 700 mm*kg^2 for males, and Sokolow-Lyon index*BMI ≥ 885 mm*kg^2 for females. These criteria had an improved sensitivity (47% in males and 26% in females), approaching known sensitivity of the most commonly used ECG criteria in lean subjects. However, it may seem difficult to implement these new criteria into daily clinical practice, because of three reasons. First, males and females have different criteria, second because the BMI must be entered, and third because the criteria may be difficult to remember. A solution for this is to program the algorithms into the modern ECG devices, allowing easy clinical use without extra effort. Finally, off course when the ECG criteria for LVH are met an echocardiography should be performed to confirm the presence of LVH.

Early signs of cardiac dysfunction in obesity patients

Heart failure is a major public health problem in developed countries.[12] The risk of developing heart failure is particularly elevated in obesity patients.[13] In order to optimise management and treatment of obesity patients it is necessary to improve early identification of cardiac dysfunction.[14] The combination of biomarkers, Holter monitoring and new, more sensitive methods, such as advanced echocardiography may be eligible for this.

We studied which parameters could be best used to detect early signs of left ventricular (LV) diastolic dysfunction in a large animal model of metabolic dysfunction, using conventional and advanced speckle tracking echocardiography (STE).[15] STE can be used to quantify subtle changes in LV mechanics.[6] For example, it can be used to assess LV systolic twist and diastolic untwisting.[16] By applying STE we were able to conclude that LV peak untwisting velocity was the best parameter for the early detection of LV diastolic dysfunction in this animal model. Although previous studies already showed that LV untwisting may be a meaningful parameter of diastolic dysfunction,[17,18] so far its potential as an early marker of diastolic dysfunction was unclear. The findings suggest an important role for STE in the detection of early changes in cardiac dysfunction.

Until recently, the prevalence of subclinical cardiac dysfunction in obesity patients was largely unknown. However, we studied a group of 100 obesity patients and 50 non-obese controls both without known cardiovascular disease.[19] Next to advanced echocardiography, we also collected

blood samples and affixed a 24-hour Holter monitoring. The studied group (48 [42-50] years, 70% female) of obesity patients had a high prevalence (61%) of subclinical cardiac dysfunction, compared to only one non-obese control. GLS, a measurement of LV systolic function measured by STE, was by far the best parameter to identify cardiac dysfunction (57 out of 60 patients). For example, GLS performed much better compared to conventional echocardiographic parameters such as LV ejection fraction and diastolic function. Also, we were unable to identify subclinical cardiac dysfunction by Holter monitoring or assessment of hs Troponin I and brain natriuretic peptide (BNP). Previous studies regarding detection of early stages of cardiac dysfunction had already shown benefits of using STE over LV ejection fraction,[20,21] however, none of these studies applied STE in a group of obese patients. Therefore, it can be concluded that GLS may be the preferred measurement to evaluate early changes in LV systolic function in obesity patients.

Changes after weight loss

Clinically important weight loss is generally defined as 5% of usual body weight.[22] This is difficult to achieve with lifestyle interventions, and results are often temporary. In contrast, bariatric surgery is an effective and safe treatment option resulting in large long-term weight loss.[23,24] Also, weight loss and associated metabolic improvement achieved by bariatric surgery has a positive impact on heart morphology even in obesity patients without known heart failure.[25]

We followed 72 obesity patients one-year after bariatric surgery.[26] Again echocardiography, Holter monitoring, and blood biomarkers were combined. Forty of these patients had subclinical cardiac dysfunction pre-surgery (mainly based on a decreased GLS) as described earlier. As expected, there was significant weight loss, lipid levels and HbA1c improved, inflammation decreased, and comorbidities decreased. LV function improved significantly in obesity patients one year after bariatric surgery, resulting in normalized cardiac function in half of the patients with cardiac dysfunction before surgery. We also studied the relative changes of 92 cardiovascular biomarkers from before to one-year after bariatric surgery.[27] A total of 72 (78%) biomarkers were significantly different after surgery, indicating alterations in a wide range of processes related to metabolic status and cardiovascular function. Also, comparison of obesity patients with and without cardiac dysfunction suggested an important role for inflammation, atherosclerosis and insulin resistance in the underlying pathophysiology of cardiac dysfunction in obesity patients.

Cardiac rehabilitation (CR) is a valuable treatment option for patients with a broad spectrum of cardiac disease.[28] Currently, at entry into CR, over 40% of the patients are obese.[29] However, usual CR programs are far from optimal in obesity patients, because obesity patients have a higher cardio-metabolic risk and poorer fitness.[30] Also, intentional weight loss, accomplished through behavioral weight loss and exercise, can improve insulin sensitivity and associated cardio-metabolic risk factors.[31] Therefore, we hypothesized that a novel tailor-made CR program specially designed for obesity patients with either coronary artery disease or nonvalvular atrial fibrillation had better outcomes as compared to usual CR regarding parameters of cardiac function as measured by (speckle tracking) echocardiography.[32] We compared 48 obesity patients who were referred to CR, which were randomized to either usual CR or to the novel tailor-made CR program for obesity patients. There was a mild reduction in weight in both groups, however, this was not clinically significant. Moreover, this weight loss was comparable between groups. Also, all echocardiographic parameters were comparable for both groups. Therefore, unfortunately, we had to conclude that a novel tailor-made CR program for obesity patients had no added value compared to usual CR regarding echocardiographic changes. This is in contrast with the improvement in cardiac function previously demonstrated in bariatric surgery after one year. Therefore, it could be considered to advise obesity patients to undergo bariatric surgery in addition to being referred for CR.

Pathophysiology of cardiac dysfunction in obesity patients

The pathophysiology of obesity leading to cardiac dysfunction is incompletely understood and most likely multifactorial.[1,33] However, significant advances in the understanding of the pathophysiological consequences of obesity for the cardiovascular system have been made of the past two decades.[34,35] For example, we know that obesity is associated with diabetes mellitus, dyslipidaemia, and hypertension. However, the onset of heart failure in obesity cannot be fully explained by the presence of these traditional cardiac risk factors.[36] Moreover, the enormous and still growing prevalence of obesity warrants efficient screening of obesity patients with the highest need for further risk assessment, follow-up, and treatment. Current knowledge on the role of obesity in causing cardiac dysfunction is insufficient to optimally develop such strategies.

In order to better investigate the pathophysiology of cardiac dysfunction in obesity, we compared obesity patients with and without cardiac dysfunction. Again, we applied a combination of techniques: Holter monitoring, blood biomarkers, and (advanced)

echocardiography.[37] By this comparison, we were able to conclude that a decreased SDNN-index and male gender are predictors of subclinical cardiac dysfunction. The SDNN-index is measured by Holter monitoring and is a measure of heart rate variability (HRV) and thereby of autonomic function.[38] A balanced autonomic function is crucial for normal cardiac function.[39] A depressed HRV has been confirmed to be a prognostic marker and is correlated with morbidity and mortality.[40-42] Previous studies already described a decreased HRV in obesity patients,[43,44] linking this to inflammatory processes.[45,46] However, our study not only confirmed the presence of a decreased HRV in obesity patients, it was also the first to show that decreased HRV may play a crucial role in the development of cardiac dysfunction in these patients.
Alongside a decreased SDNN-index, male gender was also a predictor of cardiac dysfunction. Previous studies already described an association between obesity and more severe heart failure symptoms in male patients.[47] Also, overweight and obese males have higher adjusted mortality.[48] However, the reason for these findings is not clear. It cannot be excluded that there are unidentified confounders related to gender that may explain the suggested relationship.

