New Directions in Myocardial Stress Imaging

ISBN 90-77017-10-0

Front cover (background): Optical section microscopy of cardiac muscle.
Back cover: Desiderius -Erasmus.

Print: Optima Grafische Communicatie, Rotterdam.

New Directions in Myocardial Stress Imaging

Nieuwe ontwikkelingen in beeldvormend cardiaal stress onderzoek

Proefschrift

ter verkrijging van de graad van doctor
aan de Erasmus Universiteit Rotterdam
op gezag van de Rector Magnificus

Prof.dr.ir. J.H. van Bemmel
en volgens besluit van het College voor Promoties

De openbare verdediging zal plaatsvinden op
woensdag 31 oktober 2001 om 15.45 uur

door

Fabiola Anna Margherita Alessandra Sozzi

geboren te Cremona, Italië

Promotiecommissie

Promotor	:	Prof.dr. J.R.T.C. Roelandt
Overige leden	:	Prof.dr.ir. N. Bom Prof.dr. C.A. Visser Prof.dr. D. Ardissino
Copromotor	:	Dr. D. Poldermans

In de drukkosten van dit proefschrift werd bijgedragen door de Netherlands Heart Foundation (NHS).

Ai miei genitori ed ai miei tre fratelli

CONTENTS

CHAPTER 1

INTRODUCTION AND OVERVIEW OF THE THESIS

INTRODUCTION

Non-invasive stress imaging techniques such as echocardiography and myocardial perfusion imaging are widely used for the diagnosis and functional evaluation of coronary artery disease and for the assessment of myocardial viability.[1-8] The aim of this thesis was to analyse methods that may expand the clinical utility of stress echocardiographic and perfusion imaging, for the diagnosis of myocardial ischemia and viability in patients with suspected or known coronary artery disease.

One of the major limitations of stress echocardiography is the suboptimal endocardial border definition, which is encountered in approximately 30% of patients evaluated by fundamental imaging.[9] This interferes with the proper analysis of left ventricular function at rest or during stress.[10-13] In this thesis, we studied the role of second harmonic imaging in improving the delineation of the endocardial border at rest and during dobutamine stress. Furthermore, we analysed the impact of using this method on the diagnostic information obtained by dobutamine stress echocardiography. Myocardial perfusion imaging has been reported to have a higher sensitivity, than dobutamine stress echocardiography for the detection of myocardial viability.[14-16] Myocardial perfusion imaging is based on the detection of the integrity of the cells membrane with preserved perfusion and metabolism (structural viability), whereas dobutamine stress echocardiography relies on the demonstration of preserved contractile reserve (functional viability). In addition to the physiological differences between the two tests, the image quality can affect the diagnosis of myocardial viability by stress echocardiographic testing.[16] In this work, we tested the hypothesis that second harmonic imaging can improve the diagnostic accuracy of dobutamine stress echocardiography for the detection of myocardial viability. We used dual isotope simultaneous acquisition (DISA) single photon emission computed tomography (SPECT) as a reference.

The majority of patients with coronary artery disease and low ejection fraction receive beta-blocker therapy.[17,18] It is not yet clear whether beta-blockers influence the detection of myocardial viability by dobutamine stress echocardiography. We analysed the influence of continued beta-blockers therapy on the assessment of myocardial viability during dobutamine stress echocardiography in patients with severe ischemic left ventricular dysfunction using DISA-SPECT as the independent gold standard.

Previous studies have assessed the role of dobutamine stress echocardiography for the prognostic evaluation of coronary artery disease.[19-21] There are currently no published data to suggest a role for dobutamine stress echocardiography in the prognostic stratification of diabetic patients. Many diabetic patients have diminished exercise tolerance and, therefore, are candidates for pharmacologic rather than exercise stress testing. Additionally, in such a high-risk population, it is not known whether normal dobutamine stress echocardiographic study can identify a low risk population for future cardiac events. In this work, we assessed the incremental value of dobutamine stress echocardiography for the prediction of mortality and cardiac events in diabetic patients with limited exercise capacity.

Despite the favourable imaging properties of 99m-technetium-labelled agents, recent experimental studies have raised some questions regarding the unfavourable myocardial uptake of 99m-technetium-sestamibi during dobutamine infusion.[22-23] Because of these potential limitations, echocardiographic imaging during dobutamine infusion may be assumed to provide a higher sensitivity than sestamibi for the diagnosis of single-vessel coronary disease.[24-27] Our study compared the accuracy of dobutamine stress echocardiography and simultaneous sestamibi SPECT for the diagnosis of single-vessel coronary disease.

The use of 99m-technetium-labelled agents provides the advantages of improved imaging quality, increased consistency of the imaging analysis, and a larger injectable dose because of a shorter half-life as compared to 201-thallium.[28-30] Vasodilator agents are an alternative to exercise stress in patients with limited exercise capacity. Dobutamine is particularly useful as a stress agent in patients who have a contraindication to vasodilators.[31,32] We evaluated the accuracy of dobutamine stress 99m-technetium-tetrofosmin SPECT for the diagnosis of coronary artery disease in patients with limited exercise capacity.

The occurrence of myocardial perfusion abnormalities in hypertensive patients with left ventricular hypertrophy and without epicardial coronary disease is well documented.[33,34] However, the impact of this observation on the specificity and the utility of exercise stress myocardial perfusion scintigraphy in this clinical setting remains unclear. It is not known whether myocardial perfusion scintigraphy has particular limitations in hypertensive patients and whether the results are different in patients with and without left ventricular hypertrophy. Thus, we evaluated the

influence of this common risk factor on the diagnostic accuracy of exercise stress myocardial perfusion imaging.

The diagnosis of coronary artery disease by exercise stress testing is achieved with the highest accuracy in patients with intermediate pre-test probability of coronary artery disease.[35] The significance of exercise-induced ventricular arrhythmias is largely dependent on the clinical characteristics of the population studied.[36] In healthy asymptomatic subjects, exercise-induced ventricular arrhythmias are not related to functional abnormalities or an adverse prognosis.[37,38] In patients with known or high probability of coronary artery disease, there is controversy regarding the relations among exercise-induced ventricular arrhythmias, extent of functional and anatomical abnormalities and prognostic outcome.[39-43] There are a few studies that evaluated the relation between exercise-induced ventricular arrhythmias and myocardial perfusion abnormalities in patients with known or suspected coronary artery disease.[44-47] However, this relation has not been evaluated in a homogeneous group of patients with intermediate pre-test probability of coronary artery disease. In this work, we determined whether the occurrence of exercise-induced ventricular arrhythmias is predictive of a higher prevalence of myocardial perfusion abnormalities among patients with intermediate pre-test probability of coronary artery disease.

A large proportion of patients referred for functional evaluation of coronary artery disease and for consideration of the need of revascularisation has a history of myocardial infarction. Some investigators described an association between increased mortality for patients with stable coronary disease and exercise-induced ventricular arrhythmias early after acute myocardial infarction,[39] whereas other investigators did not find such an association.[47] Few studies have evaluated the relation between myocardial perfusion abnormalities and exercise-induced ventricular arrhythmias early after acute myocardial infarction.[48] However, this relation has not been studied in patients referred for exercise stress testing late after acute myocardial infarction. We analysed the relation between exercise-induced ventricular arrhythmias and scintigraphic markers of myocardial ischemia and viability in patients referred for exercise stress testing late after acute myocardial infarction.

REFERENCES

1. Elhendy A, van Domburg RT, Bax JJ, Poldermans D, Nierop PR, Kasprzak JD, Roelandt JRTC. Optimal criteria for the diagnosis of coronary artery disease by dobutamine stress echocardiography. *Am J Cardiol 1998;82:1339-1344.*
2. Geleijnse ML, Fioretti PM, Roelandt JRTC. Methodology, feasibility, safety and diagnostic accuracy of dobutamine stress echocardiography. *J Am Coll Cardiol 1997;30:595-606.*
3. Rahimtoola SH. Importance of diagnosing hibernating myocardium: how and in whom? *J Am Coll Cardiol 1997;30:1701-1706.*
4. Dilsizian V, Bonow RO. Current diagnostic techniques of assessing myocardial viability in hibernating and stunned myocardium. *Circulation 1993;87:1-20.*
5. Faletra F, Crivellaro W, Pirelli S, Parodi O, De Chiara F, Cipriani M, Corno R, Pezzano A. Value of transthoracic two-dimensional echocardiography in predicting viability in patients with healed Q-wave anterior wall myocardial infarction. *Am J Cardiol 1995;76:1002-1006.*
6. Meluzin J, Cigarroa CG, Brickner ME, Cerney J, Spinarova L, Frelich M, Stetka F, Groch L, Grayburn PA. Dobutamine echocardiography in predicting improvement in global left ventricular systolic function after coronary bypass or angioplasty in patients with healed myocardial infarcts. *Am J Cardiol 1995;76:877-880.*
7. Afridi I, Kleiman NS, Raizner AE, Zoghbi WA. Dobutamine echocardiography in myocardial hibernation. Optimal dose and accuracy in predicting recovery of ventricular function after coronary angioplasty. *Circulation 1995;91:663-670.*
8. Cigarroa CG, DeFilippi CR, Brickner ME, Alvarez LG, Wait MA, Grayburn PA. Dobutamine stress echocardiography identifies hibernating myocardium and predicts recovery of left ventricular function after coronary revascularisation. *Circulation 1993;88:430-436.*
9. Spencer KT, Bednarz J, Rafter PG,Korcarz C, Lang RM. Use of harmonic imaging without echocardiographic contrast to improve two-dimensional image quality. *Am J Cardiol 1998;82:794-799.*
10. Senior R, Soman P, Khattar RS, Lahiri A. Improved endocardial visualisation with second harmonic imaging compared with fundamental two-dimensional echocardiographic imaging. *Am Heart J 1999;138:163-168.*
11. Kasprzak JD, Paelinck B, Ten Cate FJ, Vletter WB, de Jong N, Poldermans D, Elhendy A, Bouakaz A, Roelandt JR. Comparison of native and contrast-enhanced harmonic echocardiography for visualisation of left ventricular endocardial border. *Am J Cardiol 1999;83:211-217.*

12. Caidahl K, Kazzam E, Lidberg J, Neumann Andersen G, Nordanstig J, Rantapaa Dahlqvist S, Waldenstrom A, Wikh R. New concept in echocardiography: harmonic imaging of tissue without use of contrast agent. *Lancet 1998;352:1264-1270.*
13. Franke A, Hoffmann R, Kühl HP, Lepper W, Breithardt OA, Schormann M, Hanrath P. Non-contrast second harmonic imaging improves interobserver agreement and accuracy of dobutamine stress echocardiography in patients with impaired image quality. *Heart 2000;83:133-140.*
14. Panza JA, Dilsizian V, Laurienzo JM, Curiel RV, Katsiyiannis PT. Relation between thallium uptake and contractile response to dobutamine. Implication regarding myocardial viability in patients with chronic coronary artery disease and left ventricular dysfunction. *Circulation 1995;91:990-998.*
15. Nagueh SF, Mikati I, Weilbaecher D, Reardon MJ, Al-Zaghrini GJ, Cacela D, He ZX, Letsou G, Noon G, Howell JF, Espada R, Verani MS, Zoghbi WA. Relation of the contractile reserve of hibernating myocardium to myocardial structure in humans. *Circulation 1999;100:490-496.*
16. Dilsizian V, Bonow RO. Current diagnostic techniques of assessing myocardial viability in hibernating and stunned myocardium. Circulation 1993;87:1-20.
17. Goldstein S. Beta-blocking drugs and coronary heart disease. *Cardiovasc Drugs Ther 1997;11:219-225.*
18. Blazing MA, O'Connor CM. Evidences supporting secondary prevention strategies. *Curr Opin Cardiol 1999;14:303-309.*
19. Poldermans D, Rambaldi R, Fioretti PM, Boersma E, Thomson IR, Van Sambeek MRHM, Van Urk H. Prognostic value of dobutamine-atropine stress echocardiography for peri-operative and late cardiac events in patients scheduled for vascular surgery. *Eur Heart J 1997;18 (Suppl D):D86-D96.*
20. McNeill AJ, Fioretti PM, El-Said M, Salustri A, Forster T, Roelandt JRTC. Enhanced sensitivity for the detection of coronary artery disease by addition of atropine to dobutamine stress echocardiography. *Am J Cardiol 1992;70:41-46.*
21. Poldermans D, Bax JJ, Thompson IR, Boersma E, et al. Role of dobutamine stress echocardiography for preoperative cardiac risk assessment before major vascular surgery: a diagnostic tool comes of age. *Echocardiography 2000;17:79-91.*
22. Wu JC, Yun JJ, Heller EN, Dione DP, DeMan P, Liu YH, Zaret BL, Wackers FJ, Sinusas AJ. Limitations of dobutamine for enhancing flow heterogeneity in the presence of single coronary stenosis: implications for technetium-99m sestamibi imaging. *J Nucl Med 1998;39:417-425.*
23. Calnon DA, Glover DK, Beller GA, Vanzetto G, Smith WH, Watson DD, Ruiz M. Effects of dobutamine stress on myocardial blood flow, technetium-99m sestamibi

uptake, and systolic wall thickening in the presence of coronary artery stenosis: implications for dobutamine stress testing. *Circulation 1997;96:2353-2360.*

24. Marwick T, D'Hondt AM, Baudhuin T, Willemart B, Wijns W, Detry JM, Melin J. Optimal use of dobutamine stress for the detection and evaluation of coronary artery disease: combination with echocardiography, scintigraphy or both? *J Am Coll Cardiol 1993;22:159-167.*
25. Senior R, Sridhara BS, Anagnostou E, Handler C, Raftery EB, Lahiri A.. Synergistic value of simultaneous stress dobutamine sestamibi single-photon emission computerised tomography and echocardiography in the detection of coronary artery disease. *Am Heart J 1994;821:713-718.*
26. Elhendy A, Geleijnse ML, Roelandt JR, van Domburg RT, Ten Cate FJ, Nierop PR, Bax JJ, El-Refaee M, Ibrahim MM, El-Said GM, Fioretti PM. Comparison of dobutamine stress echocardiograph and 99m-technetium-sestamibi SPECT myocardial perfusion scintigraphy in predicting the extent of coronary artery disease in patients with healed myocardial infarction. *Am Journal Cardiol 1997;7:7-12.*
27. Gunalp B, Dokumaci B, Uyan C, Vardareli E, Isik E, Bayhan H, Ozguven M, Ozturk E. Value of dobutamine technetium 99m sestamibi SPECT and echocardiography in detection of coronary artery disease compared with coronary angiography. *J Nucl Med 1993;34:889-894.*
28. Hendel RC, Parker MA, Wackers FJ, Rigo P, Lahiri A, Zaret B. Reduced variability of interpretation and improved imaging quality with a technetium 99m labelled tetrofosmin. *J Nucl Cardiol 1994;1:509-514.*
29. Khattar RS, Hendel RC, Crawley JC, Wackers FJ, Rigo P, Zaret BL, Sridhara BS, Lahiri A. Improved diagnostic accuracy of planar imaging with technetium 99m tetrofosmin compared with tallium-201 for the detection of coronary artery disease. *J Nuclear Cardiol 1997;4:291-297.*
30. Shanoudy H, Raggi P, Beller GA, Soliman A, Ammermann EG, Kastner RJ, Watson DD. Comparison of technetium 99m tetrofosmin and thallium 201 single photon emission computed tomography imaging for detection of myocardial perfusion defects in patients with coronary artery disease. *J Am Coll Cardiol 1998;31:331-337.*
31. Hays JT, Mahmarian JJ, Cochran AJ, Verani MS. Dobutamine thallium 201 tomography for evaluation patients with suspected coronary artery disease unable to undergo exercise or vasodilator pharmacologic stress testing. *J Am Coll Cardiol 1993;21:1583-1590.*
32. Dakik HA, Vemphaty H, Verani MS. Tolerance, haemodynamic changes and safety of dobutamine stress perfusion imaging. *J Nucl Cardiol 1996;3:410-414.*

33. Houghton JL, Frank MJ, Carr AA, von Dohlen TW, Prisant LM. Relation among impaired coronary flow reserve, left ventricular hypertrophy and thallium perfusion defects in patients without obstructive coronary artery disease. *J Am Coll Cardiol 1990;15:43-51.*
34. Aguirre JM, Rodriguez E, Ruiz de Azua E, Urrengoetxea J, Faus JM, Caso R, Iriarte M. Segmentary coronary reserve in hypertensive patients with echocardiographic left ventricular hypertrophy, gammagraphic ischemia and normal coronary angiography. *Eur Heart J 1993;14:2:25-31*
35. Gibbons RJ, Balady GJ, Beasley JW, Bricker JT, Duvernoy WF, Froelicher VF, Mark DB, Marwick TH, McCallister BD, Thompson PD Jr, Winters WL, Yanowitz FG, Ritchie JL, Cheitlin MD, Eagle KA, Gardner TJ, Garson A Jr, Lewis RP, O'Rourke RA, Ryan TJ. ACC/AHA guidelines for exercise testing. A report of the American College of Cardiology/American Heart Association Task Force of Practice Guidelines/Committee on Exercise Testing. *J Am Coll Cardiol 1997:30;260-311.*
36. Candinas R, Podrid P. Evaluation of cardiac arrhythmias by exercise testing. *Hertz 1990;15:21-27.*
37. Busby M, Shetrin EA, Fleg JL. Prevalence and long-term significance of exercise-induced frequent or repetitive ventricular ectopic beats in apparently healthy volunteers. *J Am Coll Cardiol 1989;14:1659-1665.*
38. Fleg JL, Lakatta EG. Prevalence and prognosis of exercise-induced nonsustained ventricular tachycardia in apparently healthy volunteers. *Am J Cardiol 1984,54:762-764.*
39. Califf RM, McKinnis RA, McNeer JF, Harrell FE Jr, Lee KL, Pryor DB, Waugh RA, Harris PJ, Rosati RA, Wagner GS. Prognostic value of ventricular arrhythmias associated with treadmill exercise testing in patients studied with cardiac catheterization for suspected ischaemic heart disease. *J Am Coll Cardiol 1983;2:1060-1067.*
40. Yang JC, Wesley RC Jr, Froelicher VF. Ventricular tachycardia during routine treadmill testing. Risk and prognosis. *Arch Int Med 1991;151:349-353.*
41. Specchia G, La Rovere MT, Falcone C, Campana C, Traversi E, Caizzi V, De Servi S. Cardiac arrhythmias during exercise-induced myocardial ischemia in patients with coronary artery disease. *Eur Heart J 1986; 7 (Suppl A):45-52.*
42. Sami M, Chaitman B, Fisher L, Holmes D, Fray D, Alderman E. Significance of exercise-induced ventricular arrhythmias in stable coronary artery disease: a coronary artery surgery study project. *Am J Cardiol 1984;54:1182-1188.*
43. Henry RL, Kennedy GT, Crawford MH. Prognostic value of exercise-induce ventricular ectopic activity for mortality after acute myocardial infarction. *Am J Cardiol 1987:59:1251-1255.*

44. Saunamaki KI, Andersen JD. Post-myocardial infarction exercise-testing: clinical significance of a left ventricular function index and ventricular arrhythmias. A prospective study. *Acta Med Scand 1985;218:271-278.*
45. Nair CK, Thomson W, Aronow WS, Pagano T, Ryschon K, Sketch MH. Prognostic significance of exercise-induced complex ventricular arrhythmias in coronary artery disease with normal and abnormal left ventricular ejection fraction. *Am J Cardiol 1984;54:1136-1138.*
46. Marieb MA, Beller GA, Gibson RS, Lerman BB, Kaul S. Clinical relevance of exercise-induced ventricular arrhythmias in suspected coronary artery disease. *Am J Cardiol 1990;66:172-178.*
47. Schweikert RA, Pashkow FJ, Snader CE, Marwick TH, Lauer MS. Association of exercise induced ventricular ectopic activity with thallium myocardial perfusion and angiographic coronary artery disease in stable, low-risk populations. *Am J Cardiol 1999;83:530-534.*
48. Margonato A, Mailhac A, Bonetti F, Vicedomini G, Fragasso G, Landoni C, Lucignani G, Rossetti C, Fazio F, Chierchia SL.. Exercise induced ischemia arrhythmias in patients with previous myocardial infarction: role of perfusion and tissue viability. *J Am Coll Cardiol 1996;27:593-698.*

OUTLINE OF THE THESIS

Part I:

Part I of the thesis deals with the improvement of imaging properties and of diagnostic information by dobutamine stress echocardiography, as well as with expanding its clinical utility in the diagnosis and risk stratification of coronary artery disease.

As described in chapter two, 80 patients underwent dobutamine stress echocardiography. Imaging was performed with both fundamental and second harmonic imaging at rest, at low dose and at peak dose dobutamine infusion. Our objective was to compare the additional value of second harmonic imaging with fundamental imaging for the left ventricular endocardial border delineation at various stages of dobutamine stress echocardiography.

The next step was to assess the value of second harmonic imaging compared with fundamental imaging for the diagnosis of coronary artery disease during dobutamine stress echocardiography. Sixty-four patients underwent dobutamine stress echocardiography with both fundamental and second harmonic imaging. Coronary angiography was considered the gold standard (chapter three).

Next, we considered whether second harmonic imaging improves the accuracy of dobutamine stress echocardiography for identification of viable myocardium. Thirty patients with chronic left ventricular dysfunction underwent dobutamine stress echocardiography with both fundamental and second harmonic imaging. In addition, all patients underwent nuclear imaging (DISA-SPECT) as a reference (chapter four).

Chapter five deals with the influence of a continued beta-blocker therapy in the identification of viable segments during dobutamine stress echocardiography. We studied 21 patients with reduced left ventricular function who underwent both dobutamine stress echocardiography with and without beta-blockers at 1-2 week intervals and DISA-SPECT for the evaluation of viable myocardium.

In chapter six, we assessed the incremental value of dobutamine stress echocardiography for the risk stratification of diabetic patients with known or suspected coronary heart disease. Dobutamine stress echocardiography was performed in 396 patients with diabetes mellitus. Endpoints during follow up were hard cardiac events and all causes of mortality.

Part II

Part II of the thesis deals with the value of 99m-technetium-labelled agents' scintigraphy in the assessment of myocardial ischemia and myocardial viability in specific clinical settings.

In chapter seven, we tested the hypothesis that echocardiography provides a better sensitivity than 99m-technetium-sestamibi SPECT in patients with single vessel coronary disease, due to the potential limitations of sestamibi in this particular patients population. We studied 91 patients with single-vessel coronary disease with dobutamine-atropine stress echocardiography and simultaneous sestamibi SPECT imaging. We compared the accuracy of dobutamine SPECT and of echocardiography for the diagnosis of single-vessel coronary disease. In addition, we evaluated the agreement between both techniques regarding the presence and the extent of stress induced wall motion and myocardial perfusion abnormalities.

In chapter eight, we assessed the accuracy of dobutamine stress myocardial perfusion imaging for the diagnosis and localisation of coronary artery disease in patients with limited exercise capacity. One hundred twenty-four patients with limited exercise capacity and suspected coronary artery disease were tested with dobutamine-atropine 99m-technetium-tetrofosmin SPECT imaging.

In chapter nine, our objective was to evaluate the influence of hypertension on the accuracy of stress myocardial perfusion SPECT imaging in patients with and without hypertension. An exercise stress test in conjunction with 99m-technetium-sestamibi or tetrofosmin SPECT imaging was performed on 332 patients without previous myocardial infarction who underwent coronary angiography. Of these, 137 patients had hypertension.

As described in chapter ten, our purpose was to establish whether, among patients with intermediate pre-test probability of coronary artery disease, the occurrence of exercise-induced ventricular arrhythmias should be interpreted as a marker of a higher probability of coronary artery disease. We studied 302 patients by upright bicycle exercise stress test in conjunction with 99m-technetium SPECT imaging.

Our aim in chapter eleven was to evaluate the relation between exercise-induced ventricular arrhythmias and scintigraphic markers of myocardial ischemia and viability in 171 patients referred for exercise 99m-technetium-sestamibi SPECT late after myocardial infarction.

CHAPTER 2

DOES SECOND HARMONIC IMAGING IMPROVE LEFT VENTRICULAR ENDOCARDIAL BORDER IDENTIFICATION AT HIGHER HEART RATES DURING DOBUTAMINE STRESS ECHOCARDIOGRAPHY?

Source: FB Sozzi, D Poldermans, E Boersma, A Elhendy, JJ Bax, A Borghetti, et al. *J Am Soc Echocardiogr 2000;13:1019-1024.* Adapted.

ABSTRACT

Background. The increased heart rate during dobutamine stress echocardiography may impair endocardial border visualisation. Second harmonic imaging enhances left ventricular border visualisation compared with conventional fundamental imaging at rest. However, its role during dobutamine stress echocardiography is not well established yet.

Objective. Our objective was to compare the additional value of second harmonic imaging to fundamental imaging for the left ventricular endocardial border visualisation during various stages of dobutamine stress echocardiography.

Methods. Eighty patients underwent dobutamine stress echocardiography. Imaging was performed with both fundamental imaging and second harmonic imaging at rest and at low-and peak-dose dobutamine infusion. Endocardial border visualisation was assessed by using a 16-segment/3-point score (0 = well visualised; 1 = poorly visualised; 2 = not visualised).

Results. Heart rate increased from rest (70 ± 13 bpm) to low-dose dobutamine (77 ± 17, $P < 0.01$) and showed further increase at peak dose (129 ± 16, $P < 0.001$ vs. low dose). There was a higher prevalence of segments with an invisible left ventricular endocardial border with fundamental imaging compared with second harmonic imaging at rest (9.4% vs. 6.2%, $P < 0.0001$), at low dose (10.8% vs. 6.3%, $P < 0.0001$), and at peak dose (15.0% vs. 8.2%, $P < 0.0001$). There was an increase in the number of segments with an invisible border from rest to peak stress by fundamental imaging ($P = 0.0001$), whereas the difference was less significant for second harmonic imaging ($P = 0.07$).

Conclusions. Second harmonic imaging improves visualisation of the left ventricular endocardial border compared with fundamental imaging during dobutamine stress echocardiography. The advantage of second harmonic imaging over fundamental imaging is more marked at higher heart rates than at rest.

INTRODUCTION

Stress echocardiography is an important clinical method for the diagnosis and evaluation of coronary artery disease.[1,2] The diagnostic accuracy of the test depends on adequate visualisation of the left ventricular endocardial border at rest and at peak stress.[3,4] The increased heart rate during dobutamine stress echocardiography causes more technical difficulties in the visualisation of the endocardial border, related to increased cardiac motion. Second harmonic imaging has been shown to improve echocardiographic imaging quality compared with fundamental imaging at rest.[5,6] However, limited data are available regarding the effect of heart rate changes on endocardial border visualisation during stress testing. This study examines whether second harmonic imaging improves endocardial border visualisation during dobutamine stress echocardiography and whether the observed improvement is correlated with the heart rate.

METHODS

Patients

We studied eighty patients with known or suspected coronary artery disease (56 men [70%], mean age 57 ± 11 years) referred for evaluation of myocardial ischemia by dobutamine stress echocardiography. No patients were excluded because of inadequate imaging quality. Chest pain was the major complaint in 60 patients (75%). Risk factors for coronary artery disease were diabetes mellitus in 9 patients (11%), hypertension in 20 (25%), hypercholesterolemia in 38 (47%), and smoking in 23 (29%). Forty-one patients (51%) were receiving beta-blockers, 29 (36%) calcium-antagonists, and 34 (42%) nitrates. All patients gave informed consent to undergo the study.

Dobutamine stress echocardiography

After baseline echocardiography, dobutamine was infused at a starting dose of 5 µg/kg per minute for 3 minutes, followed by 10 µg/kg per minute for 3 minutes (low-dose stage). The dobutamine dose was increased by 10 µg/kg per minute every 3 minutes up to a maximum dose of 40 µg/kg per minute. Atropine (up to 2 mg) was intravenously administered at the end of the last stage if the target heart rate was

not achieved. Test end point of dobutamine stress echocardiography was either (1) target heart rate (85% of the maximal heart rate predicted for age), (2) maximal dose of dobutamine and atropine, (3) extensive new wall motion abnormalities, (4) > 2 mV downsloping ST-segment depression measured 80 ms from the J point compared with baseline, (5) hypertension (blood pressure > 240/120 mm Hg), (6) a decrease in systolic blood pressure of > 40 mm Hg compared with rest, (7) significant arrhythmias, or (8) any intolerable adverse effect considered to be the result of dobutamine or atropine. Metoprolol (1 to 5 mg) was used intravenously to reverse the effects of dobutamine/atropine if clinical values did not revert quickly enough to those at baseline.

Echocardiographic imaging

Imaging was performed with a Hewlett-Packard Sonos 5500 (Andover, Mass) ultrasonographic system. A transducer operating at fundamental frequencies of 1.8 or 2.1 MHz and collecting second harmonic frequencies at 3.6 MHz and 4.2 MHz was used. Imaging was

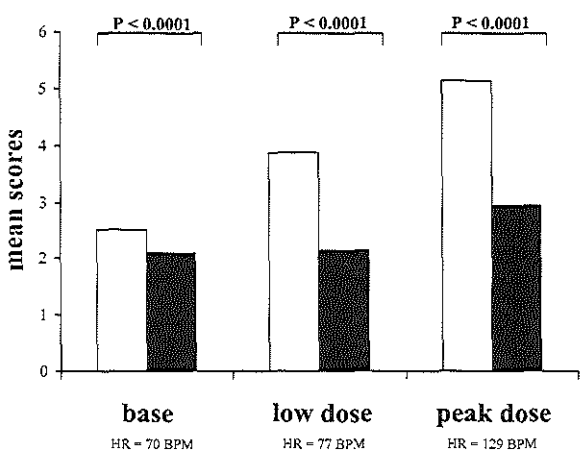


Figure 1

The scores of impairment of endocardial border visualisation at rest and low- and peak-dose dobutamine stress obtained by fundamental imaging (empty bars) and second harmonic imaging (filled bars). Scores were calculated with 16-segment/ 3-grade scoring method where 0 = well visualised, 1 = poorly visualised, 2 = not visualised. A lower score indicates a better imaging quality. HR, Heart rate.

Table 1

Number of left ventricular segments assigned for each score at rest, low-dose dobutamine stress echocardiography, and high-dose dobutamine stress echocardiography with the use of fundamental and second harmonic imaging.

Score	Fundamental imaging	Second harmonic imaging	P value
Rest			
2	121 (9.4%)	80 (6.2%)	< 0.0001
1	37 (2.9%)	22 (1.7%)	0.06
0	1122 (87%)	1178 (92%)	< 0.0001
Low dose			
2	138 (10.8%)	81 (6.3%)	< 0.0001
1	39 (3.0%)	19 (1.5%)	< 0.05
0	1103 (86%)	1180 (92.2%)	< 0.0001
Peak stress			
2	193 (15.0%)	105 (8.2%)	< 0.0001
1	36 (2.8%)	33 (2.6%)	0.8
0	1051 (82.1%)	1142 (89.2%)	< 0.0001

0, well visualised; 1, poorly visualised; 2, not visualised.

performed by using both fundamental imaging and second harmonic imaging at rest and at low- and peak-dose dobutamine infusion. Fundamental imaging was performed before second harmonic imaging. Images were acquired continuously, and analog recordings were saved to videotape at the end of every dose-step. In addition, the baseline, low-dose, peak-stress, and recovery images were displayed in a cineloop format.

Echocardiographic analysis

A 16-segment model for left ventricular wall function analysis was used (as recommended by the American Society of Echocardiography)[7] and visually scored from videotape by 2 experienced reviewers (F.S., D.P.). Each segment was scored for endocardial visualisation as follows: 0 = well visualised; 1 = poorly visualised; 2 = not visualised. Fundamental imaging and second harmonic imaging studies were randomly analysed in intervals of at least 3 days. We deemed the patient unsuitable for dobutamine stress echocardiography when ≥ 5 of the 16 segments were not visualised (score of 2).