We also followed obesity patients one-year after bariatric surgery.[49] As said earlier, cardiac dysfunction normalized in half of the obesity patients. This time we aimed to identify predictors for a lack of improvement of cardiac dysfunction. We identified a decreased SDNN and a decreased vitamin D pre-surgery as predictors for persistent cardiac dysfunction post-surgery. A decreased SDNN again indicates autonomic dysfunction. Therefore, it can be concluded that autonomic dysfunction in obesity patients not only plays a crucial role in the development of cardiac dysfunction, it also contributes to the persistence of cardiac dysfunction post-bariatric surgery.
Next to autonomic dysfunction, a decreased vitamin D pre-surgery was also a predictor for persistent cardiac dysfunction. Vitamin D has been suggested to be involved in multiple pathophysiological pathways related to heart failure, such as inflammation, atherosclerosis, endothelial dysfunction, and thrombosis.[50] Furthermore, vitamin D deficiency is a predictor of reduced survival in patients with heart failure.[51] Also, vitamin D is known to be decreased in both obesity patients[52] and in patients with known cardiovascular disease,[53] earlier findings in-line with our conclusion that vitamin D may have a role in the increased risk of cardiac dysfunction in obesity.

We also compared cardiovascular biomarker profiles between obesity patients and non-obese controls, and between obesity patients with and without cardiac dysfunction, again, in order to

better understand the underlying pathophysiology.[27] First, we concluded that obesity patients without known cardiovascular disease have cardiovascular biomarker profiles that are clearly different from non-obese controls. Since the studied biomarkers covered several processes potentially involved in the pathophysiology of cardiovascular disease in obesity, our findings support the hypothesis of a multifactorial origin of cardiovascular disease in obesity patients. Second, the comparison of obesity patients with and without cardiac dysfunction suggested an important role for inflammation, atherosclerosis, and insulin resistance in the underlying pathophysiology of cardiac dysfunction in obesity patients.

We developed a biomarker model with the aforementioned biomarkers to predict the persistence of cardiac dysfunction post-bariatric surgery by changes of biomarkers from pre- to post-surgery, again to better understand the pathophysiology.[54] The biomarkers with the highest relative changes mainly represent processes linked to insulin resistance and inflammation. Also, this study design allowed correlation of changes in cardiovascular biomarkers with a (lack of) improvement of cardiac function after bariatric surgery. Most of the biomarkers of which baseline levels were associated with persistence of cardiac dysfunction, are known to be linked to inflammation, while there also appeared to be a relatively important role for subclinical atherosclerosis. The relation between certain biomarkers and the persistence of subclinical cardiac dysfunction post-surgery again highlighted the importance of inflammation and atherosclerosis, with a potential role for hypercoagulability as well. This is in line with the knowledge that increased inflammatory status is known to have an important role in the induction of both atherosclerosis and hypercoagulability. Thus, although cardiac dysfunction in obesity seems to be a heterogeneous disorder, inflammation plays a central part.

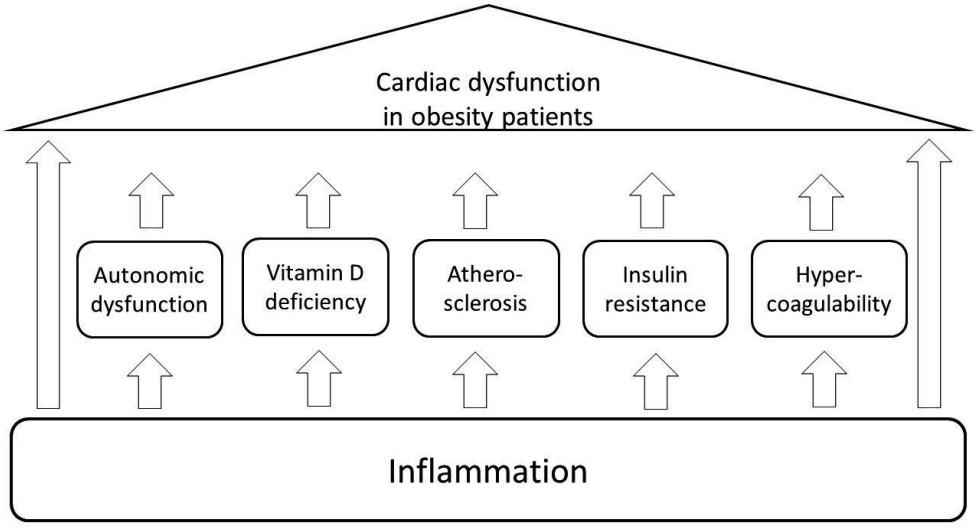

Figure 1: Summary of factors leading to cardiac dysfunction in obesity patients

In summary, as shown in Figure 1, cardiac dysfunction in obesity patients is indeed a heterogeneous disorder. The reason for the development of cardiac dysfunction in obesity appears to be due to the combination of autonomic dysfunction, a decreased vitamin D, atherosclerosis, insulin resistance, hypercoagulability, and inflammation.

Although a broad range of processes potentially involved in the pathophysiology of cardiovascular disease in obesity has been described before,[55,56] a relatively important role for the processes summarized in Figure 1 seems plausible. First, autonomic dysfunction contributes directly to cardiac dysfunction.[39] Second, Vitamin D has been suggested to be involved in multiple pathophysiological pathways related to heart failure.[50] In addition, atherosclerosis can lead to ischemia, which in its turn can lead to heart failure.[57] Also, heart failure frequently coexists with insulin resistance, and insulin resistance may accelerate the progression of cardiac dysfunction toward advanced disease.[58] Next, it is well recognized that heart failure is associated with an increased risk of hypercoagulability (both arterial and venous thrombotic events).[59] Furthermore, it has long been observed that heart failure is associated with measures of systemic inflammation.[60] Inflammation contributes to the pathogenesis and progression of heart failure through diverse pathways. Also, it is striking that all the processes described before can arise due to inflammation. For example, inflammation of the epicardial adipose tissue can lead to microvascular dysfunction and thereby cause fibrosis of the underlying left ventricle.[61]

Similarly, endothelial inflammation can lead to coronary dysfunction and thereby to myocardial fibrosis.[61,62] Also, autonomic dysfunction is associated with higher levels of inflammation.[46] Furthermore, both atherosclerosis and insulin resistance have been recognized as inflammatory diseases.[63,64] Again, inflammation mediates hypercoagulability in patients with heart failure.[59] Lastly, vitamin D deficiency is recognized as a consequence of chronic inflammation.[65] Next to being linked to heart failure, these processes are also related to obesity itself.[38,61,66-68] Therefore, although the link between these processes in obesity seems reasonable, this thesis is the first to show that these processes are the main factors responsible for the onset and persistence of subclinical cardiac dysfunction in obesity patients.

CONCLUSIONS AND FUTURE PERSPECTIVES

Diagnostics

Assessment of a broad variety of parameters of cardiac function and dimension by echocardiography is feasible in obesity patients, also no important differences regarding the variability of measurements are observed. This implies that the widespread idea of echocardiography usually being non-diagnostic in obesity patients can be rejected. Also, GLS has good feasibility and reproducibility in obesity patients. Therefore, we suggest that this parameter may be used in daily practice in obesity patients as well.

Established ECG criteria for the detection of LVH lack sufficient sensitivity in obesity patients. Therefore, new criteria were proposed ((RaVL+SV3)*BMI $\geq$700 mm*kg/m^2 for males and (SV1 + RV5/RV6)*BMI $\geq$885 mm*kg/m^2 for females) for the detection of LVH in obesity, approaching known sensitivity of the most commonly used ECG criteria in lean subjects. The applicability of these criteria in daily practice will need further investigation.

Early signs of cardiac dysfunction in obesity patients

There is a high prevalence (61%) of subclinical cardiac dysfunction in obesity patients without known cardiovascular disease. Also, GLS and LV peak untwisting velocity may serve as important markers to detect early signs of LV dysfunction. These findings suggest an important role for STE in the detection of early signs of cardiac dysfunction in obesity patients.

Changes after weight loss

LV function improves significantly in obesity patients one year after bariatric surgery, resulting in normalized cardiac function in half of the patients with cardiac dysfunction before surgery. The vast majority of cardiovascular biomarkers change one-year after bariatric-surgery, indicating alterations in a wide range of processes related to metabolic status and cardiovascular function. Also, a novel tailor-made CR program for obesity patients has no added value compared to usual CR regarding echocardiographic measurements.