Table 2

Number and location of segments in which second harmonic imaging improved endocardial border visualisation at rest and at peak dobutamine stress.

Region	Rest	Peak stress	P value
Anterior wall	16 (20%)	21 (26.2%)	0.2
Inferior wall	3 (3.7%)	6 (7.5%)	0.4
Lateral wall	16 (20%)	27 (33.7%)	< 0.005
Posterior wall	4 (5%)	14 (17.5%)	< 0.005
Septum anterior	5 (6.2%)	9 (11.2%)	0.4
Septum posterior	3 (3.7%)	5 (6.2%)	0.5
Apex	9 (11.2%)	9 (11.2%)	0.99
Overall	56 (4.4%)	91 (7.1%)	< 0.005

Statistical analysis

Continuous variables were expressed as mean ± standard deviation (SD). The chi-square test was used to compare differences between proportions. The paired Student *t* test was used for analysis of continuous data. P values < 0.05 were considered statistically significant.

RESULTS

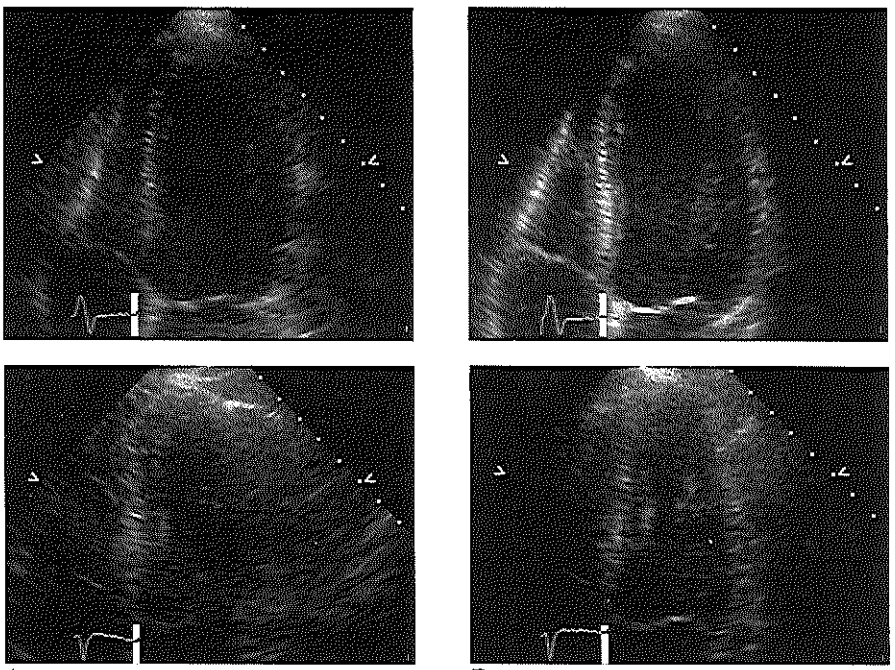
Hemodynamic response

Heart rate increased from rest (70 ± 13 bpm) to low-dose dobutamine (77 ± 17, P < 0.01) and showed further increase at peak dose (129 ± 16, P < 0.001 vs. low dose). Blood pressure was 128/73 ± 22 mm Hg at rest, 129/70 ± 24 mm Hg at low dose, and 131/70 ± 30 mm Hg at peak stress (P = 0.3 for peak vs. low dose).

Echocardiographic data

A total of 1280 myocardial segments were analysed. The number of segments assigned for each score of identification of the endocardial border at rest, low dose, and peak stress are presented in Table 1 for both fundamental imaging and second harmonic imaging.

There was a significant increase in the number of segments with an invisible endocardial border from rest to peak stress on fundamental imaging (P < 0.0001), whereas the difference was less significant for second harmonic imaging (P = 0.07).



A B

Figure 2

Apical 4-chamber views imaged in fundamental imaging (A) and second harmonic imaging (B) at rest (upper panels) and at peak stress (lower panels). Note improved endocardial border definition of the lateral wall in the second harmonic images at rest and at peak stress.

The mean scores of endocardial visualisation (with the 16-segment/ 3-point score) for both fundamental imaging and second harmonic imaging at various stages of dobutamine stress echocardiography are presented in Figure 1.

The score was higher for fundamental imaging than second harmonic imaging at rest, low dose, and peak stress. However, the differences in the scores between the two imaging methods were most significant at peak stress compared with the difference at rest ($P < 0.0001$) and at low dose compared with the difference at rest ($P < 0.013$). Second harmonic imaging improved the score of visualisation of left ventricular endocardial border, compared with fundamental imaging, in 56 segments (4.4%) at rest and 91 segments (7.1%) at peak stress ($P < 0.005$) (Table 2).

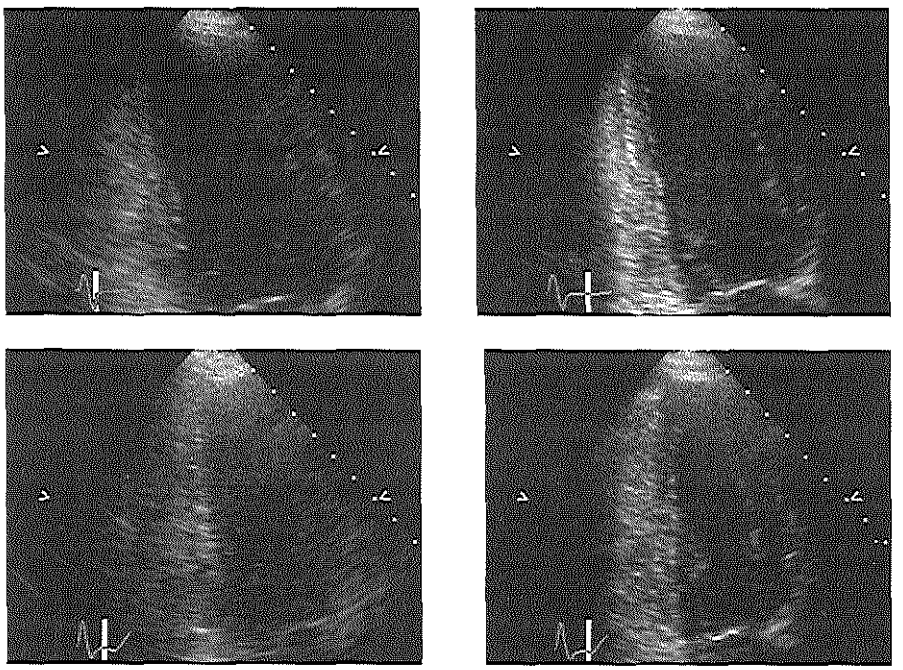


Figure 3

Apical 2-chamber views imaged in fundamental (A) and second harmonic imaging (B) at rest (upper panels) and at peak stress (lower panels). Note improved endocardial border definition of the anterior wall in the second harmonic images at rest and at peak stress.

The distributions of segments in which second harmonic imaging improved endocardial border visualisation at rest and at peak stress are shown in Table 2. The anterior and the lateral walls were the most frequent locations for such improvement. The proportion of segments in which second harmonic imaging improved endocardial visualisation was larger at peak stress compared with rest. This was most marked in the lateral and the posterior wall. Figures 2 and 3 are examples of improved endocardial border visualisation by second harmonic imaging.

The quality of endocardial border delineation by second harmonic imaging improved more in the basal area than in the middle or apical areas, in particularly at peak stress. However, the difference between the two techniques was not statistically significant.

The number of patients deemed unsuitable for dobutamine stress echocardiography (invisible endocardial border in ≥ 5 segments) was 3 by fundamental imaging (4%) vs. 2 patients by second harmonic imaging (2%) at rest (P = 0.99), 4 patients by fundamental imaging (5%) vs. 1 patient by second harmonic imaging (1%) at low dose, and 9 patients by fundamental imaging (11%) vs. 3 by second harmonic imaging (4%) at peak stress (P = 0.13).

The improved endocardial border definition obtained by second harmonic imaging was observed both in myocardial segments expressing normal wall motion and in ischemic segments. In fact, at peak stress, the numbers of ischemic segments well visualised (score of 0) were 146 (64%) of the total 229 ischemic segments with the use of fundamental imaging and 253 (80%) of the total 317 with second harmonic imaging. Reduced wall motion did not limit the definition of endocardial motion.

Discussion

Our study demonstrated that the advantage of second harmonic imaging over fundamental imaging for left ventricular endocardial border delineation is sustained during dobutamine stress echocardiography. The use of second harmonic imaging resulted in a higher feasibility of the left ventricular endocardial border visualisation at rest and low- and peak-dose dobutamine.[8] The difference between both imaging modalities was more marked during stress. In addition, at peak stress the percentage of patients with invisible endocardial border in ≥ 5 segments, indicating infeasible dobutamine stress echocardiography results, increased from 4% to 11% with fundamental imaging. This percentage increased only marginally from 3% to 4% with second harmonic imaging. These data indicate that the image quality of second harmonic imaging is less affected by an increase in heart rate compared with fundamental imaging; however, the difference is not statistically significant (P = 0.13). Second harmonic imaging improved the score of visualisation of the left ventricular endocardial border compared with fundamental imaging in 56 segments (4.4%) at rest and 91 segments (7.1%) at peak stress (P < 0.005 vs. rest). The majority of left ventricular segments with invisible borders by fundamental imaging both at rest and at peak stress were located in the anterior and lateral walls. This may be explained by the fact that these segments are tangential to the ultrasound beam.[9-12] The

improvement with second harmonic imaging was particularly evident in these walls. These results are in agreement with a previous study by Zaglavara et al,[8] which showed improved endocardial border delineation by second harmonic imaging, especially in the anterior and lateral walls.

The diagnostic accuracy of dobutamine stress echocardiography is mainly dependent on proper endocardial border visualisation during rest and stress. Therefore techniques that can potentially improve endocardial border visualisation are important in the optimisation of the clinical utility of stress testing and in the reduction of interobserver variability.[13,14] Our study showed that the value of second harmonic imaging is even more evident during stress than rest. Therefore, its role is extended and is more valuable during stress echocardiography than in rest studies.

Basic considerations

With second harmonic imaging, the signal returned by the tissue includes not only the transmitted fundamental frequency, but also the signals of other frequencies—most notably the harmonic frequency, which is twice the fundamental frequency. The ultrasonographic system separates out the two components and then processes the harmonic signal alone. Ultrasound beams formed with the harmonic signals have interesting properties. One of those properties is that the beam implied by the space between the dashed lines of focus is narrower than the beam for the conventional narrow aperture technique, and it also involves fewer side lobes.[15] Harmonic imaging provides a double benefit: it produces a narrower beam (which improves resolution) and produces more energy in the harmonic beam (which benefits imaging). The improvement in beam width and reduction in side lobes will significantly improve grey-scale contrast resolution. In addition, second harmonic imaging eliminates undesirable near-field artefacts and decreases the clutter.[16] For these reasons, the image results are improved.

Limitations of the study

Second harmonic imaging yields a characteristic grainy appearance of the myocardium. Therefore it was not possible to blind the observer to whether a particular image was obtained in fundamental or harmonic mode because the images are easily distinguishable. The identification of the type of imaging could result in some bias during interpretation of the images.

CONCLUSION

Second harmonic imaging provides better endocardial border visualisation at rest and at low- and peak-dose dobutamine stress when compared with fundamental imaging. The advantage of second harmonic imaging over fundamental imaging is more significant during stress in association with an increased heart rate. Therefore, second harmonic imaging can significantly improve interpretation of the results of dobutamine stress echocardiography.

REFERENCES

1. Segar DS, Brown SE, Sawada SG, Ryan T, Feigenbaum H. Dobutamine stress echocardiography: correlation with coronary lesion severity as determined by quantitative angiography. *J Am Coll Cardiol 1992;19:1197-1202.*
2. Elhendy A, van Domburg RT, Bax JJ, Poldermans D, Nierop PR, Kasprzak JD, Roelandt JRTC. Optimal criteria for the diagnosis of coronary artery disease by dobutamine stress echocardiography. *Am J Cardiol 1998;82:1339-1344.*
3. Crouse LJ, Cheirif J, Hanly DE, Kisslo JA, Labovitz AJ, Raichlen JS, Schutz RW, Shah PM, Smith MD. Opacification and border delineation improvement in patients with suboptimal endocardial border definition in routine echocardiography: results of the Phase III Albumex Multicenter Trial. *J Am Coll Cardiol 1993; 22:1494-1500.*
4. Porter TR, Xie F, Kricsfeld A, Chiou A, Dabestani A. Improved endocardial border resolution during dobutamine stress echocardiography with intravenous sonicated dextrose albumin. *J Am Coll Cardiol 1994;23:1440-1443.*
5. Kasprzak JD, Paelinck B, Ten Cate FJ, Vletter WB, de Jong N, Poldermans D, Elhendy A, Bouakaz A, Roelandt JRTC. Comparison of native and contrast-enhanced harmonic echocardiography for visualisation of left ventricular endocardial border. *Am J Cardiol 1999;83:211-217.*
6. Mulvagh SL, Foley DA, Belohlavek M, Seward JB. Image enhancement by noncontrast harmonic echocardiography. Part I. Qualitative assessment of endocardial visualisation. *Mayo Clin Proc 1998;73:1062-1065.*
7. Bourdillon PD, Broderick TM, Sawada SG, Armstrong WF, Ryan T, Dillon JC, Fineberg NS, Feigenbaum H. Regional wall motion index for infarct and noninfarct regions after reperfusion in acute myocardial infarction: comparison with global wall motion index. *J Am Soc Echocardiogr 1989;2:398-407.*
8. Zaglavara T, Norton M, Cumberledge B, Morris D, Irvine T, Cummins C, Schuster J, Kenny A. Dobutamine stress echocardiography: improved endocardial border definition and wall motion analysis with tissue harmonic imaging. *J Am Soc Echocardiogr 1999;12:706-713.*
9. Spencer KT, Bednarz J, Rafter PG, Korkarz C, Lang RM. Use of harmonic imaging without echocardiographic contrast to improve two-dimensional image quality. *Am J Cardiol 1998;82:794-899.*
10. Lafitte S, Lasserre R, Couffinhal T, Dos Santos P, Coste P, Roudaut R. Superiority of second harmonic imaging for echocardiographic measurement of left ventricular volumes: comparison with angiocardiography. *Arch Mal Coeur 1999;92:867-874.*

11. Kornbluth M, Liang DH, Paloma A, Schnittger I. Native tissue harmonic imaging improves endocardial border definition and visualisation of cardiac structures. *J Am Soc Echocardiogr 1998;11:693-701.*
12. Belohlavek M, Tanabe K, Mulvagh SL, Foley DA, Greenleaf JF, Seward JB. Image enhancement by noncontrast harmonic echocardiography. Part II. Quantitative assessment with use of contrast-to-speckle ratio. *Mayo Clin Proc1998;73:1066-1070.*
13. Caidahl K, Kazzam E, Lidberg J, Neumann Andersen G, Nordanstig J, Rantapaa Dahlqvist S, Waldenstrom A, Wikh R. New concept in echocardiography: harmonic imaging of tissue without use of contrast agent. *Lancet 1998;352:1264-1270.*
14. Senior R, Soman P, Khattar RS, Lahiri A. Improved endocardial visualisation with second harmonic imaging compared with fundamental two-dimensional echocardiographic imaging. *Am Heart J 1999;138:163-168.*
15. Tranquart F, Grenier N, Eder V, Pourcelot L. Clinical use of ultrasound tissue harmonic imaging. *Ultrasound Med Biol 1999;25:889-894.*
16. Thomas JD, Rubin DN. Tissue harmonic imaging: why does it work? *J Am Soc Echocardiogr 1998;11:803-808.*

CHAPTER 3

SECOND HARMONIC IMAGING IMPROVES SENSITIVITY OF DOBUTAMINE STRESS ECHOCARDIOGRAPHY FOR THE DIAGNOSIS OF CORONARY ARTERY DISEASE

Source: FB Sozzi, D Poldermans, JJ Bax, E Boersma, W Vletter, A Elhendy, et al. *Am Heart J 2001;142:153-159.* Adapted.

ABSTRACT

Objective. Our purpose was to assess the value of second harmonic imaging compared with fundamental imaging for the diagnosis of coronary artery disease during dobutamine stress echocardiography.

Methods. Sixty-four patients underwent dobutamine stress echocardiography with both fundamental imaging and second harmonic imaging. Coronary angiography was performed within 3 months. Ischemia was defined as new or worsening wall motion abnormalities in 1 segment during dobutamine stress echocardiography. Coronary artery disease was defined as a 70% luminal diameter stenosis in 1 coronary artery by coronary angiography.

Results. There was a higher prevalence of segments with invisible border with fundamental compared with second harmonic imaging both at rest (11% vs. 8%, $P < 0.05$) and at peak stress (17% vs. 10%, $P < 0.001$). Significant coronary artery disease was present in 49 (77%) patients. The sensitivity of dobutamine stress echocardiography for detection of coronary artery disease by fundamental and second harmonic imaging was, respectively, 78% and 94% ($P < 0.05$), whereas specificity was similar (73% vs. 73%). Second harmonic imaging had a particularly higher sensitivity for the diagnosis of 1-vessel disease (93% vs. 50%, $P < 0.05$).

Conclusion. The use of second harmonic imaging improves the sensitivity of dobutamine stress echocardiography for the diagnosis of coronary artery disease compared with fundamental imaging, particularly for one-vessel coronary disease, whereas specificity remains unchanged.

Introduction

Dobutamine stress echocardiography is an increasingly used technique for the diagnosis and functional evaluation of coronary artery disease. The accuracy of dobutamine stress echocardiography relies on the detection of transient new wall motion abnormalities. However, inadequate visualisation of left ventricular endocardial borders at rest and during stress may reduce the sensitivity of the test. Previous studies have shown a sensitivity of dobutamine stress echocardiography for detection of coronary artery disease ranging between 54% and 86%.[1-5] Techniques that improve left ventricular wall visualisation may increase the sensitivity of the test by providing more comprehensive and clear visualisation of the endocardial border and thereby increasing the probability of detecting myocardial ischemia. Second harmonic imaging is a recently introduced technique that differs from conventional fundamental imaging in that it transmits ultrasound at one frequency and receives at twice the transmitted frequency. This results in a better image quality compared with fundamental imaging.[6-9] However, few data are available regarding the accuracy of dobutamine stress echocardiography with second harmonic imaging for the diagnosis of coronary artery disease compared with fundamental imaging.[10] The aim of this study was to assess the additional value of second harmonic imaging during dobutamine stress echocardiography for the overall and regional diagnosis of coronary artery disease compared with fundamental imaging.

Methods

Patient selection

The study population consisted of 64 consecutive patients who underwent dobutamine stress echocardiography for evaluation of coronary artery disease and coronary angiography within 3 months from dobutamine stress echocardiography. Patients were not selected on the basis of imaging quality. Clinical characteristics are presented in Table I.

The local medical ethics committee approved the study protocol. Patients gave informed consent to undergo the test.

Table I
Clinical characteristics of the study population.

Characteristics (n = 64)	No.	%
Sex (male)	45	70
Age (yrs.)	59 ± 11	
Previous myocardial infarction	35	55
Angina pectoris	47	73
Hypertension	16	25
Diabetes mellitus	7	11
Beta-blockers	32	50
Calcium channels blockers	23	36
Nitrates	27	42

Dobutamine stress test

Dobutamine stress echocardiography was performed as described previously.[4] Imaging was performed with a Hewlett-Packard Sonos 5500 (Andover, Mass). A transducer operating at fundamental frequencies of 1.8 or 2.1 MHz and collecting second harmonic frequencies at 3.6 or 4.2 MHz was used. Imaging was performed by using both fundamental imaging and second harmonic imaging at rest, at low dose, and at peak stress. Images were continuously acquired and recorded on videotapes at the end of every dose-step with two different videotapes, one for fundamental imaging and one for second harmonic imaging. In addition, the baseline, low-dose, peak stress, and recovery images were displayed in a cineloop format. The left ventricle wall was divided into 16 segments.[11] A "visualisation score" of the endocardial border of the left ventricle was derived by scoring each of the 16 segments as follows: 0 = invisible border, 1 = partially visualised, 2 = clearly visualised. Segmental wall motion was scored by a 5-point scale, with 1 = normal, 2 = mild-hypokinesis, 3 = severe hypokinesis, 4 = akinesis, and 5 = dyskinesis. The wall motion score index was derived by dividing the sum of the individual scores of the 16 segments by 16. Ischemia was defined as new or worsened wall motion abnormalities during stress indicated by an increase of wall motion score 1 grade in 1 segment.[4] As we have previously described, ischemia was not considered when akinetic segments at rest became dyskinetic during stress.[3] The fundamental and second harmonic images were analysed

separately by 2 experienced reviewers unaware of the patients' clinical or angiographic data (F. S., D. P.). In case of disagreement, a majority decision was achieved by a third investigator. In a subset of 16 patients (256 segments), the intraobserver agreement for echocardiographic interpretation of resting imaging and dobutamine stress images was also assessed. The assessment of the images was based on both the digitised images displayed in a cineloop format and a review of the images recorded on the videotape. Echocardiographic interpretation was performed in random order in a separate setting for each individual patient. Patient identification was removed from the screen.

Coronary angiography

Coronary angiography was performed within 3 months of dobutamine stress echocardiography. Significant coronary artery disease was defined as a diameter stenosis $\geq 70\%$ in ≥ 1 major epicardial artery using the quantitative analysis method described previously from our laboratory.[12]

The anterior, apical, septal, and anteroseptal segments were assigned to the left anterior descending coronary artery. The posterior and lateral segments were assigned to the left circumflex coronary artery. The inferior and basal septal segments were assigned to the right coronary artery. The apical lateral segment was considered as an overlap segment between the left anterior descending and the left circumflex coronary artery. The apical inferior segment was considered an overlap segment between the left anterior descending and the right coronary artery. Overlap segments were assigned to the regions with concomitant abnormalities.[12]

Statistical analysis

Unless specified, data are presented as mean values ± standard deviation (SD). The chi-square test was used to compare differences between proportions. The Student *t* test was used for analysis of continuous data. Sensitivity, specificity, and accuracy were derived according to the standard definitions and were presented with the 95% confidence intervals (CI). A P value < 0.05 was considered statistically significant. The intraobserver agreement for echocardiographic assessment of resting imaging and dobutamine stress images was presented as percent agreement.

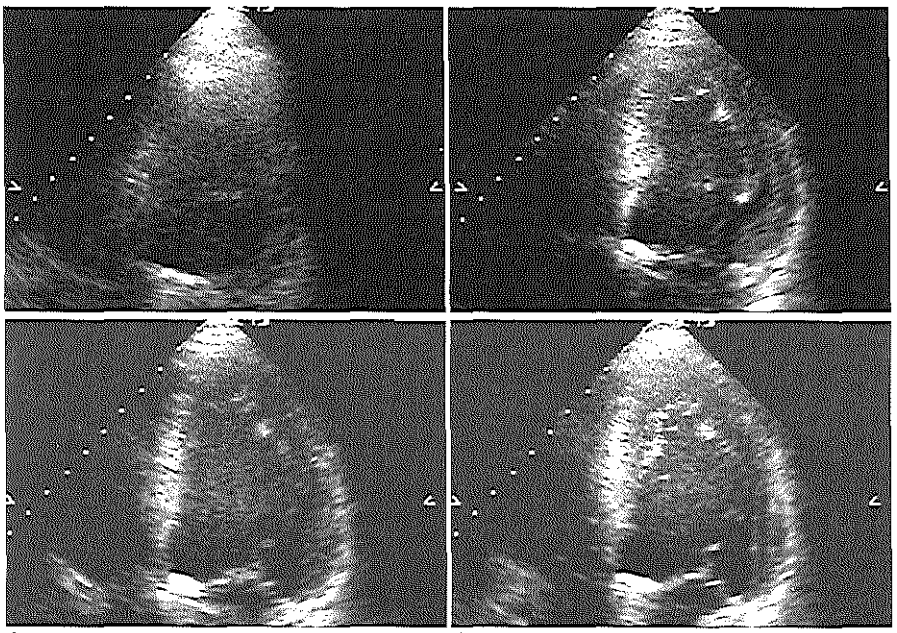


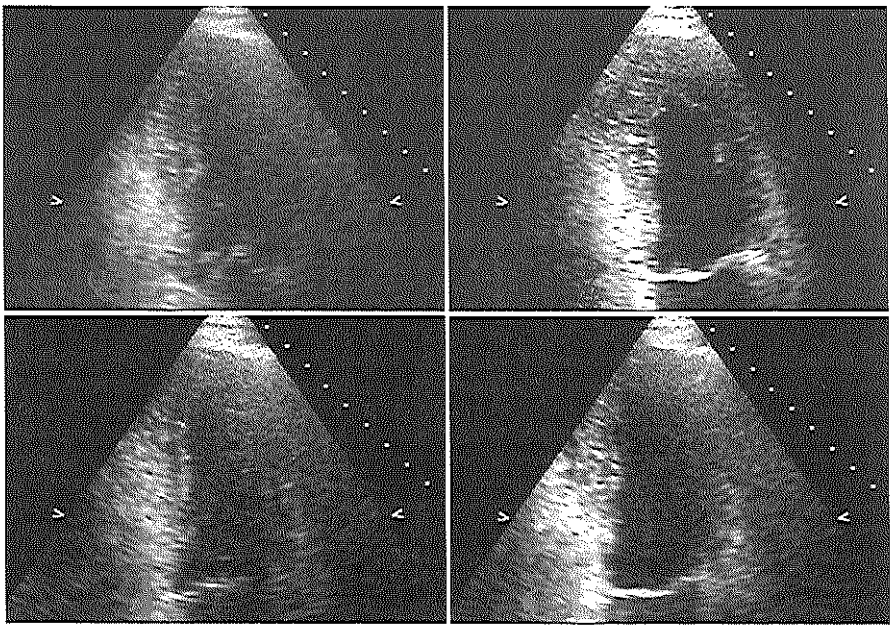
Figure 1

Example of improvement of endocardial border delineation (especially for the lateral wall) with use of second harmonic imaging during dobutamine stress echocardiography study. Images are obtained from the apical 4-chamber view at rest (upper) and at peak stress (lower), by fundamental imaging (A) and second harmonic imaging (B).

RESULTS

Hemodynamic data of dobutamine stress test

Dobutamine-atropine induced a significant increase of heart rate (70 ± 13 at rest to 129 ± 6 beats/min at peak stress, $P < 0.001$), systolic blood pressure (128 ± 22 vs. 133 ± 30 mm Hg, $P < 0.05$), and peak rate-pressure product (8960 ± 2800 to 17157 ± 6600, $P < 0.001$). Test end points were target heart rate in 55 patients (86%), maximal dose of dobutamine and atropine in 2 patients (3%), angina in 2 patients (3%), electrocardiographic changes in 3 patients (5%), supraventricular



A B

Figure 2

Example of improvement of endocardial border delineation (especially for the anterior wall) with use of second harmonic imaging during dobutamine stress echocardiography study. Images are obtained from the apical 2-chamber view at rest (upper) and at peak stress (lower), by fundamental imaging (A) and second harmonic imaging (B).

tachycardia in 1 patient (1.5%), and severe hypotension (decrease in systolic blood pressure > 40 mm Hg compared with rest) in 1 patient (1.5%).

Coronary angiography

Significant coronary artery disease was detected in 49 patients (77%). Fourteen patients (22%) had single-vessel disease, 16 (25%) had 2-vessel disease, and 19 (30%) had 3-vessel disease. Fifteen patients (23%) had no significant coronary artery disease. Significant stenosis involved the left anterior descending coronary artery in 39 patients (61%), the right coronary artery in 34 patients (53%), and the left circumflex coronary artery in 30 patients (47%).

Table II

Number (%) of left ventricular segments assigned for each endocardial border visualisation score at rest and at peak stress of dobutamine echocardiography by use of fundamental and second harmonic imaging.

	Fundamental imaging	Second harmonic imaging	P value
Rest score			
0	114 (11%)	85 (8%)	0.04
1	33 (3%)	31 (3%)	0.9
2	877 (86%)	908 (89%)	0.048
Peak stress score			
0	171 (17%)	106 (10%)	0.0001
1	23 (2%)	33 (3%)	0.2
2	830 (81%)	885 (87%)	0.001

Score 0 = invisible border, 1 = partially visualised border, 2 = well visualised border.

Table III

Accuracy of ischemic pattern at dobutamine stress echocardiography for the diagnosis of significant coronary artery disease with use of fundamental and second harmonic imaging.

Diagnostic parameters	Fundamental imaging (% [patients])	95% CI	Second harmonic imaging (% [patients])	95% CI	P value
Overall diagnosis					
Sensitivity	78 (38/49)	67 - 88	94 (46/49)	88 - 100	0.04*
Specificity	73 (11/15)	62 - 84	73 (11/15)	62 - 84	0.7
Accuracy	77 (49/64)	66 - 87	89 (57/64)	81 - 97	0.1
Sensitivity in 1-vessel disease	50 (7/14)	31 - 69	93 (13/14)	83 - 100	0.03*
Sensitivity in 2-vessel disease	81 (13/16)	68 - 95	94 (15/16)	85 - 100	0.6
Sensitivity in 3-vessel disease	95 (18/19)	87 - 100	95 (18/19)	87 - 100	0.5

*$P < 0.05$.

Table IV

Accuracy of ischemic pattern at dobutamine stress echocardiography for the diagnosis of individual coronary artery disease using fundamental and second harmonic imaging.

Diagnostic parameters	Fundamental imaging (% [patients])	95% CI	Second harmonic imaging (% [patients])	95% CI	P value
LAD					
Sensitivity	72 (28/39)	61 - 83	82 (32/39)	73 - 91	0.4
Specificity	72 (18/25)	61 - 83	64 (16/25)	52 - 76	0.8
Accuracy	72 (46/64)	61 - 83	75 (48/64)	64 - 86	0.8
LCx					
Sensitivity	50 (15/30)	38 - 62	80 (24/30)	70 - 90	0.03*
Specificity	88 (30/34)	80 - 96	91 (31/34)	84 - 98	0.99
Accuracy	70 (45/64)	59 - 82	86 (55/64)	77 - 95	0.05*
RCA					
Sensitivity	73 (25/34)	63 - 84	79 (27/34)	69 - 89	0.8
Specificity	83 (25/30)	74 - 93	73 (22/30)	62 - 84	0.5
Accuracy	78 (50/64)	68 - 88	77 (49/64)	66 - 87	0.99
All arteries					
Sensitivity	66 (68/103)	59 - 73	81 (83/103)	75 - 86	0.03*
Specificity	82 (73/89)	76 - 88	77 (69/89)	71 - 84	0.6
Accuracy	73 (141/192)	67 - 79	79 (152/192)	73 - 85	0.2

*LAD, Left anterior descending artery; LCx, left circumflex artery; RCA, right coronary artery. *P < 0.05.*

Dobutamine stress echocardiography

The score of visualisation of the left ventricle endocardial border, by both imaging methods, at rest and at peak dobutamine stress is presented in Table II.

Second harmonic imaging yielded high-quality images during dobutamine stress echocardiography at rest and at peak stress, as indicated by a lower number of invisible segments (score 0) compared with fundamental imaging. Figures 1 and 2 are examples of improved endocardial border delineation during dobutamine stress echocardiography by the use of second harmonic imaging.

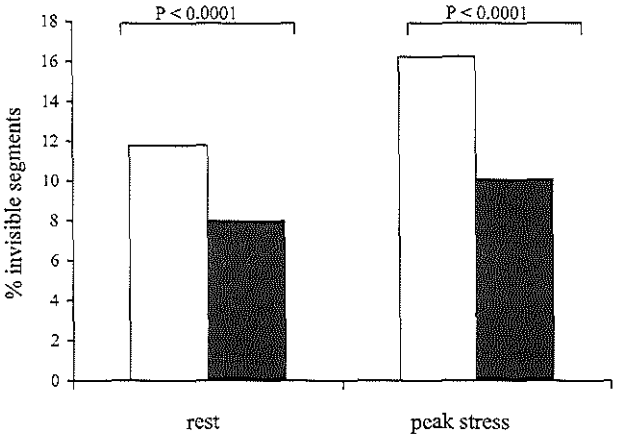


Figure 3

Number (%) of invisible segments (score = 0) at rest and at peak dobutamine stress determined with use of fundamental imaging (open bars) and second harmonic imaging (closed bars).