Pathophysiology of cardiac dysfunction in obesity patients

Obesity patients without known cardiovascular disease have cardiovascular biomarker profiles that are clearly different from non-obese controls, suggesting a multifactorial origin of cardiovascular disease in obesity patients. Also, comparison of obesity patients with versus without cardiac dysfunction indicates a heterogeneous disorder. However, there appears to be a central role for inflammation. The reason for the development and persistence of cardiac dysfunction in obesity appears to be due to the combination of autonomic dysfunction, a decreased vitamin D, atherosclerosis, insulin resistance, hypercoagulability, again also factors with an important role for inflammation.

Future perspectives

In the ideal world obesity patients with an increased cardiovascular risk would be identified as early as possible. The method of choice should be echocardiography, by measuring GLS. Another option may be to first provide risk-stratification (in other words: which patients need an echocardiogram and which patients should be followed-up to allow early detection of cardiac dysfunction) by measurement of the HRV, since autonomic dysfunction seems to play a major role in the development and persistence of cardiac dysfunction in obesity. Despite remarkable insights into the relation between autonomic dysfunction and heart failure, several issues remain poorly understood and are in need of further investigation. For instance, it must be clarified whether activation of the autonomic nervous system is the driver of heart failure or a consequence of the disease. Therefore, future research on cardiac dysfunction in obesity patients should focus on the role of autonomic dysfunction. In order to do so, the analysis of HRV may be a useful and simple non-invasive method.

Finally, inflammation appears to play a very important role in cardiac dysfunction in obesity patients. It seems to contribute to cardiac dysfunction through diverse pathways. In order to

develop a proper treatment to prevent heart failure in obesity patients, it may be most rational to, apart from aiming at weight loss, focus on the treatment and consequences of inflammation. However, although numerous studies have validated the association between measures of inflammation and heart failure severity and prognosis, so far clinical trials of anti-inflammatory therapies were mostly unsuccessful.[60] Hopefully, future research regarding inflammation could lead to novel treatment modalities to combat cardiac dysfunction in obesity patients in the future.

REFERENCES

1. Afshin A, Reitsma MB, Murray CJL. Health Effects of Overweight and Obesity in 195 Countries. N Engl J Med 2017;377:1496-7.
2. Murphy NF, MacIntyre K, Stewart S, Hart CL, Hole D, McMurray JJ. Long-term cardiovascular consequences of obesity: 20-year follow-up of more than 15 000 middle-aged men and women (the Renfrew-Paisley study). Eur Heart J 2006;27:96-106.
3. Martin RP. American Society of Echocardiography president's message: echocardiography and the epidemics. J Am Soc Echocardiogr 2003;16:16A-7A.
4. Robinson C, Woodiwiss AJ, Libhaber CD, Norton GR. Novel Approach to the Detection of Left Ventricular Hypertrophy Using Body Mass Index-Corrected Electrocardiographic Voltage Criteria in a Group of African Ancestry. Clin Cardiol 2016;39:524-30.
5. Snelder SM, Younge JO, Dereci A, et al. Feasibility and Reproducibility of Transthoracic Echocardiography in Obese Patients. J Am Soc Echocardiogr 2019;32:1491-3 e5.
6. Lang RM, Badano LP, Mor-Avi V, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. Eur Heart J Cardiovasc Imaging 2015;16:233-70.
7. Himeno E, Nishino K, Nakashima Y, Kuroiwa A, Ikeda M. Weight reduction regresses left ventricular mass regardless of blood pressure level in obese subjects. Am Heart J 1996;131:313-9.
8. de Vries SO, Heesen WF, Beltman FW, et al. Prediction of the left ventricular mass from the electrocardiogram in systemic hypertension. Am J Cardiol 1996;77:974-8.
9. Domienik-Karlowicz J, Rymarczyk Z, Lisik W, et al. Questionable validity of left ventricular hypertrophy cutoff values in morbidly and super-morbidly obese patients. Ann Noninvasive Electrocardiol 2018;23:e12564.
10. Okin PM, Roman MJ, Devereux RB, Kligfield P. Electrocardiographic identification of left ventricular hypertrophy: test performance in relation to definition of hypertrophy and presence of obesity. J Am Coll Cardiol 1996;27:124-31.
11. Snelder SM, van de Poll SWE, de Groot-de Laat LE, Kardys I, Zijlstra F, van Dalen BM. Optimized electrocardiographic criteria for the detection of left ventricular hypertrophy in obesity patients. Clin Cardiol 2020;43:483-90.
12. Zarrinkoub R, Wettermark B, Wandell P, et al. The epidemiology of heart failure, based on data for 2.1 million inhabitants in Sweden. Eur J Heart Fail 2013;15:995-1002.
13. Kenchaiah S, Evans JC, Levy D, et al. Obesity and the risk of heart failure. N Engl J Med 2002;347:305-13.
14. Benjamin EJ, Muntner P, Alonso A, et al. Heart Disease and Stroke Statistics-2019 Update: A Report From the American Heart Association. Circulation 2019;139:e56-e528.
15. van den Dorpel MMP, Heinonen I, Snelder SM, et al. Early detection of left ventricular diastolic dysfunction using conventional and speckle tracking echocardiography in a large animal model of metabolic dysfunction. Int J Cardiovasc Imaging 2018;34:743-9.
16. van Dalen BM, Soliman OI, Vletter WB, ten Cate FJ, Geleijnse ML. Insights into left ventricular function from the time course of regional and global rotation by speckle tracking echocardiography. Echocardiography 2009;26:371-7.
17. Notomi Y, Lysyansky P, Setser RM, et al. Measurement of ventricular torsion by two-dimensional ultrasound speckle tracking imaging. J Am Coll Cardiol 2005;45:2034-41.
18. Dong SJ, Hees PS, Siu CO, Weiss JL, Shapiro EP. MRI assessment of LV relaxation by untwisting rate: a new isovolumic phase measure of tau. Am J Physiol Heart Circ Physiol 2001;281:H2002-9.
19. Snelder SM, de Groot-de Laat LE, Biter LU, et al. Cross-sectional and prospective follow-up study to detect early signs of cardiac dysfunction in obesity: protocol of the CARDIOBESE study. BMJ Open 2018;8:e025585.
20. Ersboll M, Valeur N, Mogensen UM, et al. Prediction of all-cause mortality and heart failure admissions from global left ventricular longitudinal strain in patients with acute myocardial infarction and preserved left ventricular ejection fraction. J Am Coll Cardiol 2013;61:2365-73.