The wall motion score index increased significantly from rest to peak stress with both techniques (P was 0.007 with fundamental imaging and 0.04 with second harmonic imaging). By use of fundamental and second harmonic imaging, the wall motion score index was, respectively, 1.9 ± 0.7 vs. 1.8 ± 0.6 at rest (P = 0.1) and 2.1 ± 0.5 vs. 2.0 ± 0.5 at peak stress (P = 0.08).

The intraobserver agreement for echocardiographic assessment of resting images and dobutamine stress images was, respectively, 89% and 90% with fundamental imaging and 92% and 94% with second harmonic imaging.

Sensitivity of fundamental imaging and second harmonic imaging for the diagnosis of coronary artery disease

The sensitivity of dobutamine stress echocardiography, for diagnosis of coronary artery disease, was higher with use of second harmonic imaging (P < 0.05). The difference in the sensitivity between fundamental and second harmonic imaging was most marked in patients with 1-vessel coronary artery disease (Table III).

Similarly, sensitivity was significantly improved in the regional diagnosis of coronary artery disease by the use of second harmonic imaging (Table IV).

In particular, the improvement was significantly higher for the diagnosis of left circumflex coronary artery disease ($P < 0.05$). The overall and regional specificity was similar by both techniques.

Discussion

Adequate endocardial border visualisation by echocardiography is a prerequisite for accurate interpretation of regional wall motion abnormalities, which are the hallmark of coronary artery disease. One of the limitations of stress echocardiography has been incomplete segmental endocardial visualisation and therefore impaired interpretability of wall motion in some myocardial regions.[6] Failure to visualise a segment may reduce the ability to detect coronary artery disease. Second harmonic imaging was shown to enhance the left ventricle endocardial border delineation compared with fundamental imaging, especially in patients with a poor acoustic window.[7-10]

This study shows that second harmonic imaging yields high imaging quality during dobutamine stress echocardiography at rest and at peak stress by increasing the number of adequately visualised segments. The sensitivity of dobutamine stress echocardiography for the diagnosis of coronary artery disease was improved by the use of second harmonic imaging, particularly in patients with single-vessel coronary artery disease, without reduction of specificity. The higher sensitivity of second harmonic imaging can be explained by the frequent occurrence of ischemia limited to only one segment.[4] Therefore the increased sensitivity by the use of second harmonic imaging was mostly evident in patients with single-vessel disease as a result of the smaller magnitude of inducible ischemia in these patients compared with patients with multivessel disease.

The lower sensitivity for detection of disease in the left circumflex artery, obtained by fundamental imaging, can be related to the problems with resolution of the endocardium of the lateral wall. The parallel orientation of the wall and the ultrasound beam generates more clutter and near-field artefacts, with consequent loss of lateral resolution. Conversely, second harmonic imaging characterised to reduce these noises produces better imaging quality.[8,9] Therefore, in this study, sensitivity for the diagnosis of left circumflex coronary artery disease was enhanced by the use of second harmonic imaging.

Previous studies with dobutamine stress echocardiography have demonstrated lower sensitivity in patients with single-vessel disease, ranging between 40% and 70%.[5,13-15] The major implication from our study is that second harmonic imaging, by improving endocardial border delineation, makes accurate wall motion interpretation more feasible and thus more reliable in the diagnosis of 1-vessel coronary artery disease. The group of patients with 1-vessel disease may account for the relatively high number of negative test results because the magnitude of transient wall motion abnormalities is less than in patients with multivessel disease. Therefore, failure to evaluate all segments adequately may result in failure to detect ischemia in these patients. Additionally, this study showed that second harmonic imaging improves regional sensitivity for the diagnosis of individual coronary artery disease. Therefore the technique can provide better estimation of the extent of coronary artery disease, which may have important implications in the management and the prognostic stratification of patients with coronary artery disease.

Comparison with previous studies

The sensitivity of dobutamine stress echocardiography with use of fundamental imaging for the diagnosis of coronary artery disease is comparable to that reported by other authors[1,2,13-15] and from previous studies at our center.[4,5]

Kasprzak et al[6] showed that second harmonic imaging with and without contrast agent significantly improves left ventricle endocardial border detection. Without use of contrast, the overall quality of endocardial visualisation reflected by the total endocardial visualisation index was significantly lower at fundamental imaging than at second harmonic imaging. Caidahl et al[7] showed that in 27 patients with possible myocardial disease and in 22 control subjects second harmonic imaging increased the number of acceptable echocardiograms by 14% to 46% in different views. The most pronounced benefit was obtained in the apical 2-chamber view. This finding was confirmed by Spencer et al.[8] In a study of 20 patients with both fundamental and second harmonic imaging, myocardial segments were better visualised with second harmonic imaging in 30% to 73% of cases. During dobutamine stress echocardiography, performed in 17 patients, the number of interpretable segments improved from 64% with fundamental imaging to 84% with second harmonic imaging. Franke et al[10] have shown

that second harmonic imaging improves the accuracy of dobutamine stress echocardiography in patients with impaired image quality. In our study we did not use contrast agents and we may speculate that second harmonic imaging reduces the need of contrast agents for border detection and thus may reduce the costs associated with dobutamine stress echocardiography.

Limitations of the study

The study population was rather small. However, the number of patients in the 3 subgroups was comparable and the analysis showed significance for 1-vessel coronary artery disease.

The interval of 3 months between dobutamine stress echocardiography and angiography can be considered relatively long. However, the clinical course of all these patients was stable within this period of time.

The reviewers of the echocardiograms were not blinded to the type of imaging because of the characteristics of images obtained by second harmonic imaging. Although this may have resulted in interpretation bias, the maintained specificity in association with an increased sensitivity indicates that the additional findings of ischemia, by second harmonic imaging, were representing underlying coronary artery disease and not an overestimation of abnormalities. The high prevalence of patients with underlying coronary artery disease may increase the sensitivity of dobutamine stress echocardiography. However, because the same patients were studied by both techniques, patient population will not influence the improved sensitivity.

Conclusion

The use of second harmonic imaging improves the sensitivity of dobutamine stress echocardiography for the overall and regional diagnosis of coronary artery disease compared with fundamental imaging, without reduction of specificity. Sensitivity is mostly enhanced in patients with single-vessel coronary artery disease.

REFERENCES

1. Schroder K, Schultheiss HP. Coronary artery disease—diagnosis of ischaemia: general considerations. *Eur Heart J 1997;18(D Suppl): D57-62.*
2. Geleijnse ML, Fioretti PM, Roelandt JRTC. Methodology, feasibility, safety and diagnostic accuracy of dobutamine stress echocardiography. *J Am Coll Cardiol 1997;30:595-606.*
3. Arnese M, Fioretti PM, Cornel JH, Postma-Tjoa J, Reijs AE, Roelandt JR. Akinesis becoming diskinesis during high-dose dobutamine stress echocardiography: a marker of myocardial ischemia or a mechanical phenomenon? *Am J Cardiol 1994;73:896-899.*
4. Elhendy A, van Domburg RT, Bax JJ, Poldermans D, Nierop PR, Kasprzak JD, Roelandt JRTC. Optimal criteria for the diagnosis of coronary artery disease by dobutamine stress echocardiography. *Am J Cardiol 1998;82:1339-1344.*
5. Salustri A, Fioretti PM, McNeill AJ, Bozzoli MM, Roelandt JRTC. Pharmacological stress echocardiography in the diagnosis of coronary artery disease and myocardial ischaemia: a comparison between dobutamine and dipyridamole. *Eur Heart J 1992;13:1356-1362.*
6. Kasprzak JD, Paelinck B, Ten Cate FJ, Vletter WB, de Jong N, Poldermans D, Elhendy A, Bouakaz A, Roelandt JR. Comparison of native and contrast-enhanced harmonic echocardiography for visualisation of left ventricular endocardial border. *Am J Cardiol 1999;83:211-217.*
7. Caidahl K, Kazzam E, Lidberg J, Neumann Andersen G, Nordanstig J, Rantapaa Dahlqvist S, Waldenstrom A, Wikh R. New concept in echocardiography: harmonic imaging of tissue without use of contrast agent. *Lancet 1998;352:1264-1270.*
8. Spencer KT, Bednarz J, Rafter PG, Korcarz C, Lang RM. Use of harmonic imaging without echocardiographic contrast to improve two-dimensional image quality. *Am J Cardiol 1998;82:794-799.*
9. Senior R, Soman P, Khattar RS, Lahiri A. Improved endocardial visualisation with second harmonic imaging compared with fundamental two-dimensional echocardiographic imaging. *Am Heart J 1999; 138:163-168.*
10. Franke A, Hoffmann R, Kühl HP, Lepper W, Breithardt OA, Schormann M, Hanrath P. Non-contrast second harmonic imaging improves interobserver agreement and accuracy of dobutamine stress echocardiography in patients with impaired image quality. *Heart 2000;83:133-140.*
11. Shiller NB, Shah PM, Crawford M, DeMaria A, Devereux R, Feigenbaum H, Gutgesell H, Reichek N, Sahn D, Schnittger I. Recommendations of quantitation of the left ventricle by two-dimensional echocardiography: American Society of

Echocardiography committee on standards, subcommittee on quantitation of two-dimensional echocardiograms. *J Am Soc Echocardiogr 1989;2:358-367.*

12. Baptista J, Arnese M, Roelandt JR, Fioretti P, Keane D, Escaned J, Boersma E, di Mario C, Serruys PW. Quantitative coronary angiography in the estimation of the functional significance of coronary stenosis: correlations with dobutamine-atropine stress test. *J Am Coll Cardiol 1994;23:1434-1439.*
13. Rallidis L, Cokkinos P, Tousoulis D, Nihoyannopoulos P. Comparison of dobutamine and treadmill exercise echocardiography in inducing ischemia in patients with coronary artery disease. *J Am Coll Cardiol 1997;30: 1660-1668.*
14. Cohen JL, Ottenweller JE, George AK, Duvvuri S. Comparison of dobutamine and exercise echocardiography for detecting coronary artery disease. *Am J Cardiol 1993;72:1226-1231.*
15. Dagianti A, Penco M, Agati L, Sciomer S, Dagianti A, Rosanio S, Fedele F. Stress echocardiography: comparison of exercise, dipyridamole and dobutamine in detecting and predicting the extent of coronary artery disease. *J Am Coll Cardiol 1995;26:18-25.*

CHAPTER 4

IMPROVED IDENTIFICATION OF VIABLE MYOCARDIUM USING SECOND HARMONIC IMAGING DURING DOBUTAMINE STRESS ECHOCARDIOGRAPHY: COMPARISON WITH FLUORINE-18 FLUORODEOXYGLUCOSE DISA-SPECT

Source: FB Sozzi, D Poldermans, JJ Bax, A Elhendy, EC Vourvouri, R Valkema, et al. *Heart 2001, in press.* **Adapted.**

ABSTRACT

Objective. To determine whether second harmonic imaging can improve the accuracy of dobutamine stress echocardiography for identification of viable myocardium compared to fundamental imaging using nuclear imaging as a reference.

Methods. We studied 30 patients with chronic left ventricular dysfunction (mean ± SD age 60 ± 8 years, 22 male) by dobutamine stress echocardiography. Both fundamental imaging and second harmonic imaging were used. All patients underwent dual-isotope simultaneous acquisition single photon emission computerised tomography (DISA-SPECT) with 99m-technetium-tetrofosmin/18F-fluorodeoxyglucose on a separate day. Myocardial viability was considered present by dobutamine stress echocardiography, when segments with severe dysfunction demonstrated a biphasic, sustained improvement or ischaemic response. Viability criteria on DISA-SPECT were normal or mildly reduced perfusion and metabolism or perfusion/metabolism mismatch.

Results. Using fundamental imaging, 330 segments exhibited severe dysfunction at baseline; 144 (44%) were considered viable. The agreement between dobutamine stress echocardiography by fundamental imaging and DISA-SPECT was 78%, kappa = 0.56. Using second harmonic imaging, 288 segments exhibited severe dysfunction; 138 (48%) were viable. The agreement between dobutamine stress echocardiography and DISA-SPECT was significantly higher when second harmonic imaging was used (89%, kappa = 0.77, P = 0.001 vs. fundamental imaging).

Conclusion. Second harmonic imaging applied during dobutamine stress echocardiography increases the agreement with DISA-SPECT for detection of myocardial viability.

INTRODUCTION

In patients with severe left ventricular dysfunction, myocardial revascularisation reduces heart failure symptoms and improves long-term survival. There is a relationship between the amount of viable tissue and the expected benefit of revascularisation.[1,2] A variety of tests are available and can be broadly divided into two groups, nuclear testing and stress echocardiography. Single-photon emission computed tomography (SPECT) with either 201-thallium or 99m-technetium-labelled agents evaluates myocardial perfusion, which is dependent on cell membrane integrity and active cellular uptake. Positron emission tomography (PET) evaluates myocardial metabolism and allows the detection of metabolic activity in the hypoperfused myocardium.[3-6]

Nuclear imaging techniques are more sensitive as compared to dobutamine stress echocardiography for the detection of viability.[4,7,8] This is most likely due to the fact that nuclear imaging techniques are based on the detection of integrity of cell membrane and preserved perfusion and metabolism (structural viability), whereas dobutamine stress echocardiography relies on the assessment of preserved contractile reserve (functional viability).[8] Dysfunctional myocardium that has suffered more profound ultrastructural damage will probably loose contractile reserve but can still demonstrate intact cell membrane integrity and preserved perfusion and metabolism.[9,10] Besides this physiological explanation for the discrepancy between the tests, technical limitations may be responsible for this discordance due to the suboptimal segmental endocardial border definition, present in at least 30% of patients evaluated by echocardiography using fundamental imaging fundamental imaging.[11-15]

The aim of this study is to determine whether second harmonic imaging can improve the accuracy of dobutamine stress echocardiography for identification of viable myocardium compared to fundamental imaging, using dual isotope (99m-technetium-tetrofosmin and 18F-fluorodeoxyglucose) simultaneous acquisition (DISA) method as a reference.[16]

Table I

Clinical and angiographic characteristics of the study population.

Characteristics (N = 30) Number	%	
Sex (male)	22	73%
Age (years)	60 ± 8*	
Ejection fraction		37.7 ± 15.3*
History of angina pectoris	26	87%
Previous myocardial infarction	28	93%
Anterior	15	50%
Inferior	13	43%
Hypertension	2	7%
Hypercholesterolemia	22	73%
Diabetes mellitus	4	13%
Smoking	10	33%
Beta-blockers	20	67%
Calcium channels blockers	9	30%
Previous coronary artery by-pass	10	33%
Previous PTCA	7	23%
Significant coronary artery disease	30	100%
1-vessel disease	13	43%
2-vessel disease	10	34%
3-vessel disease	7	23%

PTCA = percutaneous transluminal coronary angioplasty

**Mean ± SD*

METHODS

Patients

Thirty patients underwent both dobutamine stress echocardiography and DISA-SPECT for evaluation of myocardial viability. The tests were performed in a random order within 1 week. All patients underwent coronary angiography within 3 months of the two tests. Patients were referred to our imaging laboratory for evaluation of myocardial viability and were not selected on basis of echocardiographic or nuclear imaging quality. Patients' characteristics are presented in Table I. Local medical ethics committee approved the study protocol and all patients gave informed consent to undergo the test.

Dobutamine stress test

After baseline echocardiography, dobutamine was infused at a starting dose of 5 μg/kg per minute for 5 minutes, followed by 10 μg/kg per minute for 5 minutes (low-dose stage). The dobutamine dose was increased by 10 μg/kg per minute every 3 minutes up to a maximum dose of 40 μg/kg per minute. Atropine (up to 2 mg) was administered intravenously at the end of the last stage if the target heart rate was not achieved. End points of the test were: achievement of target heart rate (85% of the maximal heart rate predicted for age); maximal dose of dobutamine and atropine; extensive new wall motion abnormalities; > 2 mV downsloping ST-segment depression measured 80 ms from the J point compared to baseline; hypertension (blood pressure > 240/120 mm Hg), a decrease in systolic blood pressure of > 40 mm Hg compared with rest, significant arrhythmias or any intolerable adverse effect considered to be the result of dobutamine or atropine. Metoprolol (1-5 mg) was used intravenously to reverse the side effects of dobutamine.

Echocardiographic imaging

Imaging was performed with a Hewlett-Packard Sonos 5500 (Andover, Mass, USA) ultrasonographic system. A transducer operating at fundamental frequencies of 1.8 or 2.1 MHz and collecting second harmonic frequencies at 3.6 MHz or 4.2 MHz was used. Imaging was performed by using both fundamental imaging and second harmonic imaging at rest, at low-dose and peak-dose dobutamine infusion. Images were continuously recorded on videotape. Additionally for both fundamental imaging and second harmonic imaging, images were also digitized. The assessment of the images was based on both the digitised images displayed in a cineloop format and a review of the images recorded on the videotape.

Echocardiographic analysis

Two independent reviewers, blinded to the DISA-SPECT and angiographic data, randomly analysed fundamental imaging and second harmonic imaging studies. In case of disagreement, a majority decision was achieved by a third investigator. For segmental analysis of left ventricular function, a 16-segment model was used as suggested by the American Society of Echocardiography.[17] Each segment was scored for endocardial visualisation as follows: 0 = non-visualised; 1 = poorly

visualised; 2 = well visualised. Wall motion was scored at baseline, at low-dose dobutamine infusion and at peak stress. Each segment was scored using a 5-point scale, with 1 = normal, 2 = mild hypokinesis, 3 = severe hypokinesis, 4 = akinesis, 5 = dyskinesis. Four different patterns where defined in segments with severe baseline dysfunction (wall motion score > 2): (1) biphasic response: improvement of wall motion during low dose (either at 5 or 10 μg/kg per minute), followed by worsening of wall motion during high-dose dobutamine; (2) worsening: deterioration of wall motion during low- or high-dose dobutamine (ischaemic response); (3) sustained improvement: continuous improvement at low- and high-dose dobutamine (without deterioration of wall motion); (4) no change: absence of improvement or worsening during the entire test. Dysfunctional segments exhibiting a biphasic, sustained, or ischaemic response were classified as viable, whereas segments with unchanged wall motion were considered non-viable. Myocardial viability was considered absent if akinetic segments became dyskinetic during dobutamine stress echocardiography as demonstrated previously.[18]

DISA-SPECT imaging

Patients received an intravenous dose of 600 MBq 99m-technetium-tetrofosmin to evaluate resting regional perfusion. To enhance cardiac 18F-fluorodeoxyglucose uptake, the patients received an oral dose of 500 mg of Acipimox (Byk, The Netherlands) orally, followed by a carbohydrate-enriched meal. Acipimox is a potent nicotinic acid derivative that reduces plasma levels of free fatty acids, and stimulates cardiac glucose (and 18F-fluorodeoxyglucose) uptake. This meal stimulates endogenous insulin release, thereby further promoting cardiac glucose (and 18F-fluorodeoxyglucose) uptake. 18F-fluorodeoxyglucose (185 MBq) was injected 60 min after the meal. A 45-min period after 18F-fluorodeoxyglucose injection was allowed for myocardial 18F-fluorodeoxyglucose uptake, followed by the dual-isotope simultaneous acquisition SPECT. Data acquisition was performed with a triple-head gamma camera system (Picker Prism 3000 XP, Cleveland, OH, USA) equipped with 511 keV collimators. The energies were centred on the 140 keV photon peak of 99m-technetium-tetrofosmin with a 15% window and on the 511 keV photon peak of 18F-fluorodeoxyglucose with a 15% window. Imaging was performed over 360° (120 sectors of 3°) with a total imaging time of 32 min. Data were stored in a 64x64, 16-bit matrix.

The raw scintigraphic data were reconstructed by filtered back projection using a Butterworth filter (cut-off frequency at 0.17 cycle/pixel, of order 3.5). No attenuation correction was employed. Further reconstruction yielded standard long- and short-axis projections perpendicular to the heart-axis. Reconstructed slices were 6 mm in all projections.

DISA-SPECT analysis

The left ventricle was divided into 16-segments (matching the echocardiographic segments). Segmental activities were adjusted to peak myocardial activity. Segments were divided into four categories (assessed visually with the assistance of normalised tracer activity): normal tracer uptake (> 75% activity), mildly reduced tracer uptake (50-75% activity), severely reduced tracer uptake (< 50% activity) or absent tracer uptake. The perfusion and 18F-fluorodeoxyglucose short-axis slices were adjusted to peak myocardial activity (100%).

The dysfunctional segments (identified at resting echocardiography) were considered viable if these demonstrated normal perfusion and normal 18F-fluorodeoxyglucose uptake (normal activity), mildly reduced perfusion and mild reduced 18F-fluorodeoxyglucose uptake (matched activity), or severely reduced/absent perfusion with increased 18F-fluorodeoxyglucose uptake (mismatch).[16] Segments with reduced/absent perfusion and concomitant severely reduced 18F-fluorodeoxyglucose uptake were classified nonviable.

Coronary angiography

Coronary angiography was performed within 3 months of dobutamine stress echocardiography in all patients. Significant coronary artery disease was defined as a diameter stenosis ≥ 70% in ≥ 1 major epicardial artery by quantitative analysis.[19]

The anterior, apical, septal and anteroseptal segments were assigned to the left anterior descending coronary artery. The posterior and lateral segments were assigned to the left circumflex coronary artery. The inferior and basal septal segments were assigned to the right coronary artery. The apical lateral segment was considered as an overlap segment between the left anterior descending and the left circumflex coronary artery. The apical inferior segment was considered an overlap segment between the left anterior descending and the right coronary artery. Overlap segments were assigned to the regions with concomitant abnormality.[20]

Statistical analysis

Continuous variables are expressed as mean values ± standard deviation (SD). Comparison of continuous variables was performed with the Student's *t*-test. Comparison of proportions was performed with the chi-square test. Sensitivity and specificity were presented with the corresponding 95% confidence interval (CI). A p value < 0.05 was considered significant.

The agreements between DISA-SPECT and dobutamine stress echocardiography with FI and second harmonic imaging were defined as the percent of concordant diagnoses and were also assessed by calculating the kappa value: kappa values between 0.75 and 1 were considered indicative of good agreement, those between 0.40 and 0.75 indicative of moderate agreement and those between 0 and 0.40 indicative of poor agreement.

RESULTS

No significant change in the patients' symptoms or the clinical status occurred between the nuclear and echocardiographic studies.

Hemodynamic data of dobutamine stress test

Dobutamine-atropine induced a significant increase in heart rate (70 ± 15 at rest to 131 ± 11 bpm at peak stress, P < 0.001), systolic blood pressure (125 ± 16 vs. 129 ± 24 mm Hg, P < 0.05) and rate-pressure product (9432 ± 2870 to 16375 ± 6600, P < 0.001). Test endpoints were target heart rate in 27 patients (90%), maximal dose of dobutamine and atropine in 1 patient (3%), and angina in 2 patients (7%). No significant arrhythmias or severe hypotension (decrease systolic blood pressure > 40 mm Hg compared to rest) occurred during the test.

DISA-SPECT

In the 30 patients, 480 segments were analysed. Normal perfusion and 18F-fluorodeoxyglucose uptake were observed in 222 (46%) segments. Mildly reduced perfusion and 18F-fluorodeoxyglucose uptake were observed in 80 (17%) segments. A mismatch pattern was found in 37 (8%) segments. The remaining 141 (29%) segments had a matched reduction of both perfusion and metabolism and were classified as nonviable.

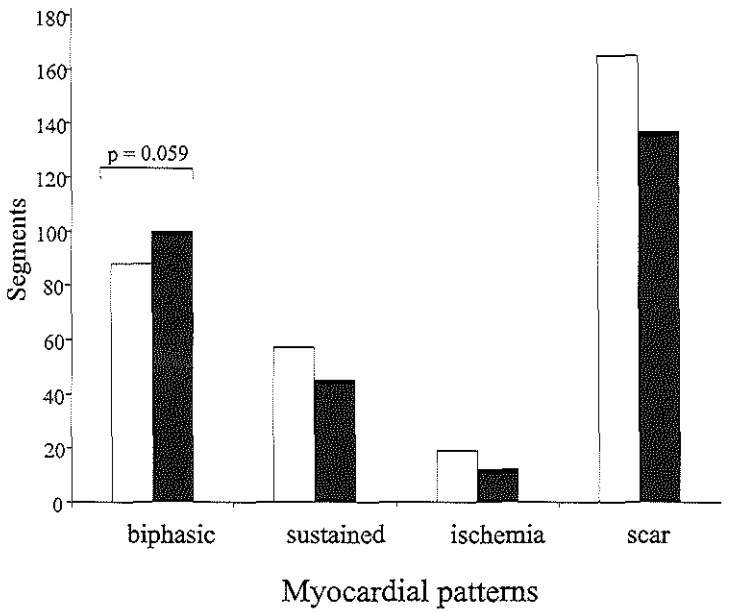


Figure 1

Different myocardial patterns during dobutamine stress echocardiography by the use of fundamental (empty bars) and second harmonic imaging (filled bars).

Dobutamine stress echocardiography: baseline characteristics

A total of 480 myocardial segments were analysed. At baseline there was a higher prevalence of segments with invisible border (score of 0) using fundamental imaging compared with second harmonic imaging [31 (12.7%) vs. 12 (10.2%), P = 0.005]. The analysis of wall motion score by fundamental imaging at baseline demonstrated 330 severely dysfunctional segments (73%) of which 181 (55%) were akinetic/dyskinetic. The analysis of wall motion score by second harmonic imaging exhibited 288 dysfunctional segments (61%; P < 0.001 vs. fundamental imaging), of which 153 (53%) were akinetic/dyskinetic (P = 0.02 vs. fundamental imaging).

The mean number ± SD of severely dysfunctional segments per patient was 10.9 ± 3.5 with fundamental imaging and 9.8 ± 3.2 with second harmonic imaging.

Figure 1 represents the different myocardial patterns during dobutamine stress echocardiography with fundamental imaging and second harmonic imaging in severe dysfunctional segments at baseline (wall motion score > 2).

Agreement between DISA-SPECT and dobutamine stress echocardiography with fundamental and second harmonic imaging

Fundamental imaging

With fundamental imaging, there were 330 segments with severe baseline dyssynergy. Of these, 144 (44%) were considered viable by both echocardiography and DISA-SPECT, whereas 113 of the dysfunctional segments (34%) were nonviable with both the techniques. The agreement

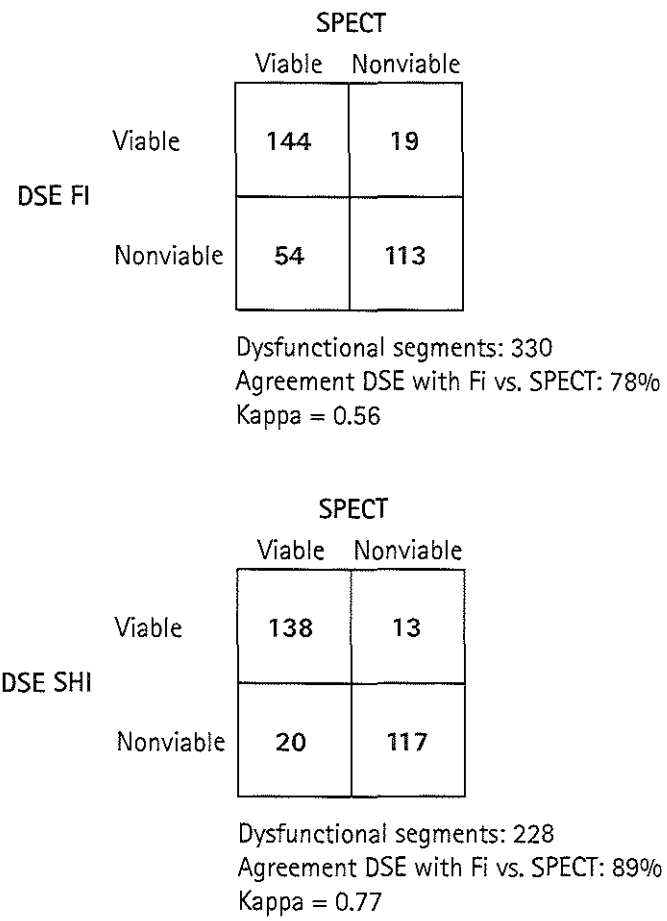


Figure 2

Agreement between DISA-SPECT and dobutamine stress echocardiography (DSE), using fundamental (FI) and second harmonic imaging (SHI), on the presence of myocardial viability in segments with wall motion score > 2 (severe hypokinesis, akinesis or dyskinesis).

between dobutamine stress echocardiography by fundamental imaging and DISA-SPECT on the presence of viability in severe dysfunctional segments was 78% (kappa = 0.56) as shown in figure 2.

The agreement between fundamental imaging and DISA-SPECT on the presence of viability in akinetic/dyskinetic segments was 80% (kappa = 0.59) [figure 3].

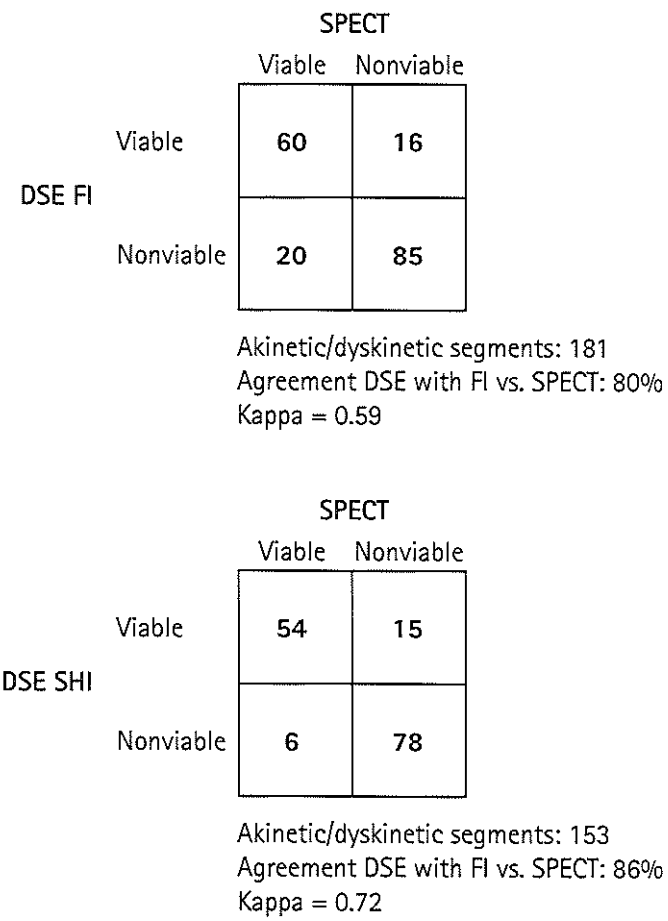


Figure 3

Agreement between DISA-SPECT and dobutamine stress echocardiography (DSE), using fundamental (FI) and second harmonic imaging (SHI), on the presence of myocardial viability in segments with wall motion score > 3 (akinesis or dyskinesis).

Second harmonic imaging

With second harmonic imaging, there were 288 segments with severe baseline dyssynergy. Of these, 138 (48%) were viable with DISA-SPECT, whereas 117 (41%) were nonviable with both techniques. The agreement between second harmonic imaging and DISA-SPECT for the dysfunctional segments was 89% (kappa = 0.77) (P = 0.001 vs. fundamental imaging).

The agreement between second harmonic imaging and DISA-SPECT on the presence of viability in akinetic/dyskinetic segments was 86% (kappa = 0.72) [figure 3].

Accuracy of fundamental and second harmonic imaging for the detection of myocardial viability

Using DISA-SPECT as the "gold standard", the capability of dobutamine stress echocardiography with fundamental imaging and second harmonic imaging to detect viable tissue was determined. Dobutamine stress echocardiography with fundamental imaging revealed signs of viable tissue in 163 dysfunctional segments (49%). This resulted in sensitivity for detection of myocardial viability of 73% (144/198) with a specificity of 86% (113/132) and accuracy of 78% (257/330).

When second harmonic imaging was used the number of viable segments was 151 (52%). A significant improvement was obtained in sensitivity (138/158 = 87%, P = 0.001 vs. fundamental imaging) and the accuracy was 88% (255/288) (P = 0.001 vs. fundamental imaging), whereas the specificity was similar 90% (117/130) (P = 0.4 vs. fundamental imaging) (table II).

Twelve segments were not-visualised at dobutamine stress echocardiography with second harmonic imaging. Of these, 8 were nonviable at DISA-SPECT, 2 had normal perfusion and normal metabolism, 1 had mildly reduced perfusion and mildly reduced metabolism and 1 had absent perfusion and increased metabolism.

In patients on beta-blocker therapy (20 patients), the agreement between dobutamine stress echocardiography with fundamental imaging and DISA-SPECT was 77% (kappa = 0.53). The agreement between dobutamine stress echocardiography with second harmonic imaging and DISA-SPECT was 88% (kappa = 0.77).

Myocardial segments were evaluated according to the different

Table II

Comparison of the accuracy between fundamental and second harmonic imaging during dobutamine stress echocardiography for the detection of myocardial viability.

	Fundamental imaging		Second harmonic imaging		P
	Number (%)	CI	Number (%)	CI	value
Sensitivity dysfunctional segments*	73% (144/198)	68 - 78	87% (138/158)	83 - 91	0.001
Specificity dysfunctional segments*	86% (113/132)	82 - 89	90% (117/130)	86 - 94	0.40
Accuracy dysfunctional segments*	78% (257/330)	73 - 82	89% (255/288)	85 - 92	0.001
Sensitivity akinetic/dyskinetic segments**	75% (60/80)	68 - 82	90% (54/60)	85 - 95	0.06
Specificity akinetic/dyskinetic segments**	84% (85/101)	78 - 90	84% (78/93)	78 - 90	0.90
Accuracy akinetic/dyskinetic segments**	80% (145/181)	74 - 86	86%(132/153)	81 - 92	0.20

CI = 95% confidence interval

* *wall motion score > 2*

** *wall motion score >3*

Table III

Sensitivity and specificity of fundamental and second harmonic imaging and agreement with nuclear studies in the three coronary territories.

Regional Arteries	Fundamental Imaging	CI	Second harmonic imaging	CI	P value
LAD					
Agreement (k value)	81% (0.56)		87% (0.69)		0.10
Sensitivity	84% (122/146)	79-89	93% (134/144)	90-97	0.02
Specificity	75% (47/63)	68-81	74% (49/66)	68-80	0.90
LCx					
Agreement (k value)	87% (0.54)		91% (0.63)		0.40
Sensitivity	89% (114/128)	84-94	96% (121/126)	93-99	0.06
Specificity	73% (16/22)	65-80	63% (15/24)	55-70	0.70
RCA					
Agreement (k value)	80% (0.60)		88% (0.74)		0.10
Sensitivity	76% (53/70)	68-83	88% (64/73)	82-94	0.10
Specificity	86% (43/50)	80-92	87% (41/47)	81-93	0.90

LAD = left anterior descending; LCx = left circumflex; RCA = right coronary artery; CI = 95% confidence interval.

vascular territories. The sensitivity for detection of myocardial viability in the region of the left anterior descending, left circumflex and right coronary artery are presented in table III. A significant improvement occurred in the territory of the left anterior descending coronary artery when second harmonic imaging was used.

Myocardial viability was also assessed on an individual patient basis. Patients were considered to have viable myocardium and candidates for revascularisation when 4 or more dysfunctional segments showed viability by dobutamine stress echocardiography.[21] According to this approach, 24 patients were classified as viable with both fundamental imaging and second harmonic imaging, 5 (17%) patients were classified as nonviable by fundamental imaging and viable by second harmonic imaging and 1 (3%) patient was classified as viable on fundamental imaging and nonviable on second harmonic imaging.

Discussion

This study showed that the use of second harmonic imaging during dobutamine stress echocardiography improved the accuracy for the detection of viable myocardium in patients with severe left ventricular dysfunction compared to fundamental imaging when DISA-SPECT was used as a reference method. The agreement between dobutamine stress echocardiography and DISA-SPECT on viability assessment increased significantly from 78% (kappa = 0.56) to 89% (kappa = 0.77) when second harmonic imaging was used, compared to fundamental imaging ($P = 0.001$).

Although the use of combined low- high dose dobutamine echocardiography has improved the accuracy of dobutamine stress echocardiography for the detection of viability,[21,22] there remains some discordance between dobutamine echocardiography and nuclear imaging.[23-25]

Previous studies have shown that 201-thallium classified a significantly higher percentage of segments as viable as compared to dobutamine stress echocardiography.[7,24] A similar discrepancy was observed when 18F-fluorodeoxyglucose imaging with PET or SPECT was compared to dobutamine stress echocardiography.[3-5]

Thus, the nuclear techniques appear to be more sensitive for the

detection of viable myocardium, probably because the detection of myocardial viability by these techniques requires less grade of cellular integrity than that required to elicit a contractile response during dobutamine echocardiography. From a pathophysiological point-of-view, this discrepancy can be explained by the fact that more severely damaged myocardium (with less viable tissue and more fibrosis) may still exhibits perfusion and glucose utilisation, but has lost contractile reserve.[9]

Besides this explanation, technical factors may also contribute to the discrepancy between dobutamine stress echocardiography and nuclear imaging. Dobutamine stress echocardiography is influenced by imaging quality to a greater extent than nuclear techniques. A suboptimal acoustic window may interfere with an accurate conclusion regarding the presence or absence of viable myocardium. In fact, a technically difficult transthoracic visualisation reduces the accuracy for the prediction of improvement of left ventricular function after revascularisation. In a recent study by Dalla Vecchia et al[26] 18 patients with chronic coronary artery disease referred for surgical revascularisation were evaluated with dobutamine stress echocardiography and with dobutamine stress radionuclide ventriculography. The agreement between these two techniques for prediction of improvement of function post-revascularisation was suboptimal. This was mainly due to a lower sensitivity of dobutamine stress echocardiography, indicating underestimation of viable tissue. However, when patients with an optimal visualisation of the endocardial border were analysed separately, the sensitivity of dobutamine stress echocardiography increased significantly. These results clearly demonstrate how the lack of adequate endocardial border visualisation can lead to an underestimation of myocardial viability.

The recent introduction of second harmonic imaging has improved image quality by facilitating endocardial border detection. Previous data have demonstrated that second harmonic imaging significantly improves visualisation of endocardial borders both at rest and during dobutamine stress echocardiography.[13] It has also been demonstrated that second harmonic imaging is superior for detection of coronary artery disease,[27] but its influence on viability assessment has not yet been evaluated.

In this population with ischaemic left ventricular dysfunction, myocardial viability was evaluated with a nuclear technique (DISA-SPECT) and dobutamine stress echocardiography, comparing both

fundamental imaging and second harmonic imaging. In dysfunctional segments, the use of fundamental imaging has shown an evident discrepancy between dobutamine stress echocardiography and DISA-SPECT imaging (agreement 78%, kappa value 0.56). Second harmonic imaging significantly increased the agreement between the two methods (89%, kappa value 0.77). The improvement in sensitivity obtained with second harmonic imaging in dysfunctional segments was mainly due to a reduction in the number of segments that were SPECT viable and dobutamine stress echocardiography nonviable; this was particularly related to better visualisation of the biphasic response (Figure 1), due to better endocardial border visualisation.

The dobutamine stress echocardiography studies were also analysed on an individual patient basis. Using the 4-segment cut-off level (allowing optimal identification of patients who will benefit from revascularisation) [21] a difference between fundamental imaging and second harmonic imaging was obtained in 6 patients. Five of them (83%) were classified ass nonviable by fundamental imaging but viable by second harmonic imaging. Thus, a substantial number of patients would have been denied revascularisation based on fundamental imaging.

Considering the 3 vascular territories, we found a significant improvement in the sensitivity in segments subtended by the left anterior descending coronary artery (Table III). These results are in line with previous work focusing on the detection of coronary artery disease using dobutamine stress echocardiography and second harmonic imaging. In fact, the well-known phenomenon of endocardial "dropout" is most frequently encountered in the lateral and anterior walls (apical view).[11-15]

Study limitation

This study used nuclear imaging as a reference to define myocardial viability, rather than improvement of function. Therefore, the impact of the use of second harmonic imaging on the improvement of the ability of dobutamine stress echocardiography for the prediction of functional recovery after revascularisation needs further evaluation.

The interval of 3 months between dobutamine stress echocardiography and angiography can be considered relatively long. However, the clinical course of all these patients was stable within this period of time.

CONCLUSION

second harmonic imaging improves the agreement between dobutamine stress echocardiography and DISA-SPECT for detection of myocardial viability in patients with ischaemic left ventricular dysfunction as compared to fundamental imaging.

REFERENCES

1. Schwaiger M, Melin J. Cardiological applications of nuclear medicine. *Lancet 1999;354:661-666.*
2. Rahimtoola SH. Importance of diagnosing hibernating myocardium: how and in whom? *J Am Coll Cardiol 1997;30:1701-1706.*
3. Matsunari I, Boning G, Ziegler SI, Nekolla SG, Stollfuss JC, Kosa I, Ficaro EP, Schwaiger M. Attenuation-corrected 99mTc-Tetrofosmin single-photon emission comparison with positron emission tomography using 18F-Fluorodeoxyglucose. *J Am Coll Cardiol 1998;32:927-935.*
4. Cornel JH, Bax JJ, Elhendy A, Visser FC, Boersma E, Poldermans D, Sloof GW, Fioretti PM. Agreement and disagreement between "metabolic viability" and "contractile reserve" in akinetic myocardium. *J Nucl Cardiol 1999;6:383-388.*
5. Bax JJ, Cornel JH, Visser FC, Fioretti PM, van Lingen A, Huitink JM, Kamp O, Nijland F, Roelandt JR, Visser CA. Prediction of improvement of contractile function in patients with ischemic ventricular dysfunction after revascularization by Fluorine-18Fluorodeoxyglucose single photon-emission computed tomography. *J Am Coll Cardiol 1997;30:377-383.*
6. Dilsizian V, Bonow RO. Current diagnostic techniques of assessing myocardial viability in hibernating and stunned myocardium. *Circulation 1993;87:1-20.*
7. Panza JA, Curiel RV, Laurienzo JM, Quyyumi AA, Dilsizian V. Relation between thallium uptake and contractile response to dobutamine. Implication regarding myocardial viability in patients with chronic coronary artery disease and left ventricular dysfunction. *Circulation 1995;91:990-998.*
8. Bax JJ, Poldermans D, Elhendy A, Boersma Rahitmoolaet al. Sensitivity, specificity and predictive accuracies of various non-invasive techniques for detecting hibernating myocardium. *Curr Probl Cardiol 2001;26:141-146.*
9. Pagano D, Townend JN, Parums DV Bonser RS Camici PG. Hibernating myocardium: morphological correlates of inotropoc stimulation and glucose uptake. *Heart 2000;83:456-461.*
10. Nagueh SF, Mikati I, Weilbaecher D, Reardon MJ, Al-Zaghrini GJ, Cacela D, He ZX, Letsou G, Noon G, Howell JF, Espada R, Verani MS, Zoghbi WA. Relation of the contractile reserve of hibernating myocardium to myocardial structure in humans. *Circulation 1999;100:490-496.*
11. Kasprzak JD, Paelinck B, Ten Cate FJ, Vletter WB, de Jong N, Poldermans D, Elhendy A, Bouakaz A, Roelandt JR. Comparison of native and contrast-enhanced harmonic echocardiography for visualisation of left ventricular endocardial border. *Am J Cardiol 1999;83:211-217.*

12. Spencer KT, Bednarz J, Rafter PG, Korcarz C, Lang RM Use of harmonic imaging without echocardiographic contrast to improve two-dimensional image quality. *Am J Cardiol 1998;82:794-799.*
13. Sozzi FB, Poldermans D, Bax JJ, Boersma E, Vletter W, Elhendy A, Borghetti A, Roelandt JRTC. Does second harmonic imaging improves left ventricle endocardial border identification at higher heart rate during dobutamine stress echocardiography? *J Am Soc Echocardiography 2000;13:1019-1024.*
14. Caidahl K, Kazzam E, Lidberg J, Neumann Andersen G, Nordanstig J, Rantapaa Dahlqvist S, Waldenstrom A, Wikh R. New New concept in echocardiography: harmonic imaging of tissue without use of contrast agent. *Lancet 1998;352:1264-1270.*
15. Senior R, Soman P, Khattar RS, Lahiri A Improved endocardial visualisation with second harmonic imaging compared with fundamental two-dimensional echocardiographic imaging. *Am Heart J 1999;138:163-168.*
16. Rambaldi R, Poldermans D, Bax JJ, Boersma E, Valkema R, Elhendy A, Vletter WB, Fioretti PM, Roelandt JR, Krenning EP. Dobutamine stress echocardiography and technetium-99m-tetrofosmin/fluorine 18F-fluorodeoxyglucose single-photon emission computed tomography and influence of resting ejection fraction to assess myocardial viability in patients with severe left ventricular dysfunction and healed myocardial infarction. *Am J Cardiol 1999;84:130-134.*
17. Shiller NB, Shah PM, Crawford M, DeMaria A, Devereux R, Feigenbaum H, Gutgesell H, Reichek N, Sahn D, Schnittger I. Recommendations of quantitation of the left ventricle by two-dimensional echocardiography. American Society of Echocardiography committee on standards, subcommittee on quantitation of two-dimensional echocardiograms. *J Am Soc Echocardiography 1989;2:358-367.*
18. Elhendy A, Cornel JH, Roelandt JR, van Domburg R, Fioretti PM. Akinesis becoming dyskinesis during dobutamine stress echocardiography. A predictor of poor functional recovery after surgical revascularization. *Chest 1996;110:155-158.*
19. Baptista J, Arnese M, Roelandt JR, Fioretti P, Keane D, Escaned J, Boersma E, di Mario C, Serruys PW. Quantitative coronary angiography in the estimation of the functional significance of coronary stenosis: correlations with dobutamine-atropine stress test. *J Am Coll Cardiol 1994;23:1434-1439.*
20. Elhendy A, van Domburg RT, Bax JJ, Poldermans D, Nierop PR, Kasprzak JD, Roelandt JRTC Optimal criteria for the diagnosis of coronary artery disease by dobutamine stress echocardiography. *Am J Cardiol 1998;82:1339-1344.*

21. Bax JJ, Poldermans D, Elhendy A, Cornel JH, Boersma E, Rambaldi R, Roelandt JR, Fioretti PM. Improvement of left ventricular ejection fraction, heart failure symptoms and prognosis after revascularisation in patients with chronic coronary artery disease and viable myocardium detected by dobutamine stress echocardiography. *J Am Coll Cardiol 1999;34:163-169.*
22. Cornel JH, Bax JJ, Elhendy A, Maat AP, Kimman GJ, Geleijnse ML, Rambaldi R, Boersma E, Fioretti PM. Biphasic response to dobutamine predicts improvement of global left ventricular function after surgical revascularization in patients with stable coronary artery disease: implications of time course of recovery on diagnostic accuracy. *J Am Coll Cardiol 1998;31:1002-1010.*
23. Arnese M, Cornel JH, Salustri A, Maat A, Elhendy A, Reijs AE, Ten Cate FJ, Keane D, Balk AH, Roelandt JR. Prediction of improvement of regional left ventricular function after surgical revascularization. A comparison of low-dose dobutamine echocardiography with ^{201}Tl single-photon emission computed tomography. *Circulation 1995;91:2748-2752.*
24. Qureshi U, Nagueh SF, Afridi I, Vaduganathan P, Blaustein A, Verani MS, Winters WL Jr, Zoghbi WA. Dobutamine echocardiography and quantitative rest-redistribution ^{201}Tl tomography in myocardial hibernation. *Circulation 1997;95:626-635.*
25. Elhendy A, Trocino G, Salustri A, Cornel JH, Roelandt JR, Boersma E, van Domburg RT, Krenning EP, El-Said GM, Fioretti PM. Low-dose dobutamine echocardiography and rest-redistribution thallium-201 tomography in the assessment of spontaneous recovery of left ventricular function after recent myocardial infarction. *Am Heart J 1996;131:1088-1096.*
26. Vecchia LD, Storti T, Cogliati C, Guzzetti S, Danna P, Scrofani R, Di Biasi P, Malliani A. Comparison of low-dose dobutamine ventriculography with low-dose dobutamine echocardiography for predicting regional improvement in left ventricular function after coronary artery bypass. *Am J Cardiol 2000;86:371-374.*
27. Franke A, Hoffmann R, Kühl HP, Lepper W, Breithardt OA, Schormann M, Hanrath P. Non-contrast second harmonic imaging improves interobserver agreement and accuracy of dobutamine stress echocardiography in patients with impaired image quality. *Heart 2000;83:133-140.*

CHAPTER 5

INFLUENCE OF CONTINUOUS BETA-BLOCKERS DURING DOBUTAMINE STRESS ECHOCARDIOGRAPHY FOR THE ASSESSMENT OF MYOCARDIAL VIABILITY IN PATIENTS WITH SEVERE ISCHEMIC LEFT VENTRICULAR DYSFUNCTION

Source: D Poldermans, FB Sozzi, JJ Bax, E Boersma, D Duncker, EC Vourvouri, et al. *Am J Cardiol 2001;88:68-70.* Adapted.

ABSTRACT

Objective. To assess myocardial viability in the same group of patients with and without beta-blockers by dobutamine stress echocardiography using a nuclear test as an independent "gold standard".

Methods. Twenty-one patients (17 men, mean age 62 ± 9 years) with reduced left ventricular function (mean ejection fraction 27 ± 6%) underwent dobutamine stress echocardiography with and without beta-blockade at 1- to 2-week intervals and dual isotope simultaneous acquisition (DISA) single-photon emission computed tomography (SPECT).

Results. Wall motion score at rest was higher with beta-blockers (2.88 ± 0.79 vs. 2.61 ± 0.74; P = 0.03). During beta-blockade, wall motion changed during dobutamine stress echocardiography in 14 of 68 segments, with an initial biphasic response. Segments that showed a scar pattern during beta-blockade were scored viable in 13 of 85 segments when beta-blockers were discontinued. Fifteen % and 11% of the viable segments at DISA-SPECT were not viable during dobutamine stress echocardiography with and without beta-blockers respectively (P = 0.052).

Conclusion. Beta-blockers reduced the number of viable segments detected by dobutamine stress echocardiography in patients with severe left ventricular dysfunction.

INTRODUCTION

Beta-blockers have a negative inotropic and chronotropic affect on the heart. They have been increasingly used in the treatment of patients with left ventricular dysfunction,[1] but may adversely affect the ability of dobutamine to detect myocardial viability. Beta-blockers have been shown to shift the dobutamine response curve to the right. The improved contraction is present at higher doses of dobutamine, and sometimes at peak dose, the ischemic response is reduced.[2] Although it is known that reduced chronotropic response during dobutamine stress echocardiography in patients on beta-blockers can be overcome by an increased dobutamine dose and/or the addition of atropine to dobutamine,[3-5] the influence of beta-blockers on low-dose dobutamine during dobutamine stress echocardiography is unknown. The aim of this study was therefore to assess myocardial viability in the same group of patients with and without beta-blockers by dobutamine stress echocardiography using a nuclear test as an independent "gold standard."[6]

METHODS

The study population comprised 21 patients (17 men, mean age 62 ± 9 years) with reduced left ventricular function (mean ejection fraction 27 ± 6%) who underwent dobutamine stress echocardiography with and without beta-blockade at 1- to 2-week intervals and dual isotope simultaneous acquisition (DISA) single-photon emission computed tomography (SPECT) for the evaluation of viable myocardium (Table 1). Eleven patients initially received beta-blockers, and in 10 patients beta-blockers were gradually withdrawn after the first dobutamine stress echocardiography. The medical ethics committee approved the study protocol and informed consent was obtained from each patient.

Dobutamine stress echocardiography was performed as previously described[6] and visually scored by 2 experienced reviewers who were blinded to the DISA-SPECT results and other data. Wall motion was scored at baseline, at 5, 10, and 20 μg/kg/min dobutamine, and at peak stress. Myocardial viability was assessed only in severely dysfunctional segments; 4 types of wall motion responses were observed: (1) biphasic pattern: improvement of wall motion at 5, 10, or 20 μg/kg/min dobutamine with worsening at higher dosages; (2) worsening;

Table 1

Clinical characteristics of patients evaluated for myocardial viability by dobutamine stress echocardiography and dual-isotope-simultaneous-acquisition single photon emission computed tomography.

Variables	Number (%) of patients.
Previous myocardial infarction	17 (81%)
History of angina pectoris	6 (29%)
New York Heart Association class	
2	4 (19%)
3	9 (43%)
4	8 (38%)
Number of coronary arteries narrowed >50%	2.5 ± 0.7
Nitrates use	13 (62%)
Diabetes mellitus	4 (19%)
Angiotensin converting enzyme-inhibitors	15 (71%)

(3) sustained improvement; and (4) no change. Severely dysfunctional segments exhibiting a biphasic, sustained, or ischemic response were considered viable, whereas segments with unchanged wall motion were considered scarred. Patients were considered viable and candidates for revascularisation by dobutamine stress echocardiography if 4 segments showed viability based on the study of Bax et al.[7] The inter- and intraobserver concordance of wall motion score at rest were 94% and 97%, respectively, and was 92% and 94% during stress, respectively.

DISA-SPECT imaging using 99m-technetium-tetrofosmin (perfusion) and 18F-fluorodeoxyglucose (metabolism) tracers was performed and scored as previously described.[6] The myocardium was divided into 16 segments (matching the echocardiographic segments). Dysfunctional segments identified by echocardiography were classified as viable or nonviable.

Continuous variables are expressed as mean values ± standard deviation (SD). Changes in these variables during dobutamine stress echocardiography with and without beta-blockade were evaluated by analysis of variance with repeated measures, followed by Student's paired t tests. The agreement between dobutamine stress echocardiography and nuclear testing with respect to myocardial viability was presented by

the kappa value, with and without beta-blockers. A McNemar test was applied to study the difference in dobutamine stress echocardiography results with and without beta-blockers in viable segments as assessed by nuclear testing. A P value of < 0.05 was considered statistically significant.

RESULTS

No serious side effects occurred during the study. Visual assessment of both echocardiograms at rest, with and without beta-blockers, was feasible in 330 of 336 segments (98%). In 225 segments (67%), severe dyssynergy at rest was present with and without beta-blockers. The analysis of DISA-SPECT was feasible in all 336 segments.

Of 225 severely dyssynergic segments, 159 (71%) were viable. Normal or mild reduction of perfusion metabolism was seen in 119 segments (53%), whereas perfusion metabolism mismatch was observed in 40 segments (17%). Sixty-six segments were nonviable (29%).

Heart rate at rest and peak heart rate-pressure product with and without beta-blockers were 62 ± 9 vs. 80 ± 15 beats/min ($P < 0.01$) and 15944 ± 3341 vs. 16249 ± 3096, respectively ($P = 0.80$). For all cases, the maximum dobutamine infusion dose was 40 μg/kg/min with beta-blockers vs. an average of 30 μg/kg/min without beta-blockers ($P < 0.001$). Additional atropine was required during beta-blockade in 15 of 21 cases compared with 1 of 21 cases without beta-blockers ($P < 0.001$).

Wall motion score at rest was higher with beta-blockers (2.88 ± 0.79 vs. 2.61 ± 0.74; $P = 0.03$). During beta-blockade, 17 mildly hypokinetic segments became severely hypokinetic at rest. The change of biphasic and scarring patterns of severely dyssynergic segments by beta-blockers are shown in Figure 1 and Figure 2. The dobutamine dose, at which initial improvement of wall motion at low-dose dobutamine occurred in 54 segments with a biphasic response with and without beta-blockers, increased during beta-blockade from 6.7 ± 2.9 to 9.4 ± 5 μg/kg/min ($P < 0.001$). During beta-blockade, wall motion changed during dobutamine stress echocardiography in 14 of 68 segments, with an initial biphasic response. Seven segments were diagnosed as nonviable; 5 segments showed sustained improvement and 2 segments showed an ischemic response (Figure 1). Segments that showed a scar pattern during beta-blockade were scored viable in 13 of 85 segments when beta-blockers were discontinued (Figure 2).

During the study of 12 patients, the number of viable segments remained unchanged, the number of viable segments increased in 8 patients who did not received beta-blockers, whereas in 1 patient the number of viable segments decreased (Figure 3). However, the number of "viable" patients (i.e., 4 viable segments) was similar with and without beta-blockers.

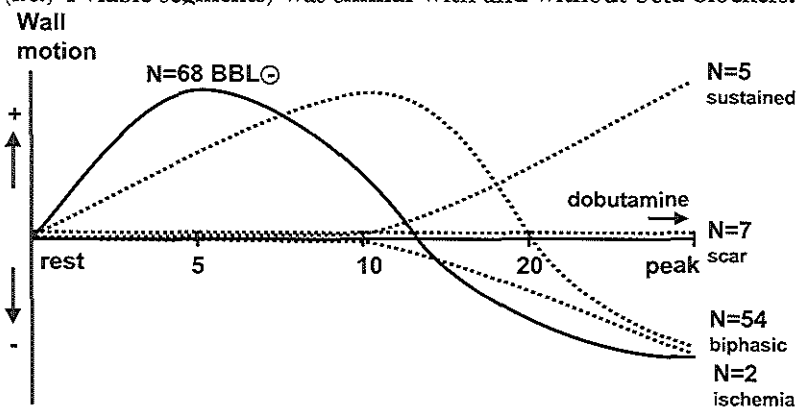


Figure 1

Wall motion change of 68 segments showing a biphasic response without beta-blockers (BBL). Solid line, the segments with a biphasic pattern without beta-blockade; dotted lines, the wall motion change of these 68 biphasic segments during beta-blockade.

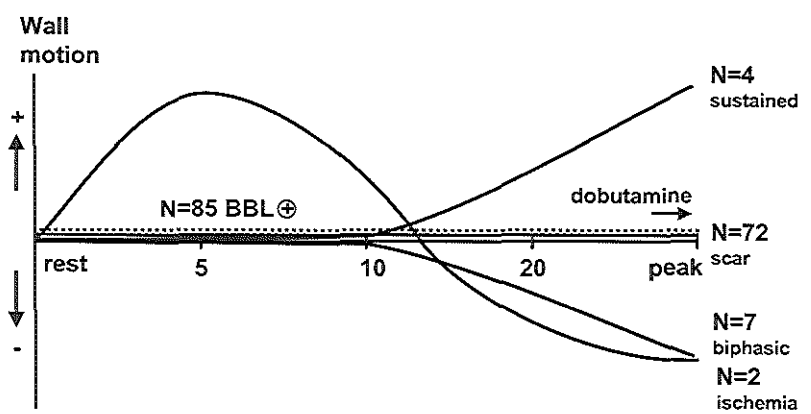


Figure 2

Wall motion change of 85 segments showing a scar response during beta-blockade after cessation of beta-blockers. Dotted line, the 85 segments with a scar response during beta-blockade; solid lines, changes in wall motion after cessation of beta-blockers.

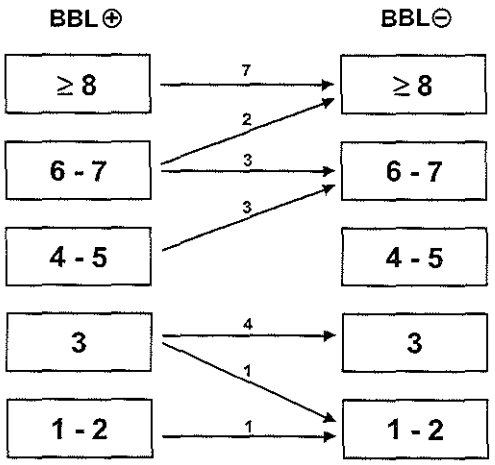


Figure 3
The change of the number of viable segments per patient assessed by dobutamine stress echocardiography with and without beta-blockers (BBL). Left side, the number of viable segments per patient on beta-blockers therapy. Right side, number of viable segments per patient without beta-blockers. The changes of the number of viable segments per patients after beta-blocker therapy was discontinued (arrows).

The kappa value for the agreement of viability of severely dyssynergic segments between dobutamine stress echocardiography with and without beta-blockers vs. DISA-SPECT was 0.71 vs. 0.78, respectively. DISA-SPECT showed viability in 159 segments. During dobutamine stress echocardiography, 15% and 11% of these segments were not viable with and without beta-blockers, respectively (P = 0.052).

Discussion

The present study showed that beta-blockers in patients with severe ischemic left ventricular dysfunction reduced the number of viable segments as assessed by dobutamine stress echocardiography when DISA-SPECT was used as a gold standard. The kappa value, which evaluated the agreement of viability between dobutamine stress echocardiography and nuclear scanning, was 0.71 and 0.78 with and without beta-blockers, respectively. Fifteen percent of segments considered viable by scan showed no viability by dobutamine stress echocardiography when patients were

taking beta-blockers compared with 11% when beta-blockers were discontinued; however, this difference was not statistically significant.

Beta-blockers also increased wall motion score at rest (2.82 ± 0.79 vs. 2.61 ± 0.74; P = 0.03). Seventeen segments with mild hypokinesia in patients not on beta-blockers worsened to severe hypokinesia when patients received beta-blockers. This worsening of wall motion occurred despite a decrease in blood pressure, and therefore, a decrease in afterload, and may be due to the direct negative inotropic effects of beta-blockers. Although a worsening of wall motion of ischemic myocardium may be difficult to explain, it appears that the effect of beta-blockade on wall motion in chronically hypoperfused myocardium[8,9] differs from the effect of beta-blockade on acutely ischemic myocardium, in which acute beta-blockade results in improved perfusion and wall motion.[2]

Although beta-blockers reduced the number of viable segments in patients, there were no practical implications. All "viable" patient segments were scored with and without beta-blockers. However, if a study on beta-blockers shows only limited viability, it is useful to repeat the test after the beta-blocker dosage has been reduced, especially when there is a fixed heart rate during low-dose dobutamine, or the test should be repeated using DISA-SPECT. If the latter test is used, it should be noted that the number of viable segments assessed by scan will not recover after revascularisation.

This study was performed in a small number of patients. The change in wall motion pattern on beta-blockers may be related to the subjective nature of visual wall motion scoring. Although there is a good inter- and intra-observer concordance of interpretation of stress echocardiographic results, a more objective response may improve consistency. This study was performed using a nuclear scan as gold standard to assess myocardial viability instead of the effects of coronary revascularisation.

Conclusion

This study showed that beta-blockers reduced the number of viable segments detected by dobutamine stress echocardiography in patients with severe left ventricular dysfunction.