21. Dalen H, Thorstensen A, Romundstad PR, Aase SA, Stoylen A, Vatten LJ. Cardiovascular risk factors and systolic and diastolic cardiac function: a tissue Doppler and speckle tracking echocardiographic study. J Am Soc Echocardiogr 2011;24:322-32 e6.
22. Jensen MD, Ryan DH, Apovian CM, et al. 2013 AHA/ACC/TOS guideline for the management of overweight and obesity in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and The Obesity Society. Circulation 2014;129:S102-38.
23. DeMaria EJ. Bariatric surgery for morbid obesity. N Engl J Med 2007;356:2176-83.
24. Sjostrom L, Lindroos AK, Peltonen M, et al. Lifestyle, diabetes, and cardiovascular risk factors 10 years after bariatric surgery. N Engl J Med 2004;351:2683-93.
25. Vest AR, Heneghan HM, Agarwal S, Schauer PR, Young JB. Bariatric surgery and cardiovascular outcomes: a systematic review. Heart 2012;98:1763-77.
26. Snelder SM, Aga Y, Laat LEdGd, et al. Cardiac function normalizes after bariatric surgery in half of the obesity patients with subclinical cardiac dysfunction. Submitted 2020.
27. Snelder SM, Pouw N, Aga Y, et al. Biomarker profiles in obesity patients and relation to cardiac dysfunction. Submitted 2020.
28. McMahon SR, Ades PA, Thompson PD. The role of cardiac rehabilitation in patients with heart disease. Trends Cardiovasc Med 2017;27:420-5.
29. Ades PA, Savage PD, Harvey-Berino J. The treatment of obesity in cardiac rehabilitation. J Cardiopulm Rehabil Prev 2010;30:289-98.
30. Savage PD, Ades PA. The obesity epidemic in the United States: role of cardiac rehabilitation. Coron Artery Dis 2006;17:227-31.
31. Ades PA, Savage PD. Potential benefits of weight loss in coronary heart disease. Prog Cardiovasc Dis 2014;56:448-56.
32. Snelder SM, Uijl Id, Sunamura M, Zijlstra F, Hoeve Nt, Dalen BMv. Echocardiographic follow-up of obesity patients after tailor-made cardiac rehabilitation. Submitted 2020.
33. Kitzman DW, Shah SJ. The HFpEF Obesity Phenotype: The Elephant in the Room. J Am Coll Cardiol 2016;68:200-3.
34. Sanchez AA, Levy PT, Sekarski TJ, et al. Markers of cardiovascular risk, insulin resistance, and ventricular dysfunction and remodeling in obese adolescents. J Pediatr 2015;166:660-5.
35. Kibar AE, Pac FA, Ece I, et al. Effect of obesity on left ventricular longitudinal myocardial strain by speckle tracking echocardiography in children and adolescents. Balkan Med J 2015;32:56-63.
36. Barbosa JA, Mota CC, Simoes ESAC, Nunes Mdo C, Barbosa MM. Assessing pre-clinical ventricular dysfunction in obese children and adolescents: the value of speckle tracking imaging. Eur Heart J Cardiovasc Imaging 2013;14:882-9.
37. Snelder SM, Laat LEdG-d, Biter LU, et al. Subclinical cardiac dysfunction in obesity patients is linked to autonomic dysfunction: findings from the CARDIOBESE study ESC Heart Failure 2020.
38. Yadav RL, Yadav PK, Yadav LK, Agrawal K, Sah SK, Islam MN. Association between obesity and heart rate variability indices: an intuition toward cardiac autonomic alteration - a risk of CVD. Diabetes Metab Syndr Obes 2017;10:57-64.
39. Florea VG, Cohn JN. The autonomic nervous system and heart failure. Circ Res 2014;114:1815-26.
40. Bauer A, Kantelhardt JW, Barthel P, et al. Deceleration capacity of heart rate as a predictor of mortality after myocardial infarction: cohort study. Lancet 2006;367:1674-81.
41. Ali A, Holm H, Molvin J, et al. Autonomic dysfunction is associated with cardiac remodelling in heart failure patients. ESC Heart Fail 2018;5:46-52.
42. Forslund L, Bjorkander I, Ericson M, et al. Prognostic implications of autonomic function assessed by analyses of catecholamines and heart rate variability in stable angina pectoris. Heart 2002;87:415-22.
43. Lewis MJ. Heart rate variability analysis: a tool to assess cardiac autonomic function. Comput Inform Nurs 2005;23:335-41.
44. Karason K, Molgaard H, Wikstrand J, Sjostrom L. Heart rate variability in obesity and the effect of weight loss. Am J Cardiol 1999;83:1242-7.
45. Williams DP, Koenig J, Carnevali L, et al. Heart rate variability and inflammation: A meta-analysis of human studies. Brain Behav Immun 2019;80:219-26.

46. Lampert R, Bremner JD, Su S, et al. Decreased heart rate variability is associated with higher levels of inflammation in middle-aged men. Am Heart J 2008;156:759 e1-7.
47. Heo S, Moser DK, Pressler SJ, et al. Association between obesity and heart failure symptoms in male and female patients. Clin Obes 2017;7:77-85.
48. Vest AR, Wu Y, Hachamovitch R, Young JB, Cho L. The Heart Failure Overweight/Obesity Survival Paradox: The Missing Sex Link. JACC Heart Fail 2015;3:917-26.
49. Snelder SM, Aga Y, Laat LEdG-d, et al. Normalization of cardiac function after bariatric surgery is related to autonomic dysfunction and vitamin D. Submitted 2020.
50. Brinkley DM, Ali OM, Zalawadiya SK, Wang TJ. Vitamin D and Heart Failure. Curr Heart Fail Rep 2017;14:410-20.
51. Gotsman I, Shauer A, Zwas DR, et al. Vitamin D deficiency is a predictor of reduced survival in patients with heart failure; vitamin D supplementation improves outcome. Eur J Heart Fail 2012;14:357-66.
52. Plesner JL, Dahl M, Fonvig CE, et al. Obesity is associated with vitamin D deficiency in Danish children and adolescents. J Pediatr Endocrinol Metab 2018;31:53-61.
53. Kendrick J, Targher G, Smits G, Chonchol M. 25-Hydroxyvitamin D deficiency is independently associated with cardiovascular disease in the Third National Health and Nutrition Examination Survey. Atherosclerosis 2009;205:255-60.
54. Snelder SM, Pouw N, Aga Y, et al. Cardiovascular biomarker profiles in obesity and relation with normalization of subclinical cardiac dysfunction after bariatric surgery. Submitted 2020.
55. Ebong IA, Goff DC, Jr., Rodriguez CJ, et al. The relationship between measures of obesity and incident heart failure: the multi-ethnic study of atherosclerosis. Obesity (Silver Spring) 2013;21:1915-22.
56. Aurigemma GP, de Simone G, Fitzgibbons TP. Cardiac remodeling in obesity. Circ Cardiovasc Imaging 2013;6:142-52.
57. Gheorghiade M, Sopko G, De Luca L, et al. Navigating the crossroads of coronary artery disease and heart failure. Circulation 2006;114:1202-13.
58. Dei Cas A, Khan SS, Butler J, et al. Impact of diabetes on epidemiology, treatment, and outcomes of patients with heart failure. JACC Heart Fail 2015;3:136-45.
59. Kim JH, Shah P, Tantry US, Gurbel PA. Coagulation Abnormalities in Heart Failure: Pathophysiology and Therapeutic Implications. Curr Heart Fail Rep 2016;13:319-28.
60. Murphy SP, Kakkar R, McCarthy CP, Januzzi JL, Jr. Inflammation in Heart Failure: JACC State-of-the-Art Review. J Am Coll Cardiol 2020;75:1324-40.
61. Packer M. Do most patients with obesity or type 2 diabetes, and atrial fibrillation, also have undiagnosed heart failure? A critical conceptual framework for understanding mechanisms and improving diagnosis and treatment. Eur J Heart Fail 2020;22:214-27.
62. Paulus WJ, Tschope C. A novel paradigm for heart failure with preserved ejection fraction: comorbidities drive myocardial dysfunction and remodeling through coronary microvascular endothelial inflammation. J Am Coll Cardiol 2013;62:263-71.
63. Rocha VZ, Libby P. Obesity, inflammation, and atherosclerosis. Nat Rev Cardiol 2009;6:399-409.
64. Theuma P, Fonseca VA. Inflammation, insulin resistance, and atherosclerosis. Metab Syndr Relat Disord 2004;2:105-13.
65. Mangin M, Sinha R, Fincher K. Inflammation and vitamin D: the infection connection. Inflamm Res 2014;63:803-19.
66. Lumeng CN, Saltiel AR. Inflammatory links between obesity and metabolic disease. J Clin Invest 2011;121:2111-7.
67. Walsh JS, Bowles S, Evans AL. Vitamin D in obesity. Curr Opin Endocrinol Diabetes Obes 2017;24:389-94.
68. Kornblith LZ, Howard B, Kunitake R, et al. Obesity and clotting: Body mass index independently contributes to hypercoagulability after injury. J Trauma Acute Care Surg 2015;78:30-6; discussion 7-8.

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Chapter 13.1

Summary

SUMMARY

Both obesity and heart failure are major public health problems. The pathophysiology of heart failure is very complex, most likely multifactorial, and not completely understood. Also, the current knowledge on the role of obesity in causing cardiac dysfunction is insufficient to optimally identify patients with the highest need for further risk assessment, follow-up, and treatment.