REFERENCES

1. Wijns W, Vatner SF, Camici PG. Mechanisms of disease: hibernatig myocardium. *N Engl J Med 1998,339:173-181.*
2. Chen L, Ma L, de Prada VA, Chen M, Feng YJ, Waters D, Gillam L, Chen C. Effects of beta-blockade and atropine on ischemic responses in left ventricular regions subtending coronary stenosis during dobutamine stress echocardiography. *J Am Coll Cardiol 1996;28:1866-1876.*
3. Fioretti PM, Poldermans D, Salustri A, Forster T, Bellotti P, Boersma E, McNeill AJ, El-Said ES, Roelandt JRTC. Atropine increases the accuracy of dobutamine stress echocardiography in patients taking beta-blockers. *Eur Heart J 1994;15:355-360.*
4. McNeill AJ, Fioretti PM, El-Said EM, Salustri A, Forster T, Roelandt JRTC. Enhanced sensitivity for detection of coronary artery disease by addition of atropine to dobutamine stress echocardiography. *Am J Cardiol 1992;70:41-46.*
5. Ling LH, Pellikka PA, Mahoney DW, Oh JK, McCully RB, Roger VL, Seward JB. Atropine augmentation in dobutamine stress echocardiography: role and incremental value in clinical practice setting. *J Am Coll Cardiol 1996;28:551-557.*
6. Rambaldi R, Poldermans D, Bax JJ, Boerma E, Valkema R, Elhendy A, Vletter WB, Fioretti PM, Roelandt JRTC, Krenning EP. Dobutamine stress echocardiography and 99mTc-tetrofosmin/fluorine 18-fluorodeoxyglucose single photon emission computed tomography and influence of resting ejection fraction to assess myocardial viability in patients with severe left ventricular dysfunction and healed myocardial infarction. *Am J Cardiol 1999;84:130-134.*
7. Bax JJ, Poldermans D, Elhendy A, Cornel JH, Boersma E, Rambaldi R, Roelandt JRTC, Fioretti PM. Improvement of left ventricular ejection fraction, heart failure symptoms and prognosis after revascularization in patients with chronic coronary artery disease and viable myocardium detected by dobutamine stress echocardiography. *J Am Coll Cardiol 1999;34:163-169.*
8. Cohn PF, Brown EJ Jr, Swinford R, Atkins HL. Effect of beta blockade on silent regional left ventricular wall motion abnormalities. *Am J Cardiol 1986;57:521-526.*
9. Andersson B, Caidahl K, Waagstein F. Recovery from left ventricular asynergy in ischemic cardiomyopathy following long-term beta blockade treatment. *Cardiology 1994;85:14-22.*

CHAPTER 6

PROGNOSTIC VALUE OF DOBUTAMINE STRESS ECHOCARDIOGRAPHY IN PATIENTS WITH DIABETES MELLITUS

Source: FB Sozzi; D Poldermans; A Elhendy; RT van Domburg; JJ Bax; AFL Shinkel, et al. *Am J Med 2001, submitted.* Adapted.

ABSTRACT

Background. Exercise capacity is frequently impaired in patients with diabetes mellitus. The role of pharmacologic stress echocardiography in the risk stratification of diabetic patients has not been well defined.

Objective. The aim of this study was to assess the incremental value of dobutamine stress echocardiography for the risk stratification of diabetic patients.

Methods. We studied 396 diabetic patients [mean age 61 ± 11 years, 252 men (64%)] who underwent dobutamine stress echocardiography for evaluation of known or suspected coronary artery disease. End points were hard cardiac events (cardiac death and non-fatal myocardial infarction) and all causes of mortality.

Results. During a median follow-up of 3 years, 97 patients (24%) died (55 cardiac deaths) and 27 patients had non-fatal myocardial infarction. In an incremental multivariate analysis model, clinical predictors of hard cardiac events were history of congestive heart failure and previous myocardial infarction. The percentage of ischemic segments was incremental to the clinical model in the prediction of hard cardiac events (chi-square 37 vs. 18, $P < 0.05$). Clinical predictors of all causes of mortality were history of congestive heart failure, age and hypercholesterolemia. Wall motion score index at peak stress was incremental to the clinical model in the prediction of mortality (chi-square = 47 vs. 33, $P < 0.05$).

Conclusions. Dobutamine stress echocardiography provides incremental data for the prediction of mortality and hard cardiac events in patients with diabetes mellitus.

INTRODUCTION

Diabetes mellitus is a major risk factor for coronary artery disease and its complications.[1-7] Identification of diabetic patients at a high risk of death and myocardial infarction is an essential step for planning the appropriate management strategy. Exercise stress testing is the most widely used method for evaluation of coronary artery disease.[8-10] However, exercise capacity is frequently impaired in diabetic patients, particularly because of the higher prevalence of peripheral neuropathy and vascular disease in this population.[11-14] Dobutamine stress echocardiography has been reported as a safe and feasible method for evaluation of coronary artery disease in diabetic patients with limited exercise capacity.[15,16] However, data regarding the incremental value of the technique in the risk stratification of diabetic patients are scarce.[2] Additionally, there is currently no outcome data to support the role of stress echocardiography in the prediction of all causes of mortality in diabetic patients.

The aim of this study was to assess the value of dobutamine stress echocardiography in the prediction of death and hard cardiac events in diabetic patients with known or suspected coronary artery disease and to determine whether this method provides incremental prognostic information relative to clinical data.

METHODS

Patients

The study included 408 patients with diabetes mellitus unable to perform an adequate exercise test, who underwent dobutamine stress echocardiography at the Thoraxcenter, Rotterdam, The Netherlands between January 1994 and June 2000. Diabetes mellitus was defined in the presence of a fasting blood glucose ≥ 140 mg/dl or requirement for insulin or oral hypoglycemic agents. Seven patients were excluded because of inadequate echocardiographic images and 5 patients were lost to follow-up. The final population of the study consisted of 396 patients. Hypercholesterolemia was defined as total cholesterol > 200 mg/dl or use of a cholesterol lowering agent. Hypertension was defined as systolic blood pressure ≥ 140 mm Hg, diastolic blood pressure ≥ 90 mm Hg, or use of antihypertensive medication. Previous myocardial infarction was diagnosed by the criteria of chest pain, enzymatic elevation and

serial of electrocardiographic changes. Patients' clinical characteristics are presented in Table 1. The local medical ethics committee approved the study protocol. Patients gave an informed consent to undergo the study.

Dobutamine stress echocardiography protocol

After baseline echocardiography, dobutamine was infused at a starting dose of 5 μg/kg per minute for 3 minutes, followed by 10 μg/kg per minute for 3 minutes (low-dose stage). The dobutamine dose was increased by 10 μg/kg per minute every 3 minutes up to a maximum dose of 40 μg/kg per minute. Atropine (up to 1 mg) was administered intravenously at the end of the last stage if the target heart rate was not achieved. End points of the test were achievement of target heart rate (85% of the maximal heart rate predicted for age), maximal dose of dobutamine and atropine, extensive new wall motion abnormalities, > 2 mV downsloping ST-segment depression measured 80 ms from the J point compared to baseline, hypertension (blood pressure > 240/120 mm Hg), a decrease in systolic blood pressure of > 40 mm Hg compared with rest, significant arrhythmias or any intolerable adverse effect considered to be the result of dobutamine or atropine. Metoprolol (1-5 mg) was used intravenously to reverse the side effects of dobutamine if these did not revert quickly after termination of dobutamine infusion.

Echocardiographic imaging and interpretation

Imaging was acquired at rest, and continuously during the test and recovery. Images were recorded on videotapes and in addition, the baseline, low-dose, peak-stress and recovery images were recorded in a quad-screen format.

The interpretation of images was performed by two independent observers blinded of the patients' clinical data. In case of disagreement, a majority decision was achieved by a third observer. In our laboratory, the inter- and intra-observer agreement for dobutamine stress echocardiography assessment are 92% and 94% respectively.[17] For segmental analysis of left ventricular function, a 16-segment model was used as suggested by the American Society of Echocardiography.[18] Wall motion score index was determined at rest and peak stress as the sum of the segmental scores of the 16 segments divided by 16. Each segment was scored using a 5-point scale, with 1 = normal, 2 = mild hypokinesis, 3 = severe hypokinesis, 4 = akinesis, 5 = dyskinesis. Ischemia was defined

Table 1
Clinical characteristics of the study population.

Characteristics (N = 396)	Number	%
Sex (male)	252	64%
Age (years)	61 ± 11	
Previous myocardial infarction	205	52%
Previous myocardial revascularisation	191	48%
History of typical angina pectoris	140	35%
History of heart failure	84	21%
Hypertension	183	46%
Hypercholesterolemia	145	37%
Smoking	123	31%
Beta-blockers	144	36%
Calcium channels blockers	151	38%
Reason for referral:		
Evaluation of chest pain	234	59%
Preoperative assessment	4	1%
Evaluation of risk factors	141	36%
Functional assessment after myocardial infarction	17	4%

as new or worsened wall motion abnormalities during stress indicated by an increase of wall motion score ≥ 1 grade in ≥ 1 segment.[19] As previously described, ischemia was not considered to be present when akinetic segments at rest became dyskinetic during stress.[20] Dobutamine stress echocardiography results were defined as abnormal if there was ischemia during stress or fixed wall motion abnormalities.[19]

Follow-up

Follow-up was obtained by mailed questionnaires and scripted telephone interviews. Events were verified by contacting the patients' primary physician and reviewing medical records and death certificates. The end points considered were all causes of mortality and hard cardiac events defined as non-fatal myocardial infarction and cardiac death. Sudden unexpected death occurring without another explanation was included as cardiac death. Myocardial infarction was defined according to usual clinical, electrocardiographic and enzymatic criteria.

Statistical analysis

Continuous variables were presented as mean ± standard deviation. Comparisons between groups were based on the Wilcoxon Rank Sum Test. Categorical variables were summarised as percentages and group comparisons were based on the chi-square test. Survival free of the end point of interest was estimated by the Kaplan-Meier method. Univariable and multivariable association of clinical and stress echocardiographic parameters with the end points of interest were assessed in the Cox proportional hazards framework. Variables were selected in a stepwise forward selection manner with entry and retention set at a significance level of 0.05. The results of these analyses were summarised as hazard ratios with corresponding 95% confidence intervals. The incremental value of dobutamine stress echocardiographic information over clinical data was assessed in two modelling steps. The first step consisted of fitting a multivariable model of only clinical data. Variables selected from the first step were then used as baseline risk factors, and dobutamine echocardiographic variables were added in a stepwise forward selection manner.

RESULTS

Clinical features of the study population are presented in table 1. Dobutamine-atropine induced a significant increase of heart rate (77 ± 13 at rest to 132 ± 16 beats/min at peak dose, $P < 0.0001$) and peak rate-pressure product (10496 ± 2874 vs. 17966 ± 4799, $P = 0.01$). Systolic blood pressure did not increase (137 ± 27 mm Hg at rest and 136 ± 32 mm Hg at peak stress). Atropine was administered in 179 patients (45%). Angina occurred in 89 patients (22%), and ST-segment depression occurred in 61 patients (15%). Reasons for termination of the test were achievement of target heart rate in 320 patients (81%), angina in 42 patients (11%), ST-segment depression in 22 (5%), hypotension in 7 patients (2%) and ventricular arrhythmias in 5 patients (1%).

Resting wall motion abnormalities were detected in 309 patients (78%). Ischemia (stress induced wall motion abnormalities) was detected in 144 patients (36%). Dobutamine stress echocardiography was considered abnormal (rest and/or stress induced wall motion abnormalities) in 324 patients (82%).

Outcome

During a median follow-up of 3 years, 97 patients (24%) died (55 cardiac deaths) and 27 patients had non-fatal myocardial infarction (82 hard cardiac events). Clinical and stress echocardiographic variables associated with an increased risk of hard cardiac events and of all causes of mortality in the univariate analysis are respectively demonstrated in table 2 and 3.

Table 2

Univariate Cox regression analysis of variables associated with hard cardiac events.

Univariate analysis	$\chi 2$	P value	HR	95% CI
History heart failure	13	0.0004	2.3	1.4 - 3.7
Previous MI	8	0.004	2.1	1.2 - 3.4
WMSI rest	18	0.0001	2.5	1.6 - 4.0
Rest WMA	21	0.0001	0.91	0.88 - 0.95
Ischemic segments (%)*	4	0.02	1.11	1.02 - 1.22

** Per increase of 10%; HR = hazard ratio; CI = confidence interval; MI = myocardial infarction; WMSI = wall motion score index; WMA = wall motion abnormalities.*

Table 3

Univariate Cox regression analysis of variables associated with all causes of mortality.

Univariate analysis	$\chi 2$	P value	HR	95% CI
History heart failure	21	0.0001	2.7	1.7 - 4.1
Age	9	0.003	1.03	1.01 - 1.05
WMSI rest	15	0.0001	2.3	1.5 - 3.4
WMSI peak	18	0.0001	2.4	1.6 - 3.7
Rest WMA	16	0.0001	0.89	0.84 - 0.94
Ischemic segments (%)*	4	0.03	1.10	1.01 - 1.20

** Per increase of 10%; HR = hazard ratio; CI = confidence interval; WMSI = wall motion score index; WMA = wall motion abnormalities.*

Table 4

Independent predictors of hard cardiac events using 2 steps model.

Model	Parameters	$\chi 2$	P value	HR (95% CI)	Model $\chi 2$
Clinical	History heart failure	8	0.004	2.1 (1.3 - 3.3)	18
	Previous MI	6	0.01	1.9 (1.1 - 3.1)	
Clinical + DSE	Rest WMA	11	0.001	1.13 (1.05 - 1.22)	37
	Ischemia (%)*	3	0.07	1.11 (1.00 - 1.23)	

* *Per increase of 10%; DSE = dobutamine stress echocardiography; HR = hazard ratio; CI = confidence interval; MI = myocardial infarction; WMA = wall motion abnormalities.*

Table 5

Independent predictors of all causes of mortality using 2 steps model.

Model	Parameters	$\chi 2$	P value	HR (95% CI)	Model $\chi 2$
Clinical	Age	10	0.001	1.04 (1.01 - 1.06)	33
	History heart failure	20	0.0001	2.8 (1.8 - 4.4)	
	Hypercholesterolemia	4	0.04	1.6 (1.0 - 2.5)	
Clinical + DSE	WMSI peak	13	0.0004	1.9 (1.36 - 2.65)	47

Per increase of 10%; HR = hazard ratio; CI = confidence interval; WMSI = wall motion score index; DSE = dobutamine stress echocardiography.

Predictors of events in the multivariate analysis models

Predictors of hard cardiac events and total mortality in the multivariate analysis model are presented in tables 4 and 5. Histories of congestive heart failure and of myocardial infarction were the clinical predictors of hard cardiac events. Resting wall motion abnormalities and extension of ischemia during stress were incremental to clinical data. Clinical predictors of all causes of mortality were a history of congestive heart failure, hypercholesterolemia and age. Peak dobutamine wall motion score index was incremental to clinical data in the prediction of mortality.

Event-free survival curves according to the results of dobutamine stress echocardiography are presented in figures 1 for hard cardiac events. Both fixed and transient wall motion abnormalities (ischemia) were associated with higher event rate. The cumulative hard cardiac event

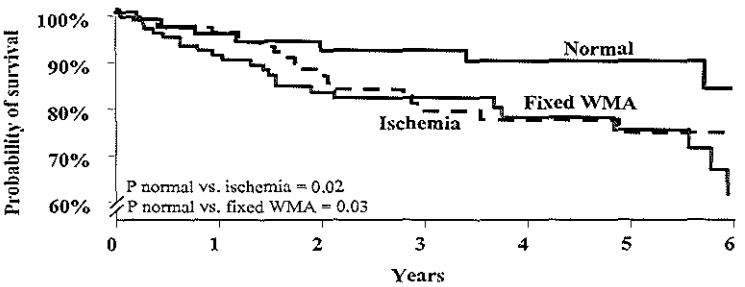


Figure 1

Kaplan-Meier curves for survival free of hard cardiac events in patients with normal dobutamine stress echocardiography, ischemia and fixed wall motion abnormalities (WMA).

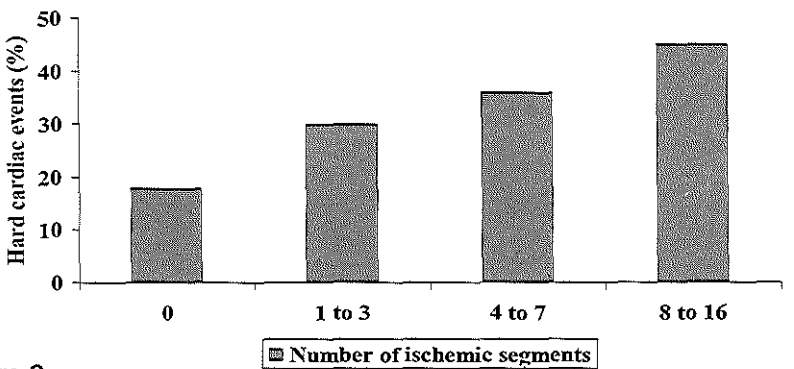


Figure 2

Cumulative event rates according to the presence and extent of myocardial ischemia during dobutamine stress echocardiography.

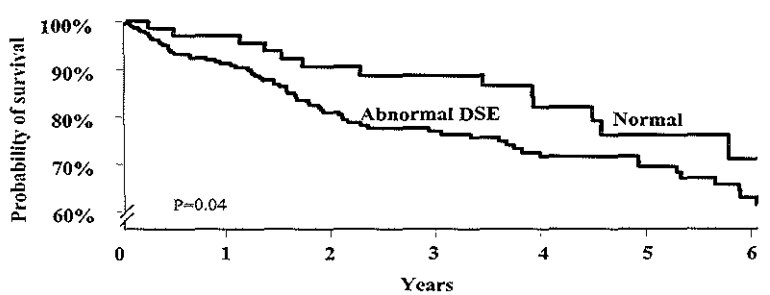


Figure 3

Kaplan-Meier survival curves of patients with normal and abnormal dobutamine stress echocardiography (DSE) results.

rate was higher in patients with abnormal as compared to patients with normal dobutamine stress echocardiography results (7% vs. 5% at one year, 18% vs. 8% at three years and 23% vs. 10% at five years, overall P = 0.01). The percentage of hard cardiac events increased proportionally to the extension of myocardial ischemia at dobutamine stress echocardiography (Figure 2). Survival curves according to the presence of wall motion abnormalities during dobutamine stress are shown in figure 3. The cumulative death rate in patients with abnormal as compared to patients with normal dobutamine stress echocardiography results was 9% vs. 3% at one year, 29% vs. 11% at three years and 31% vs. 24% at five years (overall P = 0.04).

Discussion

In this study, we assessed the predictors of death and non-fatal myocardial infarction in 396 diabetic patients with limited exercise capacity and known or suspected coronary artery disease who underwent dobutamine stress echocardiography. During a median follow-up period of 3 years a total of 97 patients died, 55 of which due to cardiac causes. Non-fatal myocardial infarction occurred in 27 patients. Clinical predictors of hard cardiac events were a history of congestive heart failure and previous myocardial infarction. Clinical predictors of all causes of mortality were age, hypercholesterolemia and history of congestive heart failure. Dobutamine stress echocardiography provided incremental prognostic information for the prediction of both end points. Hard cardiac events were predicted by the presence of resting wall motion abnormalities as well as by the percentage of ischemic segments at stress. These findings demonstrate the importance of resting left ventricular function and the severity of myocardial ischemia in determining the outcome of diabetic patients.

The cumulative hard cardiac event rate was higher in patients with abnormal as compared to patients with normal dobutamine stress echocardiography (7% vs. 5% at one year, 18% vs. 8% at three years and 23% vs. 10% at five years, overall P = 0.01). Peak dobutamine wall motion score index, which measures the sum of resting and stress-induced wall motion abnormalities was incremental to clinical data in the prediction of all causes of mortality. The cumulative death rate in patients with abnormal as compared to patients with normal dobutamine

stress echocardiography results was 9% vs. 3% at one year, 29% vs. 11% at three years and 31% vs. 24% at five years (overall P = 0.04). From these data it appears that the maximal value of a normal dobutamine stress echocardiography study in the prediction of a lower risk status is obtained at an intermediate term follow-up of 3 years, where survival curves showed the greatest diversion between patients with normal and abnormal study. At 5 years, the difference in survival was less significant. As a result, in order to obtain an up-to-date risk status in patients with an initial normal study, it is recommended to repeat the test 3 years later.

Previous studies

A few studies have evaluated the prognostic value of stress echocardiography.[19,21] To date, this is the first study that evaluates the role of stress echocardiography in the prediction of all causes of mortality. The prognostic value of dobutamine stress echocardiography in diabetic patients has been a subject of controversy among previous studies. Hung et al,[22] studied 116 diabetic and 222 non-diabetic patients after acute myocardial infarction. They observed that shorter dobutamine time, as opposed to dobutamine stress echocardiography positivity has a higher value for the prediction of events in diabetic patients during a mean follow-up of 21 months. Therefore, its predictive value was not as substantial as in non-diabetic patients. Conversely, Bates et al[16] reported that dobutamine stress echocardiography was a powerful test for the prognostic stratification of 53 patients with juvenile onset, insulin-dependent diabetes mellitus, who were considered for kidney and/or pancreas transplantation. During the follow-up period of 418 ± 269 days, the cardiac event rate among patients with abnormal dobutamine stress echocardiography was 54% compared to 6% among patients with normal dobutamine stress echocardiography.

The American Heart Association recommended the use of exercise stress myocardial perfusion imaging for the evaluation of coronary artery disease in diabetic patients based on the published data on the utility of the technique in diabetic patients.[23] It was concluded that there are currently no outcome data to define the role of stress echocardiography as a prognostic tool in diabetic patients.

A recent study assessed the value of exercise echocardiography in the prediction of cardiac events in 563 diabetic patients.[10] Both, the extent of resting left ventricular dysfunction and myocardial ischemia were

predictive of cardiac events, incremental to clinical data. The event rate in that study was much lower than in our study (9% vs. 21%) reflecting the high-risk status of a population unable to perform exercise stress test in our study. The eligibility for exercise stress test is related generally to patients with a relatively lower risk profile, since the inability to exercise is a known independent predictor of adverse outcome. Although exercise stress testing is the most physiological stress method for inducing myocardial ischemia and provides data on exercise capacity, our study showed that dobutamine stress echocardiography is an alternative in patients with limited exercise capacity. Due to the high event rate in this group, stress testing is more likely to identify a larger proportion of patients at highest risk of adverse outcome. One advantage of pharmacologic stress echocardiography is that it allows continuous acquisition of the images in contrast to post exercise acquisition of images, which may underestimate the severity of myocardial ischemia due to the rapid resolution of these abnormalities.

Limitations of the study

The types and the duration of diabetes mellitus were not defined in this study. As a result, the impact of these parameters on the outcome of patients, and their correlation with echocardiographic abnormalities were not studied.

CONCLUSIONS

Dobutamine stress echocardiography provides data incremental to clinical variables for the prediction of death and cardiac events in diabetic patients with suspected or known coronary artery disease. Resting left ventricular function and extent of myocardial ischemia during dobutamine stress echocardiography are important predictors of outcome in these patients.

REFERENCES

1. Kannel WB, McGee DL. Diabetes and cardiovascular risk factors: the Framingham study. *Circulation 1979;59:8-13.*
2. Consensus development conference on the diagnosis of coronary heart disease in people with diabetes: 10-11 February 1998, Miami, Florida. American Diabetes Association. *Diabetes Care 1998;21:1551-1559.*
3. The Bypass Angioplasty Revascularization Investigation (BARI). Influence of diabetes on 5-year mortality and morbidity in a randomized trial comparing CABG and PTCA in patients with multivessel disease. *Circulation 1997;96:1761-1769.*
4. Haffner SM, Lehto S, Ronnemaa T, Pyorala K, Laakso M. Mortality from coronary heart disease in subjects with type 2 diabetes and in nondiabetic subjects with and without prior myocardial infarction. *N Engl J Med 1998;339:229-234.*
5. Natali A, Vichi S, Landi P, Severi S L'Abbate A Ferrannini E. Coronary atherosclerosis in type II diabetes: angiographic findings and clinical outcome. *Diabetologia 2000;43:632-641.*
6. Grundy SM, Benjamin IJ, Burke GL, Chait A, Eckel RH, Howard BV, Mitch W, Smith SC Jr, Sowers JR. Diabetes and cardiovascular disease: a statement for healthcare professionals from the American Heart Association. *Circulation 1999;100:1134-1146.*
7. Mak KH, Moliterno DJ, Granger CB, Miller DP, White HD, Wilcox RG, Califf RM, Topol EJ. Influence of diabetes mellitus on clinical outcome in the thrombolytic era of acute myocardial infarction. GUSTO-I Investigators. Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries. *J Am Coll Cardiol 1997;30:171-179.*
8. Mark DB, Shaw L, Harrell FE Jr, Hlatky MA, Lee KL, Bengtson JR, McCants CB, Califf RM, Pryor DB. Prognostic value of a treadmill exercise score in outpatients with suspected coronary artery disease. *N Engl J Med 1991;325:849-853.*
9. Ellestad MH, Wan MK. Predictive implications of stress testing. Follow-up of 2700 subjects after maximum treadmill stress testing. *Circulation 1975;51:363-369.*
10. Elhendy A, Arruda AM, Mahoney DW Pellikka PA. Prognostic stratification of diabetic patients by exercise echocardiography. *J Am Coll Cardiol 2001;37:1551-1557.*
11. May O, Arildsen H, Damsgaard EM, Mickley H. Cardiovascular autonomic neuropathy in insulin-dependent diabetes mellitus: prevalence and estimated

risk of coronary heart disease in the general population. *J Intern Med 2000;248:483-491.*

12. Zarich S, Waxman S, Freeman RT, Mittleman M, Hegarty P, Nesto RW. Effect of autonomic nervous system dysfunction on the circadian pattern of myocardial ischemia in diabetes mellitus. *J Am Coll Cardiol 1994;24:956-962.*
13. Nesto RW, Phillips RT, Kett KG, Hill T, Perper E, Young E, Leland OS Jr. Angina and exertional myocardial ischemia in diabetic and non-diabetic patients: assessment by thallium scintigraphy. *Ann Intern Med 1988;108:170-175.*
14. Schaper NC, Nabuurs-Franssen MH, Huijberts MS. Peripheral vascular disease and type 2 diabetes mellitus. *Diabetes Metab Res Rev 2000;16:S11-S15.*
15. Elhendy A, van Domburg RT, Poldermans D, Bax JJ, Nierop PR, Geleijnse ML, Roelandt JR. Safety and feasibility of dobutamine-atropine stress echocardiography for the diagnosis of coronary artery disease in diabetic patients unable to perform an exercise stress test. *Diabetes Care 1998;21:1797-1802.*
16. Bates JR, Sawada SG, Segar DS, Spaedy AJ, Petrovic O, Fineberg NS, Feigenbaum H, Ryan T. Evaluation using dobutamine stress echocardiography in patients with insulin-dependent diabetes mellitus before kidney and/or pancreas transplantation. *Am J Cardiol 1996;77:175-179.*
17. Bellotti P, Fioretti PM, Forster T, Poldermans D, Salustri A, Boersma E Roelandt JRTC. Reproducibility of the dobutamine-atropine echocardiography stress test. *Echocardiography 1993;10:93-97.*
18. Shiller NB, Shah PM, Crawford M, DeMaria A, Devereux R, Feigenbaum H, Gutgesell H, Reichek N, Sahn D, Schnittger I. Recommendations for quantification of the left ventricle by two-dimensional echocardiography: American Society of Echocardiography Committee on Standards, Subcommittee on Quantification of Two-Dimensional Echocardiograms. *J Am Soc Echocardiogr 1989;2:358-367.*
19. Poldermans D, Fioretti PM, Boersma E, Bax JJ Thomson IR, Roelandt JRTC, Simoons ML. Long-term prognostic value of dobutamine-atropine stress echocardiography in 1737 patients with known or suspected coronary artery disease: A single-center experience. *Circulation 1999;99:757-762.*
20. Arnese M, Fioretti PM, Cornel JH, Postma-Tjoa J, Reijs AE, Roelandt JR. Akinesis becoming dyskinesis during high-dose dobutamine stress echocardiography: a marker of myocardial ischaemia or a mechanical phenomenon? *Am J Cardiol 1994;73:896-899.*
21. Wang CH, Cherng WJ, Hua CC, Hung MJ. Prognostic value of dobutamine echocardiography in patients after Q-wave or non Q wave after acute myocardial infarction. *Am J Cardiol 1998; 82:38-42.*

22. Hung MJ, Wang CH, Cherng WJ. Can dobutamine stress echocardiography predict cardiac events in non-revascularized diabetic patients following acute myocardial infarction? *Chest 1999;116:1224-1232.*
23. Kang X, Berman DS, Lewin HC, Cohen I, Friedman JD, Germano G, Hachamovitch R, Shaw LJ. Incremental prognostic value of myocardial perfusion single photon emission computed tomography in patients with diabetes mellitus. *Am Heart J 1999;138:1025-1032.*

CHAPTER 7

ACCURACY OF DOBUTAMINE 99M-TECHNETIUM SESTAMIBI SPECT IMAGING FOR THE DIAGNOSIS OF SINGLE-VESSEL CORONARY ARTERY DISEASE: COMPARISON WITH ECHOCARDIOGRAPHY

Source: A Elhendy, RT van Domburg, JJ Bax, D Poldermans, FB Sozzi, JRTC Roelandt. *Am Heart J 2000, 139:224-230.* **Adapted.**

ABSTRACT

Background. Recent experimental studies have shown that 99m-technetium-methoxyisobutyl isonitrile (MIBI) underestimates flow heterogeneity induced by dobutamine and that this might have an impact on the sensitivity of dobutamine MIBI in patients with single-vessel coronary artery disease. This study compares the accuracy of dobutamine MIBI single-photon emission computed tomography (SPECT) and simultaneous echocardiography in the diagnosis of single-vessel coronary artery disease.

Methods. Ninety-one patients (age 57 ± 12 years) with single-vessel coronary artery disease or without significant coronary artery disease were studied with dobutamine (up to 40 µg/kg per minute)-atropine (up to 1 mg) stress echocardiography and simultaneous MIBI SPECT imaging. Coronary artery disease was predicted on the basis of myocardial ischemia (transient wall motion abnormalities by dobutamine stress echocardiography and reversible perfusion defects by MIBI).

Results. Ischemia was detected by MIBI in 30 of the 54 patients with and in 10 of the 37 patients without significant single-vessel coronary artery disease (sensitivity 56%, confidence interval [CI] 45 - 66; specificity 73%, CI 64 - 82; accuracy 63%, CI 53 - 73). Ischemia was detected by dobutamine stress echocardiography in 30 patients with and in 6 patients without significant coronary artery disease (sensitivity of dobutamine stress echocardiography 56%, CI 45 - 66; specificity 84%, CI 76 - 91; accuracy 67%, CI 57 - 77, P = not significant vs. MIBI). For both imaging methods, sensitivity was significantly higher in patients with left anterior descending than in patients with left circumflex or right coronary artery stenosis (75% vs. 40%, $P < 0.05$). The addition of echocardiography to MIBI did not improve the diagnostic accuracy (68% CI 59 to 78, = not significant vs. dobutamine stress echocardiography or MIBI alone).

Conclusions. Dobutamine stress echocardiography and MIBI SPECT imaging have similar moderate sensitivity for the diagnosis of single-vessel coronary artery disease. Sensitivity of each of these techniques is higher in patients with left anterior descending than in patients with left circumflex or right coronary artery stenosis. There is no improvement of diagnostic accuracy by use of the combination of both techniques.