The overarching aim of this thesis is to study the association between cardiac dysfunction and obesity, focussing on diagnostics in obesity patients, the early signs of cardiac dysfunction, changes after weight loss, and the possible pathophysiology.

Part I Introduction

In **Chapter 1** we provide a general background on obesity and heart failure. Diagnostics used in this thesis such as conventional and speckle tracking echocardiography are described. Left ventricular hypertrophy (LVH), heart rate variability, and the use of cardiovascular biomarker profiles are discussed in more detail. Also, background information is provided on bariatric surgery and cardiac rehabilitation in obesity patients. Finally, Chapter 1 ended with the aims and outline of this thesis. In **Chapter 2**, we report the study design of the CARdiac Dysfunction in OBesity – Early Signs Evaluation (CARDIOBESE) study, the main study of this thesis. This is the first study in which (speckle tracking) echocardiography, cardiac biomarkers, and Holter monitoring were combined in a cohort of obesity patients without known cardiovascular disease scheduled for bariatric surgery, and non-obese controls.

Part II Diagnostics in obesity patients

In **Chapter 3**, we evaluated the feasibility and reproducibility of transthoracic echocardiography in obesity patients. The feasibility of echocardiographic parameters is assessed by categorizing image quality and evaluation of available parameters in 100 obesity patients and 50 non-obese controls. Intra-observer reproducibility, inter-observer reproducibility, and test-retest variability are measured. We conclude that the assessment of a broad variety of parameters of cardiac function and dimension by transthoracic echocardiography is feasible in obesity patients. No important differences regarding the variability of measurements were observed. Moreover, global longitudinal strain has good feasibility and reproducibility in obesity patients and, therefore, we suggested that this parameter may also be used in daily clinical practice in these patients.

In **Chapter 4**, we evaluated the accuracy of the most commonly used electrocardiographic (ECG) criteria (Cornell voltage and Sokolow-Lyon index), the recently introduced Peguero-Lo Presti criteria and the correction of these criteria by body mass index (BMI) to detect LVH in obesity patients. The accuracy was retrospectively tested in a cohort of obesity patients referred for a transthoracic echocardiogram based on clinical grounds. Subsequently, the value of the proposed adjusted criteria is prospectively tested in an obese population without known cardiovascular disease. We conclude that the established ECG criteria for the detection of LVH lack sufficient sensitivity in obesity patients. Furthermore we propose new criteria: (RaVL+SV3)*BMI ≥700 mm*kg/m^2 for males, and (SV1 + RV5/RV6)*BMI ≥885 mm*kg/m^2 for females. These criteria have improved sensitivity, approaching known sensitivity of the most commonly used ECG criteria in lean subjects.

Part III Cardiac dysfunction related to obesity and changes after bariatric surgery

In **Chapter 5**, the early detection of left ventricular (LV) diastolic dysfunction is evaluated by using conventional and speckle tracking echocardiography in a large animal model of metabolic dysfunction. The study population consist of both healthy mini pigs and mini pigs with experimentally induced metabolic dysfunction. Speckle tracking echocardiography is performed at baseline and at three months follow-up. We conclude that LV peak untwisting velocity may serve as an important marker to detect early changes of LV diastolic dysfunction.

In **Chapter 6**, we evaluated the prevalence and pathophysiology of subclinical cardiac dysfunction in obesity patients by multimodality diagnostics. The aim of this study is first to estimate the prevalence of subclinical cardiac dysfunction in obesity patients without known cardiovascular disease and second to investigate the underlying pathophysiology. Conventional and speckle tracking echocardiography are combined with blood tests and Holter monitoring to detect subclinical cardiac dysfunction. The cohort consisted of 100 obesity patients without known cardiovascular disease and 50 non-obese controls. We conclude that there was a high prevalence (61%) of subclinical cardiac dysfunction in the obesity patients, which appeared to be best identified by global longitudinal strain. Also, subclinical cardiac dysfunction in obesity is linked to autonomic dysfunction and male gender.

In **Chapter 7**, we search for potential improvement of subclinical cardiac dysfunction after bariatric surgery. We conclude that LV function improves significantly in obesity patients one year after bariatric surgery, resulting in normalized cardiac function in half of the patients with cardiac dysfunction before surgery. Afterward, in **Chapter 8** we aimed to identify predictors for a lack of improvement of subclinical cardiac dysfunction one-year post-bariatric surgery.

We conclude that autonomic dysfunction at baseline is related to a lack of normalization of cardiac function. This result is in line with findings in chapter 6, confirming an important role of autonomic dysfunction in the pathophysiology of cardiac dysfunction in obesity. A decreased vitamin D before bariatric surgery is also independently related to persistent subclinical cardiac dysfunction one-year post-surgery. Therefore, signs of either autonomic dysfunction or a decreased vitamin D pre-bariatric surgery may be indicative of a need for cardiologic follow-up after bariatric surgery.

Part IV Biomarker profiles related to cardiac dysfunction in obesity patients and the impact of bariatric surgery

In **Chapter 9**, we compare cardiovascular biomarker profiles between obesity patients and non-obese controls, and between obesity patients with and without subclinical cardiac dysfunction. This is done to better understand the underlying pathophysiology of cardiac dysfunction in obesity patients. To do so we use a multiplex which allowed assessment of 92 biomarkers covering a broad spectrum of processes potentially involved in cardiac dysfunction in obesity patients. First, we conclude that obesity patients without known cardiovascular disease have cardiovascular biomarker profiles that are clearly different from non-obese controls, supporting the hypothesis of a multifactorial origin of cardiovascular disease in obesity patients. Second, comparison of obesity patients with and those without subclinical cardiac dysfunction suggests an important role for inflammation, atherosclerosis, and insulin resistance in the underlying pathophysiology of cardiac dysfunction in obesity patients.

In **Chapter 10**, we describe the changes of these biomarker profiles in obesity patients one-year after bariatric surgery. We found that the majority (78%) of the investigated biomarkers change after surgery and that the biomarkers with the highest relative changes mainly represent processes linked to insulin resistance and inflammation. Most of the biomarkers with baseline levels associated with persistence of cardiac dysfunction are known to be linked to inflammation, while there also appeared to be a relatively important role for subclinical atherosclerosis. The relation between certain biomarkers and the persistence of subclinical cardiac dysfunction post-surgery again highlighted the importance of inflammation and atherosclerosis, with a potential role for hypercoagulability as well. This is in line with the knowledge that increased inflammatory status is known to have an important role in the induction of both atherosclerosis and hypercoagulability. Thus, although cardiac dysfunction in obesity seems to be a heterogeneous disorder, inflammation plays a central part.

Part V Cardiac rehabilitation in obesity patients

In **Chapter 11**, we look at echocardiographic changes in obesity patients after tailor-made cardiac rehabilitation (CR). We hypothesized that a novel tailor-made CR program for obesity patients (OPTICARE XL) has better outcomes as compared to usual CR regarding parameters of cardiac function as measured by conventional and advanced transthoracic echocardiography at one-year follow-up. However, there is no improvement observed in echocardiographic parameters, including global longitudinal strain. Therefore, these findings suggest that a novel tailor-made CR program for obesity patients has no added value compared to the usual CR regarding echocardiographic parameters of cardiac function.

Part VI Discussion

Finally, in **Chapter 12**, the observations that were presented in this thesis are discussed and possible implications of the findings are explored. The work in this thesis describes a major role for the combination of autonomic dysfunction, decreased vitamin D, atherosclerosis, insulin resistance, hypercoagulability, and inflammation in the development of subclinical cardiac dysfunction in obesity patients and the persistence of this after bariatric surgery. Finally, future directions for new research are provided.

Chapter 13.2

Nederlandse samenvatting

NEDERLANDSE SAMENVATTING

Zowel obesitas als hartfalen zijn grote problemen van de volksgezondheid. De pathofysiologie van hartfalen is erg complex, waarschijnlijk multifactorieel en nog niet volledig bekend. Verder is ook de huidige kennis van de rol van obesitas in het ontstaan van hartfalen niet toereikend om de juiste patiënten te kunnen identificeren met de hoogste noodzaak voor verdere risico analyse, follow-up en behandeling.