INTRODUCTION

Exercise myocardial perfusion imaging is a well-established non-invasive method for the diagnosis and functional evaluation of coronary artery disease.[1-3] Pharmacologic stress testing is an alternative method for evaluation of patients with limited exercise capacity.[4-7] Although vasodilator stress agents are more widely used for myocardial perfusion imaging than dobutamine, the latter is particularly useful in patients who have contraindications for vasodilator agents.[5-7] The use of 99m-technetium-labelled agents provides the advantages of improved imaging quality, increased consistency of image analysis, and a larger injectable dose because of a shorter half-life compared with 201-thallium.[8,9] Despite the favourable imaging properties of 99m-technetium–labelled agents, recent experimental studies have raised some questions regarding the unfavourable myocardial uptake of 99m-technetium-methoxyisobutyl isonitrile (MIBI) during dobutamine infusion.[10,11] It has been demonstrated that myocardial MIBI uptake significantly underestimates the dobutamine-induced flow heterogeneity. In a canine model of a single severe coronary artery stenosis, myocardial uptake of MIBI plateaux at a flow lower than that observed during vasodilator stress.[10] Therefore myocardial perfusion at a high flow rate may be underestimated in the normally perfused myocardium. Conversely, at low flow as in myocardial regions in the distribution of stenosed coronary arteries, tracer extraction may be enhanced as the result of prolonged capillary transit time. These two effects may lead to underestimation of flow heterogeneity between the normal and the ischemic myocardium and may have implications in the sensitivity of the test, particularly in patients with single-vessel coronary artery disease.[10] Because of these potential limitations, echocardiographic imaging during dobutamine infusion may be assumed to provide a higher sensitivity than MIBI for the diagnosis of single-vessel coronary artery disease. This study compares the accuracy of dobutamine stress echocardiography and simultaneous MIBI single-photon emission computed tomography (SPECT) imaging for the diagnosis of single-vessel coronary artery disease and evaluates the agreement between both techniques regarding the presence and the extent of stress-induced wall motion and myocardial perfusion abnormalities.

METHODS

Patient selection

The study population was composed of 91 patients with suspected myocardial ischemia and limited exercise capacity who underwent dobutamine stress echocardiography with simultaneous MIBI SPECT and fulfilled the following criteria: (1) a single-vessel coronary artery disease or no significant coronary artery disease at coronary angiography performed within 3 months from the dobutamine stress test; (2) no previous Q-wave myocardial infarction; (3) no severe valvular heart disease, left-bundle branch block, or left ventricular hypertrophy. Mean age was 57 ± 12 years. There were 46 men and 45 women. Twenty-seven (30%) patients had typical anginal complaints, whereas 64 (70%) patients had atypical or noncardiac chest pain. Beta-blockers were taken by 42 (46%) patients. Other medications included nitrates in 40 (44%) patients and calcium channel blockers in 44 (48%) patients.

Dobutamine stress test

Dobutamine was infused through an antecubital vein starting at a dose of 5 μg/kg per minute followed by 10 μg/kg per minute (3-minute stages), increasing by 10 μg/kg per minute every 3 minutes to a maximum of 40 μg/kg per minute. Atropine (up to 1 mg) was given in patients not achieving 85% of age-predicted maximal heart rate, and dobutamine infusion was continued. The electrocardiogram was continuously monitored and was recorded each minute. Cuff blood pressure was measured at rest and every 3 minutes during stress. The test was interrupted if severe chest pain, ST-segment depression > 2 mm, significant ventricular or supraventricular arrhythmia, hypertension (blood pressure ≥ 240/120), systolic blood pressure fall > 40 mm Hg, or any intolerable side effect regarded as being caused by dobutamine occurred during the test. Metoprolol (1 to 5 mg) was used intravenously to reverse the effects of dobutamine if they did not revert quickly. Ischemia during the electrocardiogram was defined as 0.1 mV horizontal or downsloping ST-segment depression or 0.1 mV ST-segment elevation measured 80 ms from the J point compared with baseline.

Stress echocardiography

Echocardiographic images were acquired from the standard views at rest and during stress and recovery. The left ventricular wall was divided into 16 segments and scored by use of a 4-point scale in which 1 indicated normal; 2, hypokinesis; 3, akinesis; and 4, dyskinesis. Ischemia was defined as new or worsening wall motion abnormalities. The echocardiograms were recorded on videotapes and digitized on optical disks (Vingmed CFM 800, Vingmed Sound A/S, Horten, Norway). Images were compared side by side in quad-screen format by 2 independent observers without the knowledge of the patients' clinical, scintigraphic, or angiographic data. In the case of disagreement, a majority decision was achieved by a third investigator.

SPECT imaging

Approximately 1 minute before the termination of the stress test, an intravenous dose of 370 MBq of MIBI was administered. Stress images were acquired 1 hour after termination of the test by use of the protocol described previously.[5] Image acquisition was performed with a Siemens Gammasonics single-head Rota Camera (Orbiter; Siemens Corp, Iselin, NJ) and a low-energy, all-purpose collimator. Thirty-two projections were obtained, from the left posterior oblique to the right anterior oblique over 180 degrees, with an acquisition time of 45 seconds for each projection. A Gamma 11 computer was used to process the tomographic data. For resting studies, 370 MBq of MIBI was injected at least 24 hours after the stress study. For each study, 6 oblique (short-axis) slices from the apex to the base and 3 sagittal (vertical long-axis) slices from the septum to the lateral wall were defined. Each of the 6 short-axis slices was divided into 8 equal segments. The interpretation of the scan was semiquantitatively performed by visual analysis, assisted by the circumferential profiles analysis. Stress and rest tomographic views were reviewed side by side by an experienced observer who was unaware of the patient's clinical, echocardiographic, or angiographic data. A reversible perfusion defect was defined as a perfusion defect on stress images that partially or completely resolved at rest in 2 contiguous segments or slices. This was considered diagnostic of ischemia. Echocardiographic and scintigraphic images were matched into 6 segments: anterior, inferior, septal anterior, septal posterior, posterolateral, and apical.

Coronary angiography

Coronary angiography was performed within 3 months from the dobutamine stress test. Lesions were quantified as previously described.[12] The 35-mm films were analysed with the Cardiovascular Angiography Analysis System II (CAAS II, Pie Medical, Maastricht, The Netherlands). For edge detection, a region of interest of 512 × 512 pixels was selected and digitized with the use of a high-fidelity charge coupled device video camera. The vessel diameter was determined by computing the shortest distance between the right and left contours. A computer-derived estimation of the original arterial dimension was used to calculate the interpolated reference diameter. Significant coronary artery disease was defined as a diameter stenosis 50% in 1 major epicardial arteries. As stated previously, only patients with single-vessel coronary artery disease or without significant coronary artery disease were included. Coronary arteries were assigned to myocardial segments as previously described.[13] The anterior, apical, septal, and anteroseptal walls were assigned to the left anterior descending coronary artery, the posterior and lateral wall to the left circumflex, and inferior and basal septal segments to the right coronary artery. The apical lateral segment was considered an overlap segment between the left anterior descending coronary artery and the left circumflex and the apical inferior segment was considered an overlap segment between the left anterior descending coronary artery and the right coronary artery. Overlap segments were assigned to the regions with concomitant abnormalities.

Statistical analysis

Unless specified, data are presented as mean values ± standard deviation (SD). The chi-square test was used to compare differences between proportions. The Student t test was used for analysis of continuous data. A value of $P < 0.05$ was considered statistically significant. Agreement between echocardiography and MIBI SPECT on the diagnosis of myocardial ischemia was expressed by the kappa value. Values between 0.75 and 1 were considered indicative of strong, between 0.40 and 0.75 of fair to good, and between 0 and 0.40 of poor agreement. Sensitivity, specificity, and accuracy were derived according to the standard definitions and were represented with the 95% confidence intervals (CI).

RESULTS

Dobutamine stress test

There was a significant increase of heart rate (69 ± 14 vs. 132 ± 16 beats/min, $P < 0.0001$), systolic blood pressure (132 ± 21 vs. 142 ± 26 mm Hg, $P < 0.001$), and rate-pressure product (9145 ± 2674 vs. 18765 ± 4347, $P < 0.00001$) from rest to peak stress, respectively. Atropine was administered in 41 (45%) patients. Angina occurred in 34 (37%) patients, whereas 17 (19%) patients had atypical chest pain. Sixty-eight (75%) patients reached the target heart rate (85% of the maximal exercise heart rate predicted for age and sex). The test was interrupted before reaching the target heart rate because of angina (11 patients), ST-segment depression (2 patients), arrhythmias (3 patients), and hypotension (1 patient). Six (7%) patients failed to reach the target heart rate despite use of the maximal dobutamine and atropine dose.

Coronary angiography

Single-vessel coronary artery disease was detected in 54 (59%) patients. The stenosis involved the left anterior descending coronary artery in 24 patients, the left circumflex in 8 patients, and the right coronary artery in 22 patients. Thirty-seven patients had a normal coronary angiogram or a stenosis of < 50%.

Prediction of coronary artery disease by electrocardiographic changes

Ischemic electrocardiographic changes occurred in 17 of 54 patients with and in 5 of 37 patients without coronary artery disease (sensitivity 31%, CI 22 - 41; specificity 86%, CI 79 - 94; accuracy 54%, CI 44 - 64).

Stress echocardiography

Ischemia was detected in 30 of 54 patients with and in 6 of the 37 patients without significant coronary artery disease (sensitivity 56%, CI 45 - 66; specificity 84%, CI 76 - 91; accuracy 67%, CI 57 - 77). Sensitivity was higher than electrocardiography ($P < 0.05$). The accuracy for the detection of significant stenosis of individual coronary arteries is shown in Figure 1.

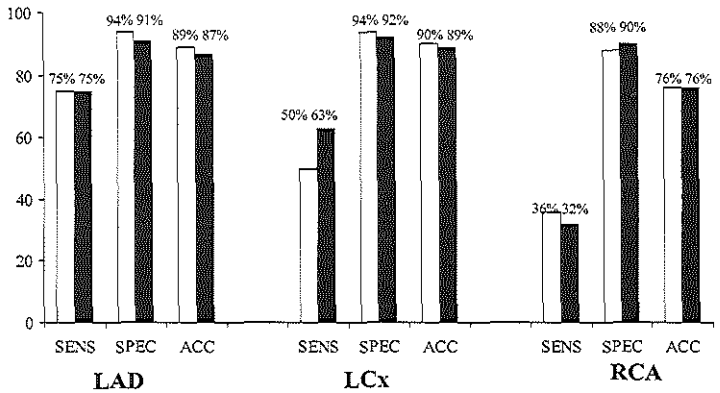


Figure 1

Sensitivity (SENS), specificity (SPEC), and accuracy (ACC) of dobutamine stress echocardiography (open bars) and MIBI SPECT (closed bars) for regional diagnosis of coronary artery disease in patients with single-vessel coronary artery disease.

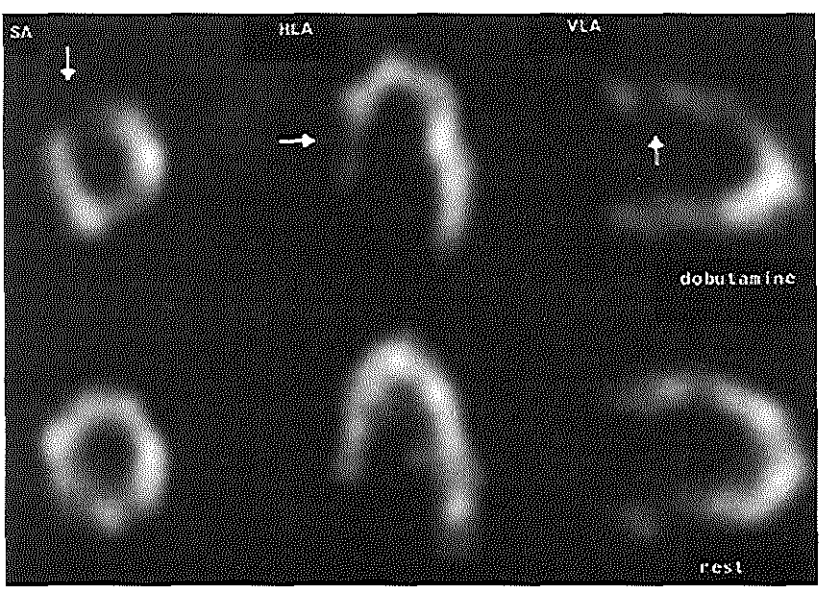


Figure 2

Dobutamine stress (top) and rest (bottom) MIBI SPECT images from the short-axis (SA), horizontal long-axis (HLA), and vertical long-axis (VLA) views in a patient with left anterior descending coronary artery stenosis show reversible perfusion defects in anterior wall and septum, indicated by arrows.

Sensitivity was significantly higher in patients with left anterior descending coronary artery than in patients with right coronary artery or left circumflex stenosis (75% vs. 40%, P < 0.05). In patients with coronary artery disease, there was no significant difference between patients with and those without ischemia regarding medication with beta-blockers (67% vs. 54%, respectively).

MIBI SPECT

Ischemia was detected in 30 of 54 patients with and in 10 of the 37 patients without significant coronary artery disease (sensitivity 56%, CI 45 - 66; specificity 73%, CI 64 - 82; accuracy 63%, CI 53 - 73). Sensitivity was higher than electrocardiography (P < 0.05). The accuracy for the detection of significant stenosis of individual coronary arteries is shown in Figure 1. Sensitivity was significantly higher in patients with left anterior descending coronary artery than in patients with right coronary artery or left circumflex stenosis (75% vs. 40%, P < 0.05). In patients with coronary artery disease, there was no significant difference between patients with and those without ischemia regarding medication with beta-blockers (70% vs. 50%, respectively). Stress and rest myocardial perfusion images of a patient with left anterior descending coronary artery stenosis are shown in Figure 2.

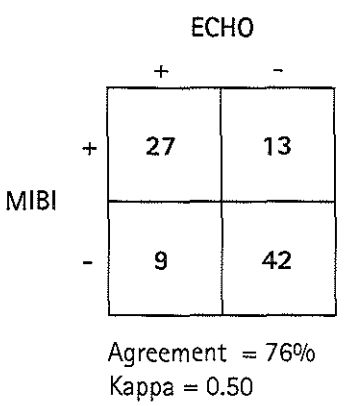


Figure 3

Agreement between dobutamine stress echocardiography (ECHO) and MIBI SPECT on overall diagnosis of myocardial ischemia.

There was no statistically significant difference between echocardiography and SPECT with regard to sensitivity, specificity, and accuracy for the overall and regional diagnosis of significant coronary artery disease. There was a fair (76%) overall agreement between both methods on the diagnosis of myocardial ischemia (69 of 91), kappa = 0.5 (Figure 3).

Agreement on the presence of ischemia in the left anterior descending coronary artery distribution was 78% (kappa = 0.24). Agreement on the presence of ischemia in the left circumflex and right coronary artery distribution was 87% (kappa = 0.87). The mean number of ischemic segments (with the use of a 6-segment model in patients with true-positive studies was not different between echocardiography and MIBI (1.5 ± 1 vs. 1.6 ± 0.9, respectively). In 4 patients without significant coronary artery disease, ischemia developed with the use of both techniques. Three of them had lesions < 50%. The addition of echocardiography to MIBI for the diagnosis of coronary artery disease increased the sensitivity to 69% (CI 59 - 78) and reduced the specificity to 68% (CI 58 - 77), whereas the accuracy did not change (68% CI 59 - 78, P = not significant vs. echocardiography or MIBI alone).

Discussion

The use of 99m-technetium-labelled radioactive agents improves imaging quality of exercise myocardial perfusion scintigraphy compared with 201-thallium.[8,9] Therefore these agents are now widely used in conjunction with exercise and pharmacologic stress testing. However, recent experimental studies demonstrated that MIBI underestimates flow heterogeneity induced by dobutamine because its uptake plateaus at a lower flow rate compared with vasodilator agents.[10] Additionally, dobutamine may interfere with MIBI uptake in the normally perfused myocardium, leading to further underestimation of flow heterogeneity.[11] The implications of these experimental studies are that MIBI scintigraphy may have limited sensitivity in patients with single-vessel coronary artery disease.[10,11] Echocardiographic imaging during dobutamine infusion provides a useful method for the diagnosis of coronary artery disease.[14,15] Although previous studies demonstrated a comparable accuracy between dobutamine echocardiography and MIBI SPECT in the overall diagnosis

of coronary artery disease[13,14,16-20] little is known about the relative merits of these imaging techniques in patients with single-vessel coronary artery disease. In this study we tested the hypothesis that echocardiography may provide a better sensitivity than MIBI in patients with single-vessel coronary artery disease because of the previously mentioned potential limitations of MIBI in this particular patient population. The results of this study showed that both echocardiography and MIBI have a similar modest sensitivity (56%) for the diagnosis of single-vessel coronary artery disease. The mean number of ischemic segments was not different between both techniques. This implies that transient wall motion and myocardial perfusion abnormalities occur with similar frequency and extent in patients with single-vessel coronary artery disease during high-dose dobutamine infusion. Despite the modest sensitivity of MIBI, echocardiography did not provide an advantage in the overall or the regional diagnosis of coronary artery disease in these patients. There was no improvement of accuracy by the synergetic use of both techniques for the diagnosis of single-vessel coronary artery disease compared with accuracy of either technique alone.

Wu et al[10] showed that in a canine model of flow-limiting single-vessel stenosis, dobutamine (10 μg/kg per minute) did not augment flow heterogeneity. In addition, relative myocardial MIBI activity underestimated microsphere flow at higher flow induced by dobutamine, leading to underestimation of ischemia. These findings might explain the modest sensitivity of MIBI in patients with single-vessel coronary artery disease. However, in our study, flow malperfusion could be detected in 56% of these patients. It is possible that at high-dose dobutamine as in our study, flow heterogeneity may be enhanced more than that achieved during the lower dose used in the study of Wu et al. Although these investigators showed that there was a sufficient flow augmentation to a level at which MIBI uptake had plateaued, the administration of a higher dose of dobutamine (and potentially atropine) may result in further augmentation of flow heterogeneity by the induction of vertical and horizontal steal in the ischemic region.

Differences in regional sensitivity

One explanation for the occurrence of flow malperfusion in 56% of patients in our study is that most of these abnormalities were detected in myocardial regions in the distribution of a diseased left

anterior descending coronary artery. In fact, the prevalence of flow malperfusion in myocardial regions in the distribution of a diseased left circumflex or right coronary artery was significantly lower compared with left anterior descending coronary artery disease (40% vs. 75%). This can be explained by the larger myocardial mass in the left anterior descending coronary artery region, which may facilitate the detection of flow heterogeneity compared with the smaller myocardial mass supplied by the left circumflex or the right coronary artery. We have recently demonstrated that the severity of fixed perfusion abnormalities influences the occurrence of reversible perfusion abnormalities in regions with infarct-related artery stenosis only in the right coronary artery and the left circumflex regions.[21] This provides more evidence for the importance of the size of the area at risk in the detection of reversible perfusion abnormalities. Interestingly, the overall and regional prevalence of transient wall motion abnormalities was similar to perfusion abnormalities. If echocardiographic imaging is a sensitive measure of true ischemia, the similar prevalence and extent of abnormalities in both techniques would indicate that MIBI does not underestimate ischemia and the alternative explanation of the relatively low sensitivity is that ischemia—at least of a detectable magnitude—is not actually induced in these patients with false-negative results. Despite the lower sensitivity of both techniques compared with previous studies with dobutamine or exercise echocardiography and myocardial perfusion scintigraphy[1,2,14] other factors might hamper the comparison with these studies such as the difference of the clinical characteristics of the study population in different reports. Therefore this moderate sensitivity may be related to the limited ability to induce ischemia in patients with single-vessel coronary artery disease rather than a limitation of dobutamine stress testing in general.

Role of the extent of coronary artery disease

Porter et al[22] reported that in dogs with experimental single-vessel stenosis, the extent of myocardial perfusion defects measured by myocardial contrast was significantly lower in the zone of the original stenosis compared with the perfusion defect in the same area when a second stenosis was made in the vessel supplying the adjacent perfusion bed. They concluded that collateral flow limits the spatial extent of inducible ischemia within the risk area of single-vessel stenosis.

Restoring blood flow to one perfusion bed reduces the extent of perfusion abnormalities that can be induced in an adjacent stenosed bed. The relatively lower sensitivity of echocardiography and MIBI for the detection of significant stenosis in the posterolateral circulation in this study compared with the previous studies[14] may be explained by the inclusion of patients with multivessel disease in the previous studies. According to the findings of Porter et al,[22] patients with multivessel disease may not have sufficient collaterals between the diseased arteries and therefore the probability of developing regional ischemia in these patients may be higher than in patients with single-vessel disease who would otherwise profit from the collateral flow from the normal arteries. Vascular overlap may also enhance regional sensitivity when patients with multivessel disease are studied.[23]

Limitations of the study

Forty-five percent of patients were receiving beta-blockers, which may reduce the sensitivity. However, only 7% of patients failed to reach the target heart rate despite the maximal dobutamine and atropine dose. In patients with coronary artery disease, there was no significant difference between patients with and those without beta-blocker medication regarding the prevalence of ischemia by either technique. A previous study has also shown that beta-blockers do not reduce the sensitivity of dobutamine perfusion imaging when atropine is used in patients without adequate chronotropic response[24] as used in our study. Similar value of atropine administration in improving the sensitivity of dobutamine stress echocardiography in patients taking beta-blockers has also been reported.[25]

CLINICAL IMPLICATIONS AND CONCLUSIONS

Dobutamine stress echocardiography and MIBI SPECT imaging have similar moderate sensitivity for the diagnosis of single-vessel coronary artery disease. The sensitivity of each of these techniques is higher in patients with left anterior descending coronary artery than in patients with left circumflex or right coronary artery stenosis. There is no improvement of the diagnostic accuracy by use of the combination of both techniques. The similar moderate sensitivity of both techniques suggests a limitation in the induction of ischemia

in patients with single-vessel coronary artery disease rather than an intrinsic limitation of MIBI SPECT imaging in conjunction with dobutamine stress testing.

REFERENCES

1. Maddahi J, Kiat H, Van Train KF, Prigent F, Friedman J, Garcia EV, Alazraki N, DePuey EG, Nichols K, Berman DS. Myocardial perfusion imaging with ^{99}mtechnetium-sestamibi SPECT in the evaluation of coronary artery disease. *Am J Cardiol 1990;66:55E-62*E.
2. Kotler TS, Diamond GA. Exercise thallium-201 scintigraphy in the diagnosis and prognosis of coronary artery disease. *Ann Intern Med 1990;113:648-702.*
3. Richie JL, Trobaugh GB, Hamilton GW, et al. Myocardial imaging with thallium-201 at rest and during exercise: comparison with coronary arteriography and rest and stress electrocardiography. *Circulation 1977;56:66-76.*
4. Verani MS, Mahmarian JJ, Hixson JB, Boyce TM, Staudacher RA. Diagnosis of coronary artery disease by controlled coronary vasodilatation with adenosine and thallium-201 scintigraphy in patients unable to exercise. *Circulation 1990;82:80-87.*
5. Elhendy A, Valkema R, van Domburg RT, Bax JJ, Nierop PR, Cornel JH, Geleijnse ML, Reijs AE, Krenning EP, Roelandt JR. Safety of dobutamine-atropine stress myocardial perfusion scintigraphy. *J Nucl Med 1998;39:1662-1666.*
6. Hays JT, Mahmarian JJ, Cochran AJ, Verani MS. Dobutamine thallium-201 tomography for evaluating patients with suspected coronary artery disease unable to undergo exercise or vasodilator pharmacologic stress testing. *J Am Coll Cardiol 1993;21:1583-1590.*
7. Pennell DJ, Underwood SR, Swanton RH, Walker JM, Ell PJ. Dobutamine thallium myocardial perfusion tomography. *J Am Coll Cardiol 1991;18:1471-1479.*
8. Hendel RC, Parker MA, Wackers FJ, Rigo P, Lahiri A, Zaret BL. Reduced variability of interpretation and improved image quality with a technetium 99m-labelled tetrofosmin. *J Nucl Cardiol 1994;1:509-514.*
9. Khattar RS, Hendel RC, Crawley JC, Wackers FJ, Rigo P, Zaret BL, Sridhara BS, Lahiri A. Improved diagnostic accuracy of planar imaging with technetium 99m-labelled tetrofosmin compared with thallium-201 for the detection of coronary artery disease. *J Nucl Cardiol 1997;4:291-297.*
10. Wu JC, Yun JJ, Heller EN, Dione DP, DeMan P, Liu YH, Zaret BL, Wackers FJ, Sinusas AJ. Limitations of dobutamine for enhancing flow heterogeneity in the presence of single coronary stenosis: implications for technetium-99m sestamibi imaging. *J Nucl Med 1998;39:417-425.*
11. Calnon DA, Glover DK, Beller GA, Vanzetto G, Smith WH, Watson DD, Ruiz M. Effects of dobutamine stress on myocardial blood flow, 99m Tc sestamibi uptake, and systolic wall thickening in the presence of coronary artery stenoses: implications for dobutamine stress testing. *Circulation 1997;96:2353-2360.*

12. Baptista J, Arnese M, Roelandt JR, Fioretti P, Keane D, Escaned J, Boersma E, di Mario C, Serruys PW. Quantitative coronary angiography in the estimation of the functional significance of coronary stenosis: correlation with dobutamine-atropine stress test. *J Am Coll Cardiol 1994;23:1434-1439.*
13. Marwick T, D'Hondt AM, Baudhuin T, Willemart B, Wijns W, Detry JM, Melin J. Optimal use of dobutamine stress for the detection and evaluation of coronary artery disease: combination with echocardiography, scintigraphy or both? *J Am Coll Cardiol 1993;22:159-167.*
14. Geleijnse ML, Fioretti PM, Roelandt JRTC. Methodology, feasibility safety and diagnostic accuracy of dobutamine stress echocardiography. *J Am Coll Cardiol 1997;30:595-606.*
15. Sawada SG, Segar DS, Ryan T, Brown SE, Dohan AM, Williams R, Fineberg NS, Armstrong WF, Feigenbaum H. Echocardiographic detection of coronary artery disease during dobutamine infusion. *Circulation 1991;83:1605-1614.*
16. Senior R, Sridhara BS, Anagnostou E, Handler C, Raftery EB, Lahiri A Synergistic value of simultaneous stress dobutamine sestamibi single-photon-emission computerized tomography and echocardiography in the detection of coronary artery disease. *Am Heart J 1994;821:713-718.*
17. Marwick T, Willemart B, D'Hondt AM, Baudhuin T, Wijns W, Detry JM, Melin J. Selection of the optimal non-exercise stress for the evaluation of ischemic regional myocardial dysfunction and malperfusion: comparison of dobutamine and adenosine using echocardiography and ^{99}mTc-MIBI single photon emission computed tomography. *Circulation 1993;87:345-354.*
18. Elhendy A, Geleijnse ML, Roelandt JR, van Domburg RT, Ten Cate FJ, Nierop PR, Bax JJ, El-Refaee M, Ibrahim MM, El-Said GM, Fioretti PM. Comparison of dobutamine stress echocardiography and 99m-technetium sestamibi SPECT myocardial perfusion scintigraphy in predicting the extent of coronary artery disease in patients with healed myocardial infarction. *Am J Cardiol 1997;79:7-21.*
19. Forster T, McNeill AJ, Salustri A, Reijs AE, el-Said ES, Roelandt JR, Fioretti PM. Simultaneous dobutamine stress echocardiography and ^{99}mtechnetium isonitrile single photon emission computed tomography in patients with suspected coronary artery disease. *J Am Coll Cardiol 1993;21:1951-1956.*
20. Gunalp B, Dokumaci B, Uyan C, Vardareli E, Isik E, Bayhan H, Ozguven M, Ozturk E. Value of dobutamine technetium-99m-sestamibi SPECT and echocardiography in detection of coronary artery disease compared with coronary angiography. *J Nucl Med 1993;34:889-894.*
21. Elhendy A, Cornel JH, Roelandt JR, van Domburg RT, Geleijnse ML, Hoeymans PA, Reijs AE, TenCate FJ, Ibrahim MM, Fioretti PM. Dobutamine 201-thallium

SPECT imaging for the assessment of peri-infarction and remote myocardial ischemia. *J Nucl Med 1996;37:1951-1956.*

22. Porter TR, Li S, Kilzer K, Deligonul U. Effect of significant two-vessel versus one-vessel coronary artery stenosis on myocardial contrast defects observed with intermittent harmonic imaging after intravenous contrast injection during dobutamine stress echocardiography. *J Am Coll Cardiol 1997;30:1399-1406.*
23. Elhendy A, Cornel JH, Roelandt JR, van Domburg RT, Geleijnse MI, Nierop PR, Bax JJ, Sciarra A, Ibrahim MM, el-Refaee M, el-Said GM, Fioretti PM. Accuracy of dobutamine stress echocardiography for the diagnosis of coronary artery stenosis in patients with myocardial infarction: the impact of extent and severity of left ventricular dysfunction. *Heart 1996;76:123-128.*
24. Huang PJ, Yen RF, Chieng PU, Chen ML, SU CT. Do beta-blockers affect the diagnostic sensitivity of dobutamine stress thallium 201 single photon emission computed tomographic imaging? *J Nucl Cardiol 1998;5:34-39.*
25. Fioretti PM, Poldermans D, Salustri A, Forster T, Bellotti P, Boersma E, McNeill AJ, el-Said ES, Roelandt JR. Atropine increases the accuracy of dobutamine stress echocardiography in patients taking beta-blockers. *Eur Heart J 1994;15:355-360.*

CHAPTER 8

DOBUTAMINE 99M-TECHNETIUM TETROFOSMIN SPECT IMAGING FOR THE DIAGNOSIS OF CORONARY ARTERY DISEASE IN PATIENTS WITH LIMITED EXERCISE CAPACITY

Source: A Elhendy, FB Sozzi, R Valkema, RT van Domburg, JJ Bax, JRTC Roelandt. *J Nucl Cardiol 2000;7:649-654.* **Adapted.**

ABSTRACT

Background. 99m-Technetium-tetrofosmin SPECT imaging is increasingly used in conjunction with exercise and vasodilator stress test for the evaluation of coronary artery disease. Dobutamine stress test is an alternative in patients with limited exercise capacity.

Objective. The aim of this study is to assess the accuracy of dobutamine-atropine stress tetrofosmin SPECT for the diagnosis and localisation of coronary artery disease.

Methods. We studied 124 patients (age = 57 ± 12 years, 88 men) with limited exercise capacity and suspected coronary artery disease with dobutamine (up to 40 μg/kg/min)-atropine (up to 1 mg) 99m-technetium-tetrofosmin SPECT. Resting images were acquired 24 hours after the stress test. Significant coronary artery disease was defined as ≥ 50% luminal diameter stenosis in ≥ 1 major coronary artery.

Results. Myocardial perfusion abnormalities (fixed and/or reversible defects) were detected in 70 of 88 patients with and in 10 of the 36 patients without coronary artery disease (sensitivity = 80%, CI 72 - 87, specificity = 72%, CI 64 - 80 and accuracy = 77%, CI 70 - 85). Sensitivity and accuracy were higher by using criteria of any defect than reversible defects only (80% vs. 51%, $P < 0.0001$ and 77% vs. 60%, $P < 0.01$ respectively). Sensitivity was higher in patients with multivessel compared to patients with single-vessel coronary artery disease (88% vs. 63%, $P < 0.05$). Patients with multivessel coronary artery disease had a larger stress perfusion defect score (4.5 ± 3.1 vs. 2.7 ± 2.5, $P < 0.01$) compared to patients with single-vessel coronary artery disease.

Conclusions. Dobutamine stress 99m-technetium-tetrofosmin SPECT is a useful method for the diagnosis and localisation of coronary artery disease in patients with limited exercise capacity. Optimal accuracy of the technique is achieved by the use of both fixed and reversible perfusion abnormalities for the diagnosis of coronary artery disease in patients without previous myocardial infarction.

INTRODUCTION

Dobutamine myocardial perfusion imaging is a feasible method for evaluation of coronary artery disease in patients with limited exercise capacity.[1,2] Previous studies have demonstrated the accuracy of dobutamine stress myocardial perfusion imaging using 201-thallium and 99m-technetium-sestamibi for the diagnosis of coronary artery disease.[3-6] 99m-Technetium-tetrofosmin is a newly introduced myocardial perfusion tracer with favourable biokinetics and imaging characteristics.[7-9] This radiopharmaceutical is distributed within the myocardium in proportion to regional myocardial blood flow. After intravenous injection, a relatively rapid clearance of the tracer from the blood and extracardiac structures occur with minimal redistribution from the myocardium.[7-9] The use of 99m-technetium-labelled agents provides the advantages of improved imaging quality, increased consistency of image analysis and a larger injectable dose due to a shorter half life compared to 201-thallium.[10-12] The accuracy of myocardial perfusion scintigraphy using 99m-technetium-tetrofosmin for the diagnosis of coronary artery disease in conjunction with exercise or vasodilator stress testing has been recently evaluated.[13-21] However, few data are available regarding the use of tetrofosmin with dobutamine stress testing. Although vasodilator stress agents are more widely used for myocardial perfusion imaging than dobutamine, the latter is particularly useful in patients who have contraindications for vasodilator agents.[1,3] The aim of this study is to assess the accuracy of dobutamine stress 99m-technetium-tetrofosmin SPECT for the diagnosis of coronary artery disease in patients with limited exercise capacity.

METHODS

Patient selection

The study population was composed of 124 patients with suspected myocardial ischemia and limited exercise capacity who underwent dobutamine stress 99m-technetium-tetrofosmin SPECT and coronary angiography within 3 months from the dobutamine stress test. Patients were included in the study if they had no history or electrocardiographic signs of previous myocardial infarction, unstable angina, severe valvular heart disease, left-bundle branch block, left ventricular hypertrophy or previous heart transplantation. Mean age was 57 ± 12 years. There were

88 men and 36 women. Forty-four patients (35%) had typical anginal complaints whereas 80 patients (65%) had atypical or non-cardiac chest pain. The pre-test probability of coronary artery disease based on age gender and chest pain characteristics was 62 ± 25%.[22] Nineteen patients (15%) were known to have diabetes mellitus. At the day of the test, 59 patients (48%) were receiving beta-blockers. Other medications included nitrates in 29 patients (23%) and calcium channel blockers in 46 patients (37%).

Dobutamine stress test

Dobutamine was infused through an antecubital vein starting at a dose of 5 followed by 10 μg/kg/min (3 minutes stages), increasing by 10 μg/kg/min every 3 minutes to a maximum of 40 μg/kg/min. Atropine (up to 1 mg) was given in patients not achieving 85% of the predicted maximal heart rate after 3 minutes of infusion of the maximal dobutamine dose (40 μg/kg/min), and dobutamine infusion was continued.[2] The electrocardiography was continuously monitored and was recorded each minute. Cuff blood pressure was measured at rest and every 3 minutes during stress. The test was interrupted if severe chest pain, ST-segment depression > 2 mm, significant arrhythmia, hypertension (blood pressure ≥ 240/120), systolic blood pressure fall > 40 mm Hg or any intolerable side effect regarded as being due to dobutamine occurred during the test. Metoprolol (1-5 mg) was used intravenously to reverse the effects of dobutamine if they did not revert quickly. Ischemia at the electrocardiogram was defined as ≥ 0.1 mV horizontal or downsloping ST-segment depression or ≥ 0.1 mV ST-segment elevation measured 80 mS from the J point compared to baseline.

SPECT imaging

Approximately 1 minute before the termination of the stress test, an intravenous dose of 370 MBq of 99m-technetium-tetrofosmin was administered. For resting studies 370 MBq of tetrofosmin were injected at least 24 hours after the stress study. Image acquisition was performed with a triple head gamma camera system (Picker Prism 3000 XP, Cleveland, Ohio). For each study six oblique (short axis) slices from the apex to the base, three sagittal (vertical long axis) slices were defined.[2] Each of the 6 short axis slices was divided into 8 equal segments. The septal part of the 2 basal slices was excluded from analysis because this region corresponds to the fibrous portion of the interventricular septum and

normally exhibits reduced uptake. Therefore, a total of 47 segments were identified (3 long axis and 44 short axis). The interpretation of the scan was semiquantitatively performed by visual analysis assisted by the circumferential profiles analysis. Stress and rest tomographic views were reviewed side by side by an experienced observer who was unaware of the patients' clinical or angiographic data. A reversible perfusion defect was defined as a perfusion defect on stress images that partially or completely resolved at rest in ≥ 2 contiguous segments or slices in the 47-segment model. A fixed perfusion defect was defined as a perfusion defect on stress images in 2 or more contiguous segments or slices, which persists on rest images in the 47 segment model. An abnormal study was considered in the presence of fixed/and or reversible perfusion defect. To assess the severity of perfusion abnormalities, the left ventricular myocardium was divided into 6 segments: anterior, inferior, septal anterior, septal posterior, posterolateral and apical. Each of the 6 major left ventricular segments was scored using a 4 grade score method (0 = normal, 1 = slightly reduced, 2 = moderately reduced, 3 = severely reduced or absent uptake). Perfusion defect score was derived by the summation of the score of the 6-myocardial segments.[2]

Coronary angiography

Coronary angiography was performed within 3 months from the dobutamine stress test according to the physician discretion. Lesions were quantified as previously described.[23] Significant coronary artery disease was defined as a diameter stenosis ≥ 50% in ≥ 1 major epicardial arteries. The anterior, apical, septal and anteroseptal wall were assigned to the left anterior descending coronary artery. The posterior and lateral walls were assigned to the left circumflex. The inferior and basal septal segments were assigned to the right coronary artery.[6] The apical lateral segment was considered as an overlap segment between the left anterior descending coronary artery and the left circumflex. The apical inferior segment was considered an overlap segment between the left anterior descending coronary artery and the right coronary artery. Overlap segments were assigned to the regions with concomitant abnormalities.

Statistical analysis

Unless specified, data are presented as mean values ± SD. The Chi square test was used to compare differences between proportions. The Student *t* test was used for analysis of continuous data. P value < 0.05 was

considered statistically significant. Sensitivity, specificity and accuracy were derived according to the standard definitions and were represented with the 95% confidence intervals (95% CI).

RESULTS

Dobutamine stress test

Dobutamine-atropine induced a significant increase of heart rate (76 ± 15 vs. 133 ± 15 beats/minute, $P < 0.0001$), systolic blood pressure (139 ± 26 vs. 154 ± 33 mm Hg, $P < 0.0001$) and rate-pressure product (11070 ± 3106 vs. 20397 ± 4898, $P < 0.00001$) from rest to peak stress respectively. Atropine was administered in 53 (43%) patients and the mean dose was 0.6 ± 0.3 mg. Angina occurred in 43 (35%) patients whereas 11 (9%) patients had atypical chest pain. The target heart rate (≥ 85% of the maximal exercise heart rate predicted for age) was reached in 98 patients (79%). The test was interrupted before reaching the target heart rate because of angina (7 patients), ST-segment depression (4 patients), arrhythmias (1 patient) and hypotension (2 patients). Twelve patients (10%) failed to reach the target heart rate despite using the maximal dobutamine and atropine dose. Minor side effects were headache in 9 patients (7%), symptomatic hypotension in 1 patient (1%), anxiety in 3 patients (2%), nausea in 10 patients (8%) and flushing in 3 patients (2%).

Coronary angiography

Significant coronary artery stenosis was detected in 88 patients (71%). Thirty patients (24%) had single-vessel coronary artery disease, 27 (22%) had 2-vessel coronary artery disease and 31 (25%) had 3-vessel coronary artery disease. Normal coronary arteries or < 50% lesions were present in 36 patients (29%). Significant stenosis involved the left anterior descending coronary artery in 70 patients (56%), the left circumflex in 53 patients (43%) and in the right coronary artery in 54 patients (44%).

Prediction of coronary artery disease by electrocardiographic changes

Ischemic electrocardiographic changes occurred in 22 of 88 patients with and in 9 of 36 patients without coronary artery disease (sensitivity = 25%, CI 17 - 33, specificity = 75% CI 67 - 83, accuracy = 40%, CI 31 - 48).

Tetrofosmin SPECT

Partially or completely reversible perfusion defects were detected in 45 of 88 patients with and in 6 of the 36 patients without significant coronary artery disease (sensitivity = 51%, CI 42 - 60, specificity = 83%, CI 77 - 90 and accuracy = 60%, CI 52 - 69). The sensitivity was 43% in patients with single-vessel coronary artery disease (13/30), 59% in patients with 2-vessel coronary artery disease (16/27) and 52% in patients with 3-vessel coronary artery disease (16/31). An abnormal test (defined as any perfusion defect, reversible and/or fixed) was detected in 70 of 88 patients with and in 10 of the 36 patients without significant coronary artery disease (sensitivity = 80%, CI 72 - 87, specificity = 72%, CI 64 - 80 and accuracy = 77%, CI 70 - 85). The sensitivity was 63% in patients with single-vessel coronary artery disease (19/30), 81% in patients with 2-vessel coronary artery disease (22/27) and 94% in patients with 3-vessel coronary artery disease (29/31). The use of any perfusion defect to identify coronary artery disease resulted in a significant increase of sensitivity ($P < 0.0001$) and overall accuracy ($P < 0.01$) without a significant reduction of specificity, compared to the use of only reversible perfusion defects. Diagnostic accuracy was higher than electrocardiography ($P < 0.005$).

Impact of the severity of coronary artery disease

Among patients with single-vessel coronary artery disease, those with perfusion abnormalities had a more severe % diameter stenosis compared to those without perfusion abnormalities ($75 \pm 15\%$ vs. $61 \pm 20\%$, $P < 0.05$). Among patients with multivessel disease, the maximal severity of the stenosis was $\geq 70\%$ in 41 of 51 (80%) patients with and in 3 of 7 (43%) patients without perfusion abnormalities ($P < 0.05$).

Abnormal perfusion in multivessel distribution

Perfusion defects in 2 different vascular territories, suggestive of multivessel coronary artery disease occurred in 33 of 58 patients with and in 8 of 66 patients without multivessel coronary artery disease (sensitivity = 57%, CI 48 - 66, specificity = 88% CI 82 - 94, accuracy = 73%, CI 66 - 81). Patients with multivessel coronary artery disease had a larger stress perfusion defect score (4.5 ± 3.1 vs. 2.7 ± 2.5, $P < 0.01$) compared to patients with single-vessel coronary artery disease. The accuracy for the detection of significant stenosis of individual coronary arteries is shown in

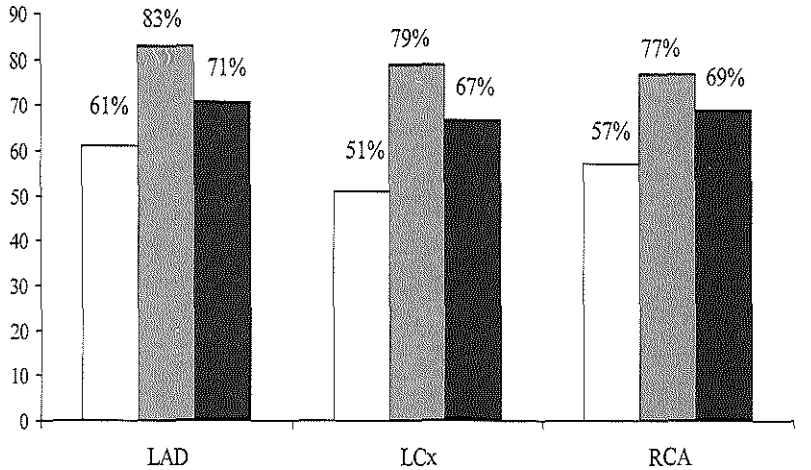


Figure 1

Sensitivity (empty bars), specificity (gray bars) and accuracy (filled bars) of dobutamine stress 99m-technetium-tetrofosmin SPECT for the regional diagnosis of coronary artery disease. LAD = left anterior descending, LCx = left circumflex, RCA = right coronary artery.

figure 1.

Patients with coronary artery disease and normal perfusion

Patients with significant coronary artery disease who demonstrated normal myocardial perfusion had a lower prevalence of multivessel coronary artery disease (39% vs. 73%, $P < 0.05$), a lower peak stress heart rate (124 ± 19 vs. 133 ± 15 beats/min, $P < 0.05$) compared to patients with coronary artery disease and abnormal perfusion. A relatively larger proportion of patients with normal perfusion were receiving beta-blockers (74% vs. 54%) although the difference was not statistically significant ($P = 0.1$).

Discussion

Our study showed that in patients with limited exercise capacity and suspected coronary artery disease, dobutamine tetrofosmin SPECT has a relatively high sensitivity and specificity for the diagnosis of coronary artery disease. Overall sensitivity was 80%. Sensitivity was higher in

patients with multivessel compared with patients with single-vessel coronary artery disease. Additionally, 57% of patients with multivessel coronary artery disease were identified on bases of perfusion abnormalities in ≥ 1 vascular region. Stress myocardial perfusion defect score was larger in patients with multivessel compared to those with single-vessel coronary artery disease. This demonstrates the ability of the test to identify patients with extensive coronary artery disease who are known to have a high risk for cardiac events.

Reversible versus fixed myocardial perfusion abnormalities

In this population without previous myocardial infarction, sensitivity and accuracy of dobutamine tetrofosmin imaging were significantly improved by the use of any perfusion defect (fixed or reversible) to predict coronary artery disease compared to the use of reversible perfusion defects alone. This improvement of a sensitivity and accuracy was accomplished with a minor non significant reduction of specificity. The improvement of sensitivity was observed in patients with single vessel as well as in patients with multivessel coronary artery disease. However, the additive value of fixed perfusion defects was more evident in patients with multivessel disease. In patients with coronary artery disease and abnormal scan, fixed perfusion defects without reversibility were detected in 32%, 27% and 45% of patients with single-vessel, two-vessel, and three-vessel coronary artery disease respectively. Nevertheless, the overall sensitivity of the test by the use of any defect was high. The presence of fixed rather than reversible perfusion defects in patients with coronary artery disease who had no previous infarction may be explained by the impairment of myocardial perfusion at rest which can not be further reduced during stress. This explanation is particularly related to the fact that myocardial uptake of tetrofosmin is largely dependent on regional blood flow with minimal if any redistribution.[7-9] Another possibility is the presence of undiagnosed non Q wave myocardial infarction. However, the possibility that tetrofosmin underestimated the magnitude of reversible hypoperfusion can not be excluded. Shanoudy et al [12] reported that in 26 patients with coronary artery disease who underwent both dipyridamole 201-thallium and tetrofosmin SPECT, tetrofosmin identified fewer and less sever reversible defects and similar fixed defects compared with 201-thallium. However, Glover et al. have concluded that with clinical imaging, greater thallium attenuation and redistribution may lessen the advantage of thallium over

tetrofosmin.[20] Despite this possible limitation, our study demonstrated that patients with multivessel coronary artery disease have a larger perfusion defects which infers the value of tetrofosmin in the evaluation of the extent of coronary artery disease.

The role of the severity of coronary stenosis

In this study, the absence of perfusion abnormalities in patients with coronary artery disease was associated with less severe coronary artery stenosis. The lower sensitivity under this condition may be explained by the early roll-off of tetrofosmin during high flow situation. The occurrence of false negative response was additionally related to a lower peak heart rate. It is possible that a higher stress level is required to induce myocardial ischemia in patients with less severe lesions.

Comparison with previous studies

The accuracy of exercise and dipyridamole tetrofosmin myocardial perfusion imaging for the diagnosis of coronary artery disease has been recently reported. Zaret et al reported that among 181 patients who underwent exercise tetrofosmin planar imaging and coronary angiography, exercise tetrofosmin had a sensitivity of 77% and specificity of 58% for the diagnosis of coronary artery disease.[8] The low specificity was explained by selection of patients with abnormal scans for coronary angiography and the possible presence of patients with microvascular ischemia. The reported sensitivity is comparable with the sensitivity of dobutamine tetrofosmin in our study (80%). Azzarelli et al reported a sensitivity and specificity of 95% and 77% respectively for exercise tetrofosmin SPECT imaging for the diagnosis of coronary artery disease in 235 patients.[13] Montz et al reported a sensitivity and specificity of 93% and 38% in 142 patients.[14] In other studies that included less than 100 patients, sensitivity ranged between 54% and 88% and specificity raged between 64% and 95%.[15-19] He et al reported a sensitivity of 85% and specificity of 55% for the diagnosis of coronary artery disease by dipyridamole tetrofosmin SPECT imaging in 59 patients.[21] Most of these previous studies included patients with and without myocardial infarction.

The detection of individual coronary artery stenosis

In our study, no significant difference was detected regarding the accuracy for the detection of individual coronary artery stenosis. Some

previous studies reported a particularly low sensitivity for the diagnosis of left circumflex stenosis.[21] The similar sensitivity for the detection of left circumflex coronary disease compared with other arteries in our study may be explained by the high prevalence of multivessel disease in the population of this study which may enhance the sensitivity due to the vascular overlap between the left circumflex and the right coronary artery in the postero-inferior region. The similar specificity in the 3 vascular regions may be explained by the better target background ratio for the inferior wall achieved by the use of technetium-labelled agents.[13]

Limitations of the study

Forty-eight percent of patients were receiving beta-blockers, which may reduce the sensitivity. However, only 10% of patients failed to reach the target heart rate despite the maximal dobutamine and atropine dose. Nevertheless, patients with a negative test had a significantly lower maximal stress heart rate compared to patients with a positive test. This demonstrates the importance of the achievement of a sufficient increment of heart rate to optimise the sensitivity of this method of stress imaging. Some investigators prefer the use of dipyridamole rather than dobutamine for pharmacologic perfusion imaging, as hyperemia is more significant with the former. However, Levine et al have recently shown that in 31 patients with coronary artery disease who underwent on separate days 99m-technetium-tetrofosmin SPECT at rest and after exercise, dipyridamole, and dobutamine stress, dipyridamole was not superior to dobutamine with regards to the extent, severity and reversibility of myocardial perfusion abnormalities.[24] Coronary angiography was performed according to the physician discretion. Therefore, referral bias for coronary angiography might have had an impact on the sensitivity and the specificity of the test. The studies were not gated. It is possible that gating might have improved the accuracy of the test or provided explanation for the presence of fixed perfusion abnormalities in some patients. Finally, the presence of a previous myocardial infarction was excluded by the absence of Q waves at the time of the test and the lack of a known history of myocardial infarction. It is possible that some of these patients had sustained a previous non-Q wave myocardial infarction, which may explain in part the relatively high prevalence of fixed myocardial perfusion abnormalities in this study.

CLINICAL IMPLICATIONS AND CONCLUSIONS

Dobutamine stress 99m-technetium-tetrofosmin SPECT imaging is a clinically useful method for the diagnosis and localisation of coronary artery disease in patients with limited exercise capacity. The sensitivity and specificity of dobutamine tetrofosmin SPECT imaging in this study are fairly comparable with the average sensitivity and specificity of exercise tetrofosmin imaging reported in previous studies. Optimal accuracy of the technique is achieved by the use of both fixed and reversible perfusion abnormalities for the diagnosis of coronary artery disease in patients without previous myocardial infarction. False negative tests occur more frequently in patients with lower peak stress heart rate, single-vessel coronary artery disease and less severe coronary stenosis.

REFERENCES

1. Dakik HB, Vempathy H, Verani MS. Tolerance, haemodynamic changes and safety of dobutamine stress perfusion imaging. *J Nucl Cardiol 1996;3:410-414.*
2. Elhendy A, Valkema R, van Domburg RT, Bax JJ, Nierop PR, Cornel JH, Geleijnse ML, Reijs AE, Krenning EP, Roelandt JR. Safety of dobutamine-atropine stress myocardial perfusion scintigraphy. *J Nucl Med 1998;39:1662-1666.*
3. Hays JT, Mahmarian JJ, Cochran AJ, Verani MS. Dobutamine thallium-201 tomography for evaluating patients with suspected coronary artery disease unable to undergo exercise or vasodilator pharmacologic stress testing. *J Am Coll Cardiol 1993;21:1583-1590.*
4. Pennell DJ, Underwood SR, Swanton RH, Walker JM, Ell PJ. Dobutamine thallium myocardial perfusion tomography. *J Am Coll Cardiol 1991;18:1471-1479.*
5. Elhendy A, Cornel JH, Roelandt JR, van Domburg RT, Geleijnse ML, Hoeymans PA, Reijs AE, TenCate FJ, Ibrahim MM, Fioretti PM. Dobutamine 201-thallium SPECT imaging for the assessment of peri-infarction and remote myocardial ischemia. *J Nucl Med 1996;37:1951-1956.*
6. Marwick T, D'Hondt AM, Baudhuin T, Willemart B, Wijns W, Detry JM, Melin J. Optimal use of dobutamine stress for the detection and evaluation of coronary artery disease: combination with echocardiography, scintigraphy or both? *J Am Coll Cardiol 1993;22:159-167.*
7. Munch G, Neverve J, Matsunari I, Schroter G, Schwaiger M. Myocardial Tc-99m-tetrofosmin and Tc-99m-sestamibi kinetics in normal subjects and patients with coronary artery disease. *J Nucl Med 1997;38:428-432.*
8. Zaret BL, Rigo P, Wackers FJ, Hendel RC, Braat SH, Iskandrian AS, Sridhara BS, Jain D, Itti R, Serafini AN. Myocardial perfusion imaging with 99m technetium tetrofosmin. Comparison to 201Tl imaging and coronary angiography in a phase III multicenter trial. Tetrofosmin International Trial Study Group. *Circulation 1995;91:313-319.*
9. Sinusas AJ, Shi Q, Saltzberg MT, Vitols P, Jain D, Wackers FJ, Zaret BL. Technetium-99m-tetrofosmin to assess myocardial blood flow: experimental validation in an intact canine model of ischemia. *J Nucl Med 1994;35:664-671.*
10. Hendel RC, Parker MA, Wackers FJ, Rigo P, Lahiri A, Zaret BL. Reduced variability of interpretation and improved image quality with a technetium 99m-labelled tetrofosmin. *J Nucl Cardiol 1994;1:509-514.*
11. Khattar RS, Hendel RC, Crawley JC, Wackers FJ, Rigo P, Zaret BL, Sridhara BS, Lahiri A. Improved diagnostic accuracy of planar imaging with technetium 99m-labelled tetrofosmin compared with thallium-201 for the detection of coronary artery disease. *J Nucl Cardiol 1997;4:291-297.*

12. Shanoudy H, Raggi P, Beller GA, Soliman A, Ammermann EG, Kastner RJ, Watson DD. Comparison of technetium-99m tetrofosmin and thallium-201 single-photon emission computed tomographic imaging for detection of myocardial perfusion defects in patients with coronary artery disease. *J Am Coll Cardiol 1998;31:331-337.*
13. Azzarelli S, Galassi AR, Foti R, Musumeci S, Giuffrida G, Tamburino C. Accuracy of 99mTc-tetrofosmin myocardial tomography in the evaluation of coronary artery disease. *J Nucl Cardiol 1999;6:183-189.*
14. Montz R, Perez-Castejon MJ, Jurado JA, Martin-Comin J, Esplugues E, Salgado L, Ventosa A, Cantinho G, Sa EP, Fonseca AT, Vieira MR. Technetium-99m tetrofosmin rest/stress myocardial SPECT with a same-day 2-hour protocol: comparison with coronary angiography. A Spanish-Portuguese multicentre clinical trial. *Eur J Nucl Med 1996;23:639-647.*
15. Heo J, Cave V, Wasserleben V, Iskandrian AS. Planar and tomographic imaging with technetium 99m-labelled tetrofosmin: correlation with thallium 201 and coronary angiography. *J Nucl Cardiol 1994;1:317-324.*
16. Sacchetti G, Inglese E, Bongo AS, Aina F, Brambilla M, Baroli A, Cernigliaro C, Dellavesa P, Pittaluga E, Rudoni M. Detection of moderate and severe coronary artery stenosis with technetium-99m tetrofosmin myocardial single-photon emission tomography. *Eur J Nucl Med 1997;24:1230-1236.*
17. Sullo P, Cuocolo A, Nicolai E, Cardei S, Nappi A, Squame F, Covelli EM, Pace L, Salvatore M. Quantitative exercise technetium-99m tetrofosmin myocardial tomography for the identification and localisation of coronary artery disease. *Eur J Nucl Med 1996;23:648-655.*
18. Benoit T, Vivegnis D, Lahiri A, Itti R, Braat S, Rigo P. Tomographic myocardial imaging with technetium-99m tetrofosmin. Comparison with tetrofosmin and thallium planar imaging and with angiography. *Eur Heart J 1996;4:635-642.*
19. Cuocolo A, Nicolai E, Soricelli A, Pace L, Nappi A, Sullo P, Cardei S, Argenziano L, Ell PJ, Salvatore M. Technetium 99m-labelled tetrofosmin myocardial tomography in patients with coronary artery disease: comparison between adenosine and dynamic exercise stress testing. *J Nucl Cardiol 1996;3:194-203.*
20. Glover DK, Ruiz M, Yang JY, Smith WH, Watson DD, Beller GA. Myocardial 99mTc-tetrofosmin uptake during adenosine-induced vasodilatation with either a critical or mild coronary stenosis: comparison with 201Tl and regional myocardial blood flow. *Circulation 1997;96:2332-2338.*
21. He ZX, Iskandrian AS, Gupta NC, Verani MS. Assessing coronary artery disease with dipyridamole technetium-99m-tetrofosmin SPECT: a multicenter trial. *J Nucl Med 1997;38:44-48.*

22. Diamond G, Forrester J. Analysis of probability as an aid in the clinical diagnosis of coronary artery disease. *N Engl J Med 1979;300:1350-1358.*
23. Baptista J, Arnese M, Roelandt JR, Fioretti P, Keane D, Escaned J, Boersma E, di Mario C, Serruys PW. Quantitative coronary angiography in the estimation of the functional significance of coronary stenosis: Correlation with dobutamine-atropine stress test. *J Am Coll Cardiol 1994;23:1434-1439.*
24. Levine MG, Ahlberg AW, Mann A, White MP, McGill CC, Mendes de Leon C, Piriz JM, Waters D, Heller GV. Comparison of exercise, dipyridamole, adenosine, and dobutamine stress with the use of Tc-99m tetrofosmin tomographic imaging. *J Nucl Cardiol 1999;6:389-396.*

CHAPTER 9

IMPACT OF HYPERTENSION ON THE ACCURACY OF EXERCISE STRESS MYOCARDIAL PERFUSION IMAGING FOR THE DIAGNOSIS OF CORONARY ARTERY DISEASE

Source: A Elhendy, RT van Domburg, FB Sozzi, D Poldermans, JJ Bax, JRTC Roelandt. *Heart 2001;85:655:661.* Adapted.

ABSTRACT

Objective. To compare the accuracy of exercise stress myocardial perfusion single photon emission computed tomography (SPECT) imaging for the diagnosis of coronary artery disease in patients with and without hypertension.

Methods. A symptom limited bicycle exercise stress test in conjunction with 99m-technetium-sestamibi or tetrofosmin SPECT imaging was performed in 332 patients (mean age ± SD, 57 ± 10 years; 257 men, 75 women) without previous myocardial infarction who underwent coronary angiography. Of these, 137 (41%) had hypertension. Rest SPECT images were acquired 24 hours after the stress test. An abnormal scan was defined as one with reversible or fixed perfusion defects.

Results. In hypertensive patients, myocardial perfusion abnormalities were detected in 79 of 102 patients with significant coronary artery disease and in nine of 35 patients without. In normotensive patients, myocardial perfusion abnormalities were detected in 104 of 138 patients with significant coronary artery disease and in 16 of 57 patients without. There were no differences between normotensive and hypertensive patients in sensitivity [77% (95% confidence interval (CI) 69% - 86%) vs. 75% (95% CI 68% - 83%)], specificity [74% (95% CI 60% - 89%) vs. 72% (95% CI 60% - 84%)], and accuracy [77% (95% CI 70%-84%) vs. 74% (95% CI 68% - 80%)] of exercise SPECT for diagnosing coronary artery disease. The accuracy of SPECT was greater than electrocardiography, both in hypertensive patients (P = 0.005) and in normotensive patients (P = 0.0001). For the detection of coronary artery disease in individual vessels, sensitivity was 58% (95% CI 51% - 65%) vs. 57% (95% CI 51% - 64%), specificity was 86% (95% CI 82% - 90%) vs. 85% (95% CI 81% - 89%), and accuracy was 74% (95% CI 70% - 78%) vs. 74% (95% CI 70% - 78%) in patients with and without hypertension (NS).

Conclusion. In the usual clinical setting, the value of exercise myocardial perfusion scintigraphy for diagnosing coronary artery disease is not degraded by the presence of hypertension.

INTRODUCTION

Evaluation of the accuracy of current techniques employed in non-invasive diagnosis is essential for the proper management and risk stratification of patients with suspected coronary artery disease. Exercise myocardial perfusion scintigraphy is widely used for this purpose.[1-3] Hypertension is one of the most common risk factors for coronary artery disease encountered in patients undergoing exercise stress testing.[4] Although exercise myocardial perfusion scintigraphy has been shown to be more accurate than exercise electrocardiography for the diagnosis of coronary artery disease,[5] myocardial perfusion abnormalities may occur in hypertensive patients without significant epicardial coronary artery disease.[6-8] Such abnormalities may not necessarily represent a false positive diagnosis of myocardial ischaemia as they may represent the sequelae of microvascular disease, impaired vasodilator reserve, and increased myocardial oxygen demand in a certain subset of hypertensive patients.[6-11] However, the findings may result in unnecessary cardiac catheterisation in the absence of significant stenosis of the epicardial coronary arteries.

Although the occurrence of myocardial perfusion abnormalities in hypertensive patients without epicardial coronary artery disease is well documented, the impact of this observation on the specificity and value of exercise stress myocardial perfusion scintigraphy for diagnosing coronary artery disease in a routine clinical setting is far from clear, and it is not known whether myocardial perfusion scintigraphy suffers particular limitations in hypertensive patients. Such information is important for physicians in deciding whether to refer hypertensive patients for this type of imaging. The aim of our study was to compare the diagnostic accuracy of exercise stress single photon emission computed tomography (SPECT) with 99m-technetium-labelled agents for the diagnosis of coronary artery disease in patients with and without hypertension.

METHODS

Patient selection

The study population consisted of 332 patients without previous myocardial infarction referred for the diagnosis of coronary artery disease by exercise stress SPECT imaging in our laboratory, who underwent

coronary angiography within three months of the exercise stress test. Exclusion criteria were a history or electrocardiographic diagnosis of previous myocardial infarction, heart failure, unstable angina, severe valvular heart disease, and left-bundle branch block. Of these patients, 137 (42%) had systemic arterial hypertension, defined as repeated blood pressure measurements exceeding 140/90 mm Hg on different occasions, or being on antihypertensive drug treatment for a known diagnosis of hypertension. The diagnosis was confirmed by medical reports from the referring physicians. The mean duration of hypertension ± SD was 7.9 ± 5.7 years. Left ventricular hypertrophy by electrocardiographic criteria was detected in 20 patients. The mean age of the entire patient population was 57 ± 10 years. There were 257 men and 75 women.

Exercise stress test

All patients underwent a symptom limited upright bicycle ergometry test with stepwise increments of 20 W each minute. Blood pressure was measured every two minutes by the cuff method. Three electrocardiographic leads were monitored continuously. A 12 lead electrocardiography was recorded at rest and every minute until the end of the recovery phase. The level of the ST segment was calculated by averaging the signals using a computerised system (Cardiovet, CSG/12, Schiller, Baar, Switzerland). An ischaemic response was defined as 0.1 mV horizontal or downsloping ST-segment depression or 0.1 mV ST-segment elevation compared with baseline, measured 80 ms from the J point.