Het overkoepelende doel van dit proefschrift is om de associatie tussen cardiale dysfunctie en obesitas te bestuderen, gefocust op de diagnostiek bij deze patiëntengroep, de eerste tekenen van cardiale dysfunctie, veranderingen na gewichtsverlies en de mogelijke pathofysiologie.

Deel 1 Introductie

In **hoofdstuk 1** geven we algemene achtergrondinformatie over obesitas en hartfalen. We beschrijven de diagnostiek die gebruikt wordt in dit proefschrift, zoals conventionele- en speckle tracking echocardiografie. Linkerventrikelhypertrofie (LVH), hartslagvariabiliteit en het gebruik van cardiovasculaire biomarkers worden in detail toegelicht. Verder wordt achtergrondinformatie over bariatrische chirurgie en hartrevalidatie bij obesitas patiënten besproken. Tot slot eindigt hoofdstuk 1 met de doelstellingen en hoofdlijnen van dit proefschrift.

In **hoofdstuk 2** beschrijven we de studie opzet van de "CARdiac Dysfunction in OBesity – Early Signs Evaluation (CARDIOBESE) studie", de belangrijkste studie van dit proefschrift. Dit is de eerste studie waarin (speckle tracking) echocardiografie, cardiovasculaire biomarkers en holter registratie zijn gecombineerd in een cohort met zowel obesitaspatiënten met een blanco cardiovasculaire voorgeschiedenis, welke deelnemen aan een traject van bariatrische chirurgie, als non-obese controles ook met een blanco cardiovasculaire voorgeschiedenis.

Deel II Diagnostiek in obesitaspatiënten

In **hoofdstuk 3** bestuderen we de haalbaarheid en reproduceerbaarheid van transthoracale echocardiografie in obesitas patiënten. De haalbaarheid van echocardiografische parameters (of het te meten is) wordt beoordeeld door de beeldkwaliteit te categoriseren en de beschikbare parameters te evalueren bij 100 obesitaspatiënten en 50 niet-obese controles. De reproduceerbaarheid van een echocardiografist, de reproduceerbaarheid tussen de verschillende echocardiografisten en de variabiliteit tussen test en hertest worden gemeten. We concluderen dat de beoordeling van een breed scala aan parameters van zowel hartfunctie als dimensie door

middel van transthoracale echocardiografie haalbaar is bij obesitaspatiënten. Er werden geen belangrijke verschillen waargenomen met betrekking tot de variabiliteit van de metingen. Bovendien heeft global longitudinale strain een goede haalbaarheid en reproduceerbaarheid bij obesitaspatiënten, daarom suggereren we dat deze parameter kan worden gebruikt in de dagelijkse klinische praktijk bij deze patiënten.

In **hoofdstuk 4** evalueren we de nauwkeurigheid van de meest gebruikt electrocardiografische (ECG) criteria (Cornell voltage en Sokolow-Lyon index), de recent geïntroduceerde Peguero-Lo Presti criteria en de correctie van al deze criteria middels de body mass index (BMI) om LVH te detecteren in obesitas patiënten. De nauwkeurigheid werd retrospectief getest in een cohort van obesitaspatiënten die een verwijzing hadden voor een transthoracaal echocardiogram op basis van klinische gronden. Vervolgens wordt de waarde van de voorgestelde aangepaste criteria prospectief getest in een populatie met obesitas zonder hart- en vaatziekten in de voorgeschiedenis. We concluderen dat de vastgestelde ECG-criteria voor de detectie van LVH onvoldoende sensitief zijn bij obesitaspatiënten. Vervolgens introduceren we nieuwe criteria: (RaVL+SV3)*BMI $\geq$700 mm*kg/m^2 voor mannen en (SV1 + RV5/RV6)*BMI $\geq$885 mm*kg/m^2 voor vrouwen. Deze criteria zijn sensitiever dan de huidige criteria en benaderen de bekende sensitiviteit van de meest gebruikte ECG-criteria bij proefpersonen zonder obesitas.

Deel III Cardiale dysfunctie gerelateerd aan obesitas en veranderingen na bariatrische chirurgie

In **hoofdstuk 5** wordt de vroege detectie van linker ventrikel (LV) diastolische dysfunctie geëvalueerd door middel van conventionele- en speckle tracking echocardiografie in een groot proefdiermodel met metabole dysfunctie. De onderzoekspopulatie bestaat uit zowel gezonde minivarkens als minivarkens met experimenteel geïnduceerde metabole disfunctie. Speckle tracking echocardiografie wordt uitgevoerd bij aanvang en na drie maanden follow-up. We concluderen dat de “LV peak untwisting velocity” kan dienen als een belangrijke marker om vroege tekenen van LV diastolische disfunctie te detecteren.

In **hoofdstuk 6** bekijken we de prevalentie en pathofysiologie van subklinische cardiale dysfunctie in obesitaspatiënten met behulp van meerdere diagnostische modaliteiten. Het doel van deze studie is als eerste om een inschatting te kunnen maken van de prevalentie van subklinische cardiale dysfunctie in obesitas patiënten zonder hart- en vaatziekten en als tweede om de onderliggende pathofysiologie te bestuderen. Conventionele- en speckle tracking

echocardiografie worden gecombineerd met bloedonderzoek en holter registratie om subklinische cardiale dysfunctie op te kunnen sporen. Het cohort bestond uit 100 obesitaspatiënten zonder cardiovasculaire ziekten en 50 niet-obese controles. We concludeerden dat er een hoge prevalentie (61%) van subklinische cardiale dysfunctie is in obesitas patiënten, welke het best opgespoord kon worden middels speckle tracking echocardiografie. Verder is subklinische cardiale dysfunctie gelinkt aan autonome dysfunctie en het mannelijk geslacht.

In **hoofdstuk 7** bekeken we of er potentieel verbetering is van subklinische cardiale dysfunctie na bariatrische chirurgie. We concludeerden dat de LV functie significant verbeterde 1-jaar na bariatrische chirurgie, resulterend in normalisatie van cardiale functie in de helft van de patiënten met cardiale dysfunctie voor de operatie. Hierna hebben we in **hoofdstuk 8** ons gericht op het identificeren van voorspellers voor een gebrek aan normalisatie van subklinische cardiale disfunctie een jaar post-bariatrische chirurgie. We concluderen dat autonome disfunctie voor chirurgie gerelateerd is aan een gebrek aan normalisatie van de cardiale functie. Dit resultaat komt overeen met de bevindingen in hoofdstuk 6 en bevestigt de belangrijke rol van autonome disfunctie in de pathofysiologie van cardiale disfunctie bij obesitaspatiënten. Een verlaagd vitamine D vóór bariatrische chirurgie is ook onafhankelijk gerelateerd aan het behoud van subklinische cardiale disfunctie een jaar na de operatie. Daarom kunnen tekenen van autonome disfunctie of een verlaagd vitamine D pre-bariatrische chirurgie wijzen op de noodzaak van cardiologische follow-up na bariatrische chirurgie.

Deel IV Biomarkerprofielen gerelateerd aan cardiale disfunctie bij obesitaspatiënten en veranderingen na bariatrische chirurgie

In **hoofdstuk 9** vergelijken we cardiovasculaire biomarkerprofielen tussen obesitaspatiënten en niet-obese controles, en tussen obesitaspatiënten met en zonder subklinische cardiale disfunctie. Dit wordt gedaan om de onderliggende pathofysiologie van cardiale dysfunctie bij obesitaspatiënten beter te begrijpen. Om dit te doen, gebruiken we een multiplex die het mogelijk maakte om 92 biomarkers te beoordelen die een breed spectrum van processen bevat die mogelijk betrokken zijn bij cardiale dysfunctie bij obesitaspatiënten. Ten eerste concluderen we dat obesitaspatiënten zonder bekende cardiovasculaire aandoeningen cardiovasculaire biomarkerprofielen hebben die duidelijk verschillen van niet-obese controles, wat de hypothese ondersteunt van een multifactoriële oorsprong van cardiovasculaire aandoeningen bij obesitaspatiënten. Ten tweede suggereert een vergelijking van obesitaspatiënten met en zonder

subklinische cardiale disfunctie een belangrijke rol voor inflammatie, atherosclerose en insulineresistentie in de onderliggende pathofysiologie van cardiale disfunctie bij obesitaspatiënten.