SPECT imaging

Approximately one minute before termination of the exercise stress test, an intravenous dose of 370 MBq of 99m-technetium-methoxyisobutyl isonitrile sestamibi (233 patients) or tetrofosmin (99 patients) was given. Stress images were acquired one hour after termination of the test. For resting studies, 370 MBq of the same isotope was injected 24 hours after the stress study. For each study six oblique (short axis) slices from the apex to the base and three sagittal (vertical long axis) slices from the septum to the lateral wall were defined. Each of the six short axis slices was divided into eight equal segments. The interpretation of the scan was performed semiquantitatively by visual analysis assisted by circumferential profile analysis. Myocardial perfusion was assessed by measuring the area between the lower limit of normal

values (± 2 SD) and the actual circumferential profile of the patient on rest and stress images. Stress and rest tomographic views were reviewed side by side by an experienced observer who was unaware of the patients' clinical, exercise stress, or angiographic data. A reversible perfusion defect was defined as a perfusion defect on stress images that partially or completely resolved at rest in two or more contiguous segments or slices. A fixed perfusion defect was defined as a perfusion defect on stress images in two or more contiguous segments or slices which persisted on rest images. There was no significant difference between patients with and without hypertension with respect to the proportion of patients who received tetrofosmin (33% vs. 28%) or sestamibi (67% vs. 72%).

Coronary angiography

Coronary angiography was performed within three months of the exercise stress test. Lesions were quantified as previously described.[12] Significant coronary artery disease was defined as a diameter stenosis of ≥ 50% in one or more major epicardial arteries. The anterior, apical, septal, and anteroseptal walls were assigned to the left anterior descending coronary artery. The posterior and lateral walls were assigned to the left circumflex coronary artery. The inferior and basal septal segments were assigned to the right coronary artery. The apical lateral segment was considered to be an overlap segment between the left anterior descending and the left circumflex arteries. The apical inferior segment was considered to be an overlap segment between the left anterior descending and the right coronary arteries. Overlapping segments were assigned to the regions with concomitant abnormalities.

Echocardiographyc assessment of left ventricular hypertrophy

Echocardiography was performed in 117 hypertensive patients (85%) within three months of the exercise stress test. Left ventricular mass was calculated using Troy's method, and measurements were made in accordance with the American Society of Echocardiography criteria[13] as follows: left ventricular mass (g) = 1.04 [(IVS + LVID + PWT)^3 (LVID)^3], where IVS = interventricular septal thickness (cm), LVID = left ventricular internal dimension (cm), and PWT = left ventricular posterior wall thickens (cm). The result was then corrected by the following equation[14] to correlate with necropsy mass: left ventricular mass (g) = 0.8 (LV mass) + 0.6. Left ventricular mass was indexed

by body surface area using normal limits from the Framingham heart study.[15] Left ventricular hypertrophy was defined as a left ventricular mass index of > 131 g/m^2 for men and > 100 g/m^2 for women.

Statistical analysis

Unless specified, data are presented as mean ± SD. The chi-square test was used to compare differences between proportions. Student's *t* test was used for analysis of continuous data. Probability values of $P < 0.05$ were considered significant.

RESULTS

Table 1 summarises the clinical features of patients with and without hypertension. There was no significant difference between the two groups for age, sex, symptoms, prevalence of hypercholesterolemia and cigarette

Table 1

Clinical features of patients with and without hypertension.

Clinical features	Hypertension		P value
	Yes (n=137)	No (n=195)	
Age (yrs.) (mean ± SD)	56 ± 9	57 ± 10	0.4
Men	101 (74%)	156 (80%)	0.2
Reasons for referral			
Typical angina	58 (42%)	72 (37%)	0.3
Atypical angina	44 (32%)	59 (30%)	0.7
Non-anginal chest pain	35 (26%)	64 (33%)	0.2
Diabetes mellitus	19 (14%)	12 (6%)	0.02
Hypercholesterolemia	30 (22%)	53 (27%)	0.3
Cigarette smoking	27 (20%)	55 (28%)	0.07
Drug treatment			
Beta-blockers	69 (50%)	92 (47%)	0.6
Calcium channel blockers	99 (72%)	39 (20%)	0.0001
Nitrates	37 (27%)	49 (25%)	0.7
ACE inhibitors	29 (21%)	3 (2%)	0.0001
Diuretics	22 (16%)	0 (%)	0.0001

Values are n (%) unless specified.

ACE, angiotensin converting enzyme.

smoking, and treatment with beta-blockers and nitrates. Hypertensive patients had a higher prevalence of diabetes mellitus and were more often on treatment with calcium channel blockers, diuretics, and angiotensin converting enzyme inhibitors than non-hypertensive patients.

Symptoms and haemodynamic response

Table 2 summarises the symptoms and the haemodynamic and electrocardiographic responses in patients with and without hypertension. Resting heart rate, systolic and diastolic blood pressure, and rate-pressure product were significantly higher in patients with hypertension. Hypertensive patients achieved a higher peak systolic and diastolic blood pressure, although the increment in systolic blood pressure was more significant in patients without hypertension ($P < 0.005$). Peak heart rate, rate-pressure product, and the proportion of patients who achieved the target heart rate or had exercise-induced angina, were not significantly different between the two groups.

Table 2

Haemodynamic data of patients with and without hypertension.

	Hypertension		
Haemodynamic and stress test variables	Yes (n=137)	No (n=195)	P value
Heart rate at rest (beats/min)	81 ± 22	74 ± 19	0.002
Heart rate at peak stress (beats/min)	137 ± 23	138 ± 23	0.8
Systolic blood pressure at rest (mm Hg)	147 ± 20	130 ± 19	0.0001
Systolic blood pressure at peak stress (mm Hg)	188 ± 26	180 ± 24	0.02
Diastolic blood pressure at rest (mm Hg)	91 ± 13	81 ± 10	0.0001
Diastolic blood pressure at peak stress (mm Hg)	92 ± 16	88 ± 12	0.0001
Rate-pressure product at rest	11975 ± 3280	9807 ± 2910	0.0001
Rate-pressure product at peak stress	25763 ± 6237	24850 ± 6322	0.4
85% of maximum heart rate achieved [n (%)]	84 (61%)	113 (58%)	0.5
Mean working capacity (W)	139 ± 40	143 ± 39	0.1
ST segment depression during the test [n (%)]	76 (55%)	91 (47%)	0.09
Angina during the test [n (%)]	37 (27%)	49 (25%)	0.7

Values are mean ± SD unless specified.

Table 3
Coronary angiographic data of patients with and without hypertension.

Coronary angiographic variables	Hypertension		P value
	Yes (n=137)	No (n=195)	
Significant coronary artery disease	102 (74%)	138 (71%)	0.5
Single-vessel coronary artery disease	54 (39%)	76 (39%)	0.9
Two-vessel coronary artery disease	22 (16%)	31 (16%)	0.9
Three-vessel coronary artery disease	26 (19%)	31 (16%)	0.5
Normal coronary arteries or < 50% lesion	35 (26%)	57 (29%)	0.5
70% stenosis in one coronary artery	66 (48%)	87 (45%)	0.5
LAD stenosis	65 (47%)	93 (48%)	0.9
LCx stenosis	51 (37%)	62 (32%)	0.3
RCA stenosis	60 (44%)	76 (39%)	0.4

LAD, left anterior descending coronary artery; LCx, left circumflex coronary artery; RCA, right coronary artery.

Angiographic findings

Significant coronary artery disease was detected in 240 patients (72%). Data on its extent and location in patients with and without hypertension are given in table 3. There was no significant difference in prevalence or distribution between the groups. No cardiac events or worsening of symptoms occurred in the interval between the exercise stress test and coronary angiography.

Accuracy of exercise SPECT for the diagnosis and localisation of coronary artery disease

Patients with hypertension

Myocardial perfusion abnormalities (reversible or fixed perfusion defects) were detected in 79 of 102 patients with significant coronary artery disease and in nine of 35 patients without coronary disease [sensitivity 77%, (95% confidence interval (CI) 69% - 86%]; specificity 74% (95% CI 60% - 89%); accuracy 77% (95% CI 70% - 84%) (table 4). In patients with single vessel disease, sensitivity was 72% (39/54), with two vessel disease it was 82% (18/22), and with three vessel disease it was 85% (22/26). Myocardial perfusion abnormalities in two vascular

Table 4

Accuracy of exercise stress SPECT for the diagnosis of significant coronary artery stenosis in patients with and without hypertension.

	Hypertension (n=137)	Numbers	No hypertension (n=195)	Numbers
Overall diagnosis of coronary artery disease				
Sensitivity	77 (69 - 86)	79/102	75 (68 - 83)	104/138
Specificity	74 (60 - 89)	26/35	72 (60 - 84)	41/57
Accuracy	77 (70 - 84)	105/137	74 (68 - 80)	145/195
LAD stenosis				
Sensitivity	63 (51 - 75)	41/65	62 (53 - 72)	58/93
Specificity	88 (80 - 95)	63/72	84 (77 - 91)	86/102
Accuracy	76 (69 - 83)	104/137	74 (68 - 80)	144/195
LCx stenosis				
Sensitivity	59 (45 - 72)	30/51	53 (41 - 66)	33/62
Specificity	83 (75 - 91)	71/86	86 (80 - 92)	114/133
Accuracy	74 (66 - 81)	101/137	75 (69 - 81)	147/195
RCA stenosis				
Sensitivity	52 (39 - 64)	31/60	54 (43 - 65)	41/76
Specificity	88 (81 - 95)	68/77	85 (78 - 91)	101/119
Accuracy	72 (65 - 80)	99/137	73 (67 - 79)	142/195
All arteries				
Sensitivity	58 (51 - 65)	102/176	57 (51 - 64)	132/231
Specificity	86 (82 - 90)	202/235	85 (81 - 89)	301/354
Accuracy	74 (70 - 78)	304/411	74 (70 - 78)	433/585

Values are percentages (95% CI).

regions, suggestive of multivessel coronary artery disease, were detected in 25 of 48 patients with multivessel disease and in six of 89 patients without multivessel disease (sensitivity for detecting coronary stenosis in more than one vascular region 52% (95% CI 38% - 66%); specificity 93% (95% CI 88% - 98%); accuracy 79% (95% CI 72% - 86%). In hypertensive patients without significant coronary artery disease, there was no difference between patients with and without perfusion abnormalities with regard to resting systolic blood pressure: 144 ± 21 vs. 146 ± 19 mm Hg (NS).

Patients without hypertension

Myocardial perfusion abnormalities were detected in 104 of 138 patients with significant coronary artery disease and in 16 of 57 patients without coronary disease (sensitivity 75% (95% CI 68% - 83%); specificity 72% (95% CI 60% - 84%); accuracy 74% (95% CI 68% - 80%). In patients with single vessel disease, sensitivity was 67% (51/76), with two-vessel disease it was 81% (25/31), and with three-vessel disease it was 90% (28/31). Myocardial perfusion abnormalities in two vascular regions, suggestive of multivessel coronary artery disease, were detected in 32 of 62 patients with multivessel disease and in 13 of 133 patients without multivessel disease (sensitivity for detecting coronary stenosis in more than one vascular region 52% (95% CI 39% - 64%); specificity 90% (95% CI 85% - 95%); accuracy 78% (95% CI 72% - 84%).

Comparison of patients with and without hypertension

There was no significant difference between patients with and without hypertension with respect to sensitivity, specificity, and accuracy for the overall and regional diagnosis of coronary artery disease (table 4). Diagnostic accuracy did not differ among different vascular regions (figure 1). The accuracy of the diagnosis of multivessel coronary artery disease on the basis of perfusion abnormalities in more than one vascular region was not significantly different between the groups. In patients

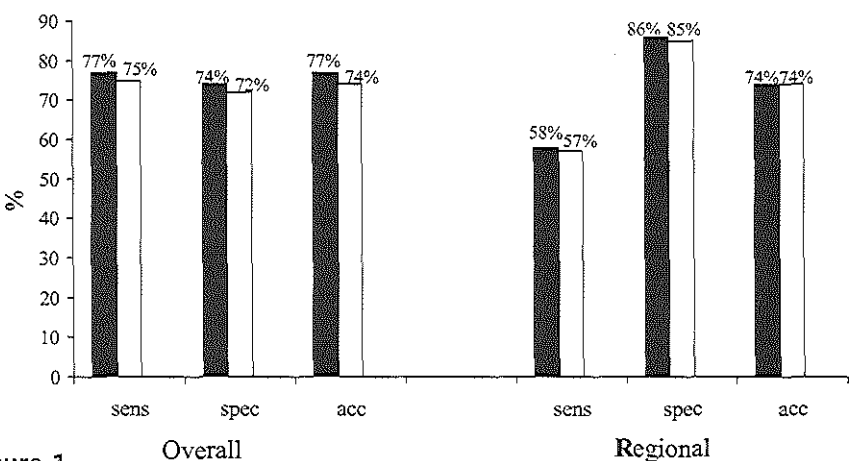


Figure 1

Sensitivity (Sens), specificity (Spec), and accuracy (Acc) of exercise stress SPECT for the overall and regional diagnosis of coronary artery disease in patients with hypertension (filled bars) and without hypertension (empty bars).

with a low to intermediate pre-test probability of coronary artery disease, there was no significant difference between those with hypertension (75 patients) and those without hypertension (111 patients) in the sensitivity [74% (35/47) vs. 72% (49/68)] or specificity [75% (21/28) vs. 72% (31/43)] of SPECT imaging for diagnosing coronary artery disease. Similarly, in patients with a high pre-test probability of coronary artery disease, there was no significant difference between those with hypertension (62 patients) and those without hypertension (84 patients) in the sensitivity [80% (44/55) vs. 79% (55/70)] or specificity [71% (5/7) vs. 71% (10/14)] of SPECT imaging.

Patients with false negative studies

In patients with coronary artery disease, those with false negative results (57 patients) had a higher prevalence of single vessel coronary artery disease (70% vs. 49%, $P < 0.01$) and a lower peak heart rate (123 $\pm$ 28 vs. 132 $\pm$ 24, $P < 0.05$) than the 183 patients with a true positive test (abnormal perfusion).

Impact of left ventricular hypertrophy

Echocardiographic criteria of left ventricular hypertrophy were fulfilled in 57 of the 117 hypertensive patients (49%) who underwent echocardiographic imaging. Significant coronary artery disease was detected in 41 of the 57 patients with left ventricular hypertrophy and in 43 of the 60 patients without. In patients with left ventricular hypertrophy, myocardial perfusion abnormalities were detected in 31 of the 41 patients with coronary artery disease and in four of the 16 patients without coronary disease. In patients without left ventricular hypertrophy, myocardial perfusion abnormalities were detected in 31 of the 43 patients with coronary disease and in four of the 17 patients without coronary disease. No significant difference was found between patients with and without left ventricular hypertrophy in the sensitivity [76% (95% CI 62% - 89%) vs. 72% (95% CI 59% - 85%)], specificity [75% (95% CI 54% - 96%) vs. 76% (95% CI 62% - 77%)], and accuracy [75% (95% CI 64% - 87%) vs. 73% (95% CI 62% - 85%)] of exercise SPECT for diagnosing coronary artery disease (NS for all).

Comparison of myocardial perfusion scintigraphy and electrocardiography

In hypertensive patients, ischaemic electrocardiographic changes were detected in 59 of 102 patients with significant coronary artery disease and in 17 of 35 patients without coronary disease [sensitivity 58% (95% CI 48% - 67%)], P = 0.03 vs. SPECT; specificity 51% (95% CI 35% - 68%), P = 0.04 vs. SPECT; accuracy 56% (95% CI 48% - 65%), P = 0.0005 vs. SPECT). In patients without hypertension, ischaemic electrocardiographic changes occurred in 73 of 138 patients with significant coronary artery disease and in 18 of 57 patients without coronary disease [(sensitivity 53% (95% CI 45% - 61%), P = 0.0001 vs. SPECT; specificity 68% (95% CI 56% - 80%); accuracy 57% (95% CI 50% - 64%), P = 0.0001 vs. SPECT)]. There was a trend towards a higher specificity of electrocardiographic changes in normotensive than in hypertensive patients, but the difference did not reach statistical significance (68% vs. 51%, P = 0.1).

Discussion

Coronary artery disease is a major cause of morbidity and mortality in patients with systemic arterial hypertension.[4] The accuracy of non-invasive methods employed in diagnosis and functional evaluation has a strong impact on the management and risk stratification of patients with known or suspected coronary artery disease.[16] Exercise electrocardiography is widely used in making a diagnosis of coronary artery disease, but the relatively low specificity of the electrocardiographic changes in patients with hypertension limits its value under those circumstances.[16] Exercise myocardial perfusion scintigraphy has been shown to provide a higher degree of diagnostic accuracy than electrocardiography in hypertensive patients.[17] However, myocardial perfusion abnormalities are reported to occur in hypertensive patients without significant epicardial coronary arterial stenosis.[6-8] Although myocardial perfusion abnormalities are well documented in hypertensive patients without significant coronary artery disease, previous studies have involved highly selected populations. It is not known whether myocardial perfusion scintigraphy suffers from any particular limitation for the diagnosis of coronary artery disease in hypertensive patients in a routine clinical setting.

Present study

To our knowledge, this is the first study evaluating the impact of systemic arterial hypertension on the accuracy of exercise stress myocardial perfusion imaging with 99m-technetium-labelled agents for diagnosing and localising coronary artery disease. We found that exercise SPECT imaging provided a relatively high sensitivity and specificity for the overall diagnosis of coronary artery disease. The diagnosis of disease in individual coronary artery territories was accomplished with moderate sensitivity and high specificity, and did not differ among the three vascular regions. This confirms the value of SPECT imaging in the correct diagnosis of regional myocardial perfusion abnormalities.

There was no significant difference between patients with and without hypertension in the sensitivity, specificity, or accuracy of exercise SPECT for overall and regional diagnosis of coronary artery disease. Similarly, the accuracy of diagnosing multivessel coronary artery disease on the basis of perfusion abnormalities in more than one vascular region was not significantly different between the two groups. SPECT imaging provided a higher sensitivity and accuracy than electrocardiography irrespective of whether there was hypertension. In hypertensive patients, the specificity of SPECT was higher than that of electrocardiography. Among hypertensive patients, the presence of left ventricular hypertrophy did not affect the sensitivity or specificity of the diagnosis of coronary artery disease.

These data show that in hypertensive patients without previous myocardial infarction referred for the diagnosis of coronary artery disease, exercise SPECT myocardial perfusion imaging is a useful method for the overall and regional diagnosis of coronary artery disease, with comparable sensitivity and specificity to those achieved in normotensive patients. The similar specificity in the three vascular regions indicates that false positive results do not tend to involve a particular myocardial segment. Patients with coronary artery disease but normal perfusion were more likely to have single vessel disease and they had a lower exercise heart rate compared with patients who had perfusion abnormalities.

Seventeen of the 110 patients (15%) with multivessel coronary artery disease had no perfusion abnormalities. This may be a reflection of the lower exercise heart rate achieved or of the effect of drugs on the induction of ischaemia. Alternatively, flow heterogeneity may not have been evident because of a diffuse pattern of hypoperfusion. Perhaps a

gated study might have detected functional abnormalities in patients with a diffuse pattern of hypoperfusion.

Comparison with previous studies

Abnormalities of myocardial perfusion have been reported in hypertensive patients with or without left ventricular hypertrophy in the absence of significant epicardial coronary artery disease.[6-8] The occurrence of myocardial ischaemia in these patients has been attributed to microvascular coronary artery disease, impaired vasodilator reserve, increased myocardial oxygen demand because of left ventricular hypertrophy, increased afterload, and diastolic dysfunction.[10] DePuey and colleagues reported that fixed perfusion defects in the lateral wall often occur in hypertensive patients with left ventricular hypertrophy accompanying end stage renal disease.[8] In contrast, Cecil and colleagues found no thallium perfusion abnormalities in 16 hypertensive patients with left ventricular hypertrophy but without renal disease.[18] Schulman and associates compared the results of exercise thallium scintigraphy in patients with and without hypertension.[19] They concluded that hypertension affects the results of 201-thallium exercise stress testing in patients with low but not with medium to high likelihood of coronary artery disease. In contrast, Grogan and colleagues reported that in patients with a low likelihood of coronary artery disease, the prevalence and extent of exercise thallium perfusion abnormalities were similar in normotensive and hypertensive patients.[20]

These previous studies compared the prevalence of myocardial perfusion abnormalities in patients with and without hypertension, and no correlations with coronary angiography were reported. Chin and colleagues studied 30 asymptomatic hypertensive patients who had a positive exercise electrocardiography or 201-thallium scintigram and underwent coronary angiography.[21] These investigators concluded that 201-thallium scintigraphy can accurately diagnose coronary artery disease in most of the patients with asymptomatic essential hypertension, and that most asymptomatic hypertensive patients with physiological evidence of myocardial ischaemia have associated coronary artery disease. Fragasso and associates reported that in 101 patients with hypertension, chest pain, and a positive exercise electrocardiography, stress sestamibi imaging had a lower specificity than dobutamine or dipyridamole echocardiography for diagnosing coronary artery disease.[22] However, the population in

that study was highly selected as it included only patients with a positive exercise electrocardiography; these represent only a proportion of hypertensive patients with suspected coronary artery disease.

Zouridakis and colleagues studied normotensive patients and hypertensive patients with angina, a positive exercise electrocardiographic, and normal coronary arteries.[23] Dobutamine stress echocardiography was normal in all patients, whereas eight normotensive patients and 10 hypertensive patients had perfusion abnormalities. In contrast to their findings, we have previously reported that dobutamine stress echocardiography and simultaneous sestamibi SPECT had similar accuracy in diagnosing coronary artery disease in 84 hypertensive patients unable to perform an exercise stress test.[24] The prevalence of myocardial perfusion abnormalities in patients with and without hypertension undergoing dobutamine stress myocardial perfusion imaging was found to be similar, regardless of the pre-test probability of coronary artery disease.[25]

Our finding that the specificity of myocardial perfusion imaging was not reduced in patients with hypertension can be explained in various ways. Although myocardial perfusion abnormalities have been reported in hypertensive patients without significant epicardial coronary artery disease, the exact prevalence of these findings in hypertensive patients with suspected coronary artery disease is not known, as previous studies evaluated a highly selected population. It is possible that the prevalence of these abnormalities is not high enough to account for a difference in the specificity of myocardial perfusion imaging between patients with and without hypertension. On the other hand, perfusion abnormalities resulting from microvascular ischaemia have also been reported in patients without hypertension.[26] Increased awareness of the cardiovascular complications of hypertension and advances in medical treatment, including the introduction of safe and effective antihypertensive drugs,[4] are expected to attenuate the pathophysiological effects of hypertension on the myocardium, thereby reducing the severity of structural changes occurring in the absence of epicardial coronary artery disease.[27] Finally, the impairment of coronary flow reserve in hypertensive patients without obstructive coronary artery disease is a diffuse process. Therefore, mild diffuse attenuation of perfusion may result in apparently normal perfusion in patients without large vessel coronary artery disease. It is also possible that in most

hypertensive patients without significant coronary artery disease the reduction in coronary flow reserve is not severe enough to account for a significant impairment of the radioactive isotope uptake during exercise, as maximum tracer uptake can occur at a submaximal level of coronary vasodilatation.

Previous studies of exercise SPECT

The reported sensitivity of exercise sestamibi SPECT in previous studies ranges between 82% and 93%. Specificity ranges between 36% and 71%.[27-31] Most of these studies were performed in a heterogeneous population with or without previous myocardial infarction. Among the studies which recruited more than 100 patients, Van Train and colleagues reported a sensitivity of 90% and specificity of 36% in 124 patients (19% had a previous myocardial infarct) who underwent exercise sestamibi SPECT and coronary angiography.29 Solot and associates reported a sensitivity of 97% and specificity of 71% for exercise sestamibi SPECT in 128 patients.[31] Previous studies of exercise tetrofosmin imaging reported a sensitivity ranging between 58% and 95% and a specificity ranging between 54% and 95% for the diagnosis of coronary artery disease.[32-34]

Limitations

The effect of drug treatments on the results of our study should be taken into account. The administration of antihypertensive drugs may attenuate the pathophysiological mechanisms involved in the genesis of myocardial ischaemia in the absence of coronary artery disease.[27] However, in clinical practice, patients with hypertension usually receive the appropriate treatment for hypertension before being evaluated for coronary artery disease, and therefore the study patients represent the hypertensive population with suspected coronary artery disease encountered in clinical practice. In such patients, non-invasive evaluation of coronary artery disease is warranted. Another aspect of drug treatment is the possible attenuation of myocardial ischaemia, with subsequent reduction in the sensitivity of exercise SPECT for diagnosing coronary artery disease. However, an underestimation of the true sensitivity of the test in our study does not detract from our conclusion about the clinical value of exercise myocardial perfusion scintigraphy for diagnosing coronary artery disease in hypertensive patients.

Although we used two different tracers in the study, previous studies

have shown comparable performance of sestamibi and tetrofosmin in diagnosing coronary artery disease.[35 36]

Referral bias for coronary angiography may have influenced our results. However, this does not affect the main conclusion of the study, as selective referral of patients with a positive scan for coronary angiography is expected to reduce specificity, and the study already showed a similar and acceptable specificity in patients with and without hypertension.

Finally, there are limitations in the use of coronary angiography as a gold standard for the presence of functionally significant coronary artery disease, as it shows only a silhouette of the arterial lumen. Thus, we cannot exclude the possibility that some of the perfusion abnormalities in patients without angiographically significant coronary artery disease represent true ischaemia. A study of coronary flow reserve in these patients could perhaps have provided more insight into the significance of such abnormalities.

Conclusions

Exercise SPECT myocardial perfusion imaging using 99m-technetium-labelled agents is an accurate method for diagnosing and localising coronary artery disease in hypertensive patients. The diagnostic accuracy of exercise SPECT in hypertensive patients is comparable with that in normotensive patients. These data indicate that in the usual clinical setting, the accuracy of exercise myocardial perfusion scintigraphy is not reduced in hypertensive patients.

REFERENCES

1. Gibbons RJ, Balady GJ, Beasley JW, Bricker JT, Duvernoy WF, Froelicher VF, Mark DB, Marwick TH, McCallister BD, Thompson PD Jr, Winters WL, Yanowitz FG, Ritchie JL, Cheitlin MD, Eagle KA, Gardner TJ, Garson A Jr, Lewis RP, O'Rourke RA, Ryan TJ. ACC/AHA guidelines for exercise testing. A report of the American College of Cardiology/American Heart Association task force on practice guidelines (committee on exercise testing). *J Am Coll Cardiol 1997;30:260-311.*
2. Maddahi J, Kiat H, Van Train KF, Prigent F, Friedman J, Garcia EV, Alazraki N, DePuey EG, Nichols K, Berman DS. Myocardial perfusion imaging with technetium-99m sestamibi SPECT in the evaluation of coronary artery disease. *Am J Cardiol 1990;66:55E-62E.*
3. Berman DS, Kiat H, Van Train K, Garcia E, Friedman J, Maddahi J. Technetium 99m sestamibi in the assessment of chronic coronary artery disease. *Semin Nucl Med 1991;21:190-212.*
4. Joint National Committee. The sixth report of the Joint National Committee on prevention, detection, evaluation, and treatment of high blood pressure. *Arch Intern Med 1997;157:2413-2446.*
5. Pringle SD, Dunn FG, Lorimer AR, McKillop JH. The role of nuclear cardiology in hypertension. *Nucl Med Commun 1994;15:4-8.*
6. Houghton JL, Frank MJ, Carr AA, von Dohlen TV, Prisant LW. Relations among impaired coronary flow reserve, left ventricular hypertrophy and thallium perfusion defects in hypertensive patients without obstructive coronary artery disease. *J Am Coll Cardiol 1990;15:43-51.*
7. Aguirre JM, Rodriguez E, Ruiz de Azua E, Urrengoetxea J, Faus JM, Caso R, Iriarte M. Segmentary coronary reserve in hypertensive patients with echocardiographic left ventricular hypertrophy, gammagraphic ischemia and normal coronary angiography. *Eur Heart J 1993;14(suppl J):25-31.*
8. DePuey EG, Guertler-Krawczynska E, Perkins JV, Robbins WL, Whelchel JD, Clements SD. Alteration in myocardial thallium-201 distribution in patients with chronic systemic hypertension undergoing single-photon emission computed tomography. *Am J Cardiol 1988;62:234-238.*
9. Frohlich ED, Apstein C, Chobanian AV, Devereux RB, Dustan HP, Dzau V, Fauad-Tarazi F, Horan MJ, Marcus M, Massie B. The heart in hypertension. *N Engl J Med 1992;327:998-1008.*
10. Harrison DG, Marcus ML, Dellsperger KC, Lamping KG, Tomanek RJ. Pathophysiology of myocardial perfusion in hypertension. *Circulation 1991;83(suppl 5):III14-III18.*

11. Hamouda MS, Kassem HK, Salama M, El Masry M, Shaaban N, Sadek E, Khandheria BK, Seward JB, Elhendy A. Evaluation of coronary flow reserve in hypertensive patients by dipyridamole transesophageal Doppler echocardiography. *Am J Cardiol 2000;86:305-308.*
12. Baptista J, Arnese M, Roelandt JR, Fioretti P, Keane D, Escaned J, Boersma E, di Mario C, Serruys PW Quantitative coronary angiography in the estimation of the functional significance of coronary stenosis: Correlation with dobutamine-atropine stress test. *J Am Coll Cardiol 1994;23:1434-1439.*
13. Troy BL, Pombo J, Rackley CE. Measurement of left ventricular thickness and mass by echocardiography. *Circulation 1972;45:602-611.*
14. Devereux RB, Alonso DR, Lutas EM, Gottlieb GJ, Campo E, Sachs I, Reichek N. Echocardiographic assessment of left ventricular hypertrophy: comparison to necropsy findings. *Am J Cardiol 1986;57:450-458.*
15. Levy D, Savage DD, Garrison RJ, Anderson KM, Kannel WB, Castelli WP. Echocardiographic criteria of left ventricular hypertrophy: the Framingham Heart Study. *Am J Cardiol 1987;59:956-960.*
16. Tarazi RC, Fouad FM. Assessment of cardiac status in hypertensive patients. *J Hypertens 1985;3:S27-S31.*
17. Osbakken MD, Okada RD, Boucher CA, Stauss HW, Pohost GM. Comparison of exercise perfusion and ventricular function imaging: an analysis of factors affecting the diagnostic accuracy of each technique. *J Am Coll Cardiol 1984;3:272-283.*
18. Cecil MP, Pilcher WC, Eisner RL, Chu TH, Merlino JD, Patterson R. Absence of defects in SPECT thallium 201 myocardial images in patients with systemic hypertension and left ventricular hypertrophy. *Am J Cardiol 1994;74:43-64.*
19. Schulman DS, Francis CK, Black HR, Wackers FJ. Thallium 201 stress imaging in hypertensive patients. *Hypertension 1987;10:16-21.*
20. Grogan M, Christian TF, Miller TD, Bailey KR, Gibbons RJ. The effect of systemic hypertension on exercise tomographic thallium-201 imaging in the absence of electrocardiographic left ventricular hypertrophy. *Am Heart J 1993;126:327-332.*
21. Chin WL, O'Kelly B, Tubau JF, Szlachcic J, Brown D, Wisneski JA, Ammon S, Massie BM. Diagnostic accuracy of exercise thallium-201 scintigraphy in men with asymptomatic essential hypertension. *Am J Hypertens 1992;5:465-472.*
22. Fragasso G, Lu C, Dabrowski P, Pagnotta P, Sheiban I, Chierchia SL. Comparison of stress/rest myocardial perfusion tomography, dipyridamole and dobutamine stress echocardiography for the detection of coronary disease in hypertensive patients with chest pain and positive exercise test. *J Am Coll Cardiol 1999;34:441-447.*

23. Zouridakis EG, Cox ID, Garcia-Moll X, Brown S, Nihoyasnnopoulos P, Kaski JC. Negative stress echocardiographic responses in normotensive and hypertensive patients with angina pectoris, positive exercise stress testing and normal coronary arteriograms. *Heart 2000;83:141-146.*
24. Elhendy A, Geleijnse ML, van Domburg RT, Bax JJ, Nierop PR, Beerens SA, Valkema R, Krenning EP, Mohsen Ibrahim M, Roelandt JR. Comparison of dobutamine stress echocardiography and 99m-technetium sestamibi SPET for the diagnosis of coronary artery disease in hypertensive patients with and without left ventricular