In **hoofdstuk 10** beschrijven we de veranderingen van deze biomarkerprofielen bij obesitaspatiënten een jaar na bariatrische chirurgie. We ontdekten dat de meerderheid (78%) van de onderzochte biomarkers verandert na chirurgie en dat de biomarkers met de grootste relatieve veranderingen voornamelijk processen vertegenwoordigen die verband houden met insulineresistentie en inflammatie. Van de meeste biomarkers met baseline-niveaus die geassocieerd zijn met persistentie van cardiale dysfunctie is bekend dat ze verband houden met inflammatie, terwijl er ook een relatief belangrijke rol leek zijn voor subklinische atherosclerose. De relatie tussen bepaalde biomarkers en het persisteren van subklinische cardiale disfunctie na de operatie benadrukte opnieuw het belang van inflammatie en atherosclerose, met ook een mogelijke rol voor hypercoagulabiliteit. Dit is in overeenstemming met de wetenschap dat een verhoogde inflammatoire status een belangrijke rol speelt bij de inductie van zowel atherosclerose als hypercoagulabiliteit. Dus hoewel cardiale dysfunctie bij obesitas een heterogene aandoening lijkt te zijn, speelt inflammatie een centrale rol.

Deel V Hartrevalidatie bij obesitaspatiënten

In hoofdstuk 11 bekijken we de echocardiografische veranderingen bij obesitaspatiënten na op maat gemaakte hartrevalidatie (HR). Onze hypothese was dat een nieuw op maat gemaakt HR-programma voor obesitaspatiënten (OPTICARE XL) betere resultaten heeft in vergelijking met gebruikelijke HR met betrekking tot parameters van de cardiale functie, zoals gemeten met zowel conventionele- als geavanceerde transthoracale echocardiografie bij 1 jaar follow-up. Er is echter geen verbetering waargenomen in de echocardiografische parameters, inclusief global longitudinal strain. Daarom suggereren deze bevindingen dat een nieuw op maat gemaakt HR-programma voor obesitaspatiënten geen toegevoegde waarde heeft ten opzichte van de gebruikelijke HR met betrekking tot echocardiografische parameters van de cardiale functie.

Deel VI Discussie

Ten slotte worden in **hoofdstuk 12** de uitkomsten die in dit proefschrift gepresenteerd zijn besproken en worden mogelijke consequenties van de bevindingen onderzocht. Dit proefschrift beschrijft een belangrijke rol voor de combinatie van autonome disfunctie, een verlaagd vitamine D, atherosclerose, insulineresistentie, hypercoagulabiliteit en inflammatie bij de

ontwikkeling van subklinische cardiale disfunctie bij obesitaspatiënten en de persistentie hiervan na bariatrische chirurgie. Ten slotte worden mogelijkheden voor toekomstig onderzoek beschreven.


VII

Chapter VII

Appendices

ABBREVIATIONS

A	late diastolic transmitralflow velocity
ALAT	alanine aminotransferase
AUC	area under the curve
BLM hydrolase	bleomycin hydrolase
BMI	body mass index
BNP	brain natriuretic peptide
CASP-3	caspase-3
CHIT-1	chitotriosidase-1
CR	cardiac rehabilitation
CRP	C-reactive protein
CTSD	cathepsin D
CTSZ	cathepsin Z
DM	diabetes mellitus
E	early diastolic transmitralflow velocity
Em	velocity of the mitral annulus early diastolic wave
ECG	electrocardiogram
FAS	tumor necrosis factor receptor superfamily member 6
Ep-CAM	epithelial cell adhesion molecule
eGFR	estimated glomerular filtration rate
GLS	global longitudinal strain
GP6	platelet glycoprotein VI
HbA1C	glycosylated hemoglobin A1C
HDL-C	high-density lipoprotein cholesterol
HRV	heart rate variability
hs-cTnI	high sensitive troponin I
IGFBP-1	insulin-like growth factor-binding protein 1
IGFBP-2	insulin-like growth factor-binding protein 2
IL-6RA	interleukin-6 receptor subunit alpha
IL-17RA	interleukin-17 receptor A
ITGBP2	integrin beta-2
IVSd	interventricular septal thickness at end-diastole
JAM-A	junctional adhesion molecule A
LAVI	left atrial volume index
LDL-C	low-density lipoprotein cholesterol
LV	left ventricular
LVEDD	left ventricular dimension at end-diastole
LVH	left ventricular hypertrophy
LVM	left ventricular mass
LVMI	left ventricular mass index
Lp(a)	lipoprotein a
NPV	negative predictive values
NPX	normalized protein expression units

NT-proBNP	N-terminal prohormone brain natriuretic peptide
OPG	osteoprotegerin
OPN	osteopontin
PAC	premature atrial contractions
PDGF subunit A	platelet-derived growth factor subunit A
PECAM-1	platelet endothelial cell adhesion molecule
PON3	paraoxonase
PPV	positive predictive values
PSP-D	pulmonary surfactant-associated protein D
PVC	premature ventricular contractions
PWd	posterior wall thickness at end-diastole
RARRES2	retinoic acid receptor responder protein 2
ROC	receiver operating characteristic
SDNN	standard deviation of all NN intervals
SELE	E-selectin
SELP	P-selectin
STE	speckle tracking echocardiography
TAPSE	tricuspid annular plane systolic excursion
TR-AP	tartrate-resistant acid phosphatase type 5
t-PA	tissue-type plasminogen activator
TLT-2	trem-like transcript 2 protein
TNFRSF13B	tumor necrosis factor ligand superfamily member 13B
TNFRSF14	tumor necrosis factor receptor superfamily member 14
TSH	thyroid-stimulating hormone
TTE	transthoracic echocardiography

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LIST OF PUBLICATIONS

Described in this thesis

1. **Snelder SM,** Pouw N, Aga Y, Castro Cabezas M, Zijlstra F, Kardys I, van Dalen BM. *Biomarker profiles in obesity patients and relation to cardiac dysfunction*. Biomarkers in Medicine 2021

2. **Snelder SM**, Aga Y, de Groot-de Laat LE, Biter LU, Castro Cabezas M, Pouw N, Boxma-de Klerk BM, Klaassen RA, Zijlstra F, van Dalen BM. *Cardiac Function Normalizes 1 Year After Bariatric Surgery in Half of the Obesity Patients with Subclinical Cardiac Dysfunction*. Obesity Surgery. 2021 Apr 21.

3. **Snelder SM**, de Groot – de Laat LE, Biter U, Castro Cabezas M, Pouw N, Birnie E, Boxma – de Klerk B, Klaassen RA, Zijlstra F, van Dalen BM. *Subclinical cardiac dysfunction in obesity patients is linked to autonomic dysfunction: findings from the CARDIOBESE study*. ESC Heart Fail. 2020 Sep 9.

4. **Snelder SM**, van de Poll SWE, de Groot – de Laat LE, Kardys I, Zijlstra F, van Dalen BM. *Optimized electrocardiographic criteria for the detection of left ventricular hypertrophy in obesity patients*. Clin Cardiol. 2020 May 25.

5. **Snelder SM,** Younge JO, Dereci A, van Velzen JE, Akkerhuis JM, de Groot-de Laat LE, Zijlstra F, van Dalen BM. *Feasibility and Reproducibility of Transthoracic Echocardiography in Obese Patients*. J Am Soc Echocardiogr. 2019 Sep 25.

6. **Snelder SM**, de Groot - de Laat LE, Biter LU, Castro Cabezas M, van de Geijn GJ, Birnie E, Boxma-de Klerk B, Klaassen RA, Zijlstra F, van Dalen BM. *Cross-sectional and prospective follow-up study to detect early signs of cardiac dysfunction in obesity: protocol of the CARDIOBESE study*. BMJ Open 2018;8:e025585.

7. van den Dorpel MMP / Heinonen I, **Snelder SM**, Vos HJ, Sorop O, van Domburg RT, Merkus D, Duncker DJ, van Dalen BM. *Early detection of left ventricular diastolic dysfunction using conventional and speckle tracking echocardiography in a large animal model of metabolic dysfunction*. Int J Cardiovasc Imaging. 2017 Dec 12.

Other publications

8. van der Zwaan HB, Kirschbaum SW, **Snelder SM**, von der Thüsen J, van Dalen BM. *Atrial Septal Defect Mimicking Right Atrial Myxoma: Multimodality Imaging of Cardiac Mass*. Circ Cardiovasc Imaging. 2020 Mar 13.

9. van Dalen BM, **Snelder SM**, Geleijnse ML. *Left Ventricular Twist: An Often Ignored But Crucial Determinant of Left Ventricular Function*. J Am Coll Cardiol. 2018 Feb 6;71(5):584.

10. **Snelder SM**, Weersink EJM, Braunstahl GJ. *4-month omalizumab efficacy outcomes for severe allergic asthma: the Dutch National Omalizumab in Asthma Registry*. Allergy Asthma Clin Immunol. 2017 Jul 26;13:34.

11. Kappen JH, van Zaanen HCT, **Snelder SM**, van Tilburg AJP, Rudolphus A. *Lymphomatoid granulomatosis with pulmonary and gastrointestinal involvement*. BMJ Case Rep. 2017 Feb 6;2017.

12. **Snelder SM**, Engels LK, van der Valk H, van Praag MCG. *Skin disorder as an indication of viral infection*. Ned Tijdschr Geneeskd. 2015;159(0):A8708.

13. Dedic A, Kurata A, Lubbers M, Meijboom WB, van Dalen B, **Snelder SM**, Korbee R, Moelker A, Ouhlous M, van Domburg R, de Feijter PJ, Nieman K; *Prognostic implications of nonculprit plaques in acute coronary syndrome: non-invasive assessment with coronary CT angiography*. Eur Heart J Cardiovasc Imaging. 2014 Nov;15(11):1231-7.

14. **Snelder SM**, Nauta ST, Akkerhuis KM, Deckers JW, van Domburg RT; *Weekend versus weekday mortality in ST-segment elevation acute myocardial infarction patients between 1985 and 2008*. Int J Cardiol. 2013 Sep 30;168(2):1576-7.

PHD PORTFOLIO

Name PhD student: S.M. Snelder Department: Cardiology Research School: COEUR	PhD period: October 2016 – April 2020 Promotor: Prof.dr. F. Zijlstra Supervisor: dr. B.M. van Dalen	
PhD training	**Year**	**Workload ECTS**
Courses		
- Good Clinical Practice	2016	1.5
- Echocardiography "Cardiac Mechanics & Speckle Tracking Technology"	2016	0.5
- Literatuur zoeken	2017	0.5
- Statistiek: Basis/beschrijvend	2017	0.5
- Statistiek: Regressie	2017	0.5
- Kritisch lezen	2017	0.5
- COEUR: Vascular clinical epidemiology	2019	0.5
- COEUR: New pharmacological targets in age-related cardiovascular disease	2019	0.5
- COEUR: Sex and gender in cardiovascular disease	2019	0.5
- COEUR: Ischemic Heart Disease	2020	0.5
- Fundamental Critical Care Support	2020	1.5
- Research integrity	2020	0.3
Posters		
- Rationale and design of the CARDIOBESE study. Euro Echo imaging, Lisbon, Portugal.	2017	1
- Evaluation of the accuracy of electrocardiographic criteria for left ventricular hypertrophy in obesity. Wetenschapsdag Franciscus, Rotterdam, the Netherlands.	2018	1
- Prevalence of diastolic dysfunction in obesity as determined by echocardiography using the currently recommended algorithm. Wetenschapsdag Franciscus, Rotterdam, the Netherlands.	2018	1
- Optimized electrocardiographic criteria for the detection of left ventricular hypertrophy in obesity patients. Wetenschapsdag Franciscus, Rotterdam, the Netherlands.	2019	1
- Feasibility and reproducibility of parameters of cardiac function and dimension by transthoracic echocardiography in obesity patients. Wetenschapsdag Franciscus, Rotterdam, the Netherlands.	2019	1
- Early signs of cardiac dysfunction in obesity patients, results of the CARDIOBESE study. Euro Echo imaging, Vienna, Austria.	2019	1
- Biomarker profiles in obesity patients and relation to cardiac dysfunction. Wetenschapsdag Franciscus, Rotterdam, the Netherlands.	2020	1
- Prevalence and pathophysiology of subclinical cardiac dysfunction in obesity patients detected by multimodality diagnostics. ESC, Amsterdam, the Netherlands	2020	1
Moderated Poster		
- Feasibility and reproducibility of parameters of cardiac function and dimension by transthoracic echocardiography in obesity patients. Euro Echo imaging, Vienna, Austria.	2019	1
Presentations		
- Samenwerking rondom wetenschap in de BeterKeten: Opzet, bereikte doelen en toekomstplannen van de CARDIOBESE-studie. Erasmus MC, Rotterdam, the Netherlands.	2017	0.5
- Doel en opzet van de CARDIOBESE-studie. Wetenschapsbijeenkomst Centrum Gezond Gewicht, Rotterdam, the Netherlands.	2017	0.5
- Doel en opzet van de CARDIOBESE-studie. Dutch Society for Metabolic and Bariatric Surgery congress, Tiel, the Netherlands.	2017	1
- De CARDIOBESE-studie. Wetenschapsdag Franciscus, Rotterdam, the Netherlands.	2017	1
- OPTICARE-XL: Cardiac dysfunction in obesity patients as assessed by echocardiography. Erasmus MC, Rotterdam, the Netherlands.	2018	1
- Bariatrische Chirurgie follow up met Speckle Tracking/ LV twist. Philips, Eindhoven, the Netherlands.	2018	0.5
- De CARDIOBESE-studie. Albert Schweitzer Ziekenhuis, Dordrecht, the Netherlands.	2018	0.5
- Early Signs of Cardiac Dysfunction in Obesity Patients, Results of the CARDIOBESE Study. NVVC voorjaarscongres, Rotterdam, the Netherlands.	2019	1
	2019	1

- Early Signs of Cardiac Dysfunction in Obesity Patients, Results of the CARDIOBESE Study. Wetenschapsdag Franciscus, Rotterdam, the Netherlands.	2020	1
- OPTICARE-XL: Cardiac dysfunction in obesity patients as assessed by echocardiography. Erasmus MC, Rotterdam, the Netherlands.	2020	1
- Prevalence and pathophysiology of subclinical cardiac dysfunction in obesity patients detected by multimodality diagnostics. Wetenschapsdag Franciscus, Rotterdam, the Netherlands.	2020	1
International conferences		
- Dutch Society for Metabolic and Bariatric Surgery congress. Tiel, the Netherlands.	2017	1
- EuroEcho-imaging. Lisbon, Portugal.	2017	2
- NVVC voorjaarscongres, Rotterdam, the Netherlands.	2019	1
- ICNC, nuclear cardiology & cardiac CT. Lisbon, Portugal.	2019	2
- EuroEcho-imaging. Vienna, Austria.	2019	2
- ESC. Amsterdam, the Netherlands	2020	1
Other tasks	2017-	
- Wetenschapsraad Franciscus Gasthuis & Vlietland	2020	3
- Organization of Wetenschapsdag Franciscus Gasthuis & Vlietland	2019	3
Teaching		
- ECG criteria voor linker ventrikel hypertrofie bij obesitas	2019	1
- Echocardiografie bij obesitas en LV functie	2019	1
- Tips van een ervaren arts-onderzoeker	2020	0.5
Total		**44.3**

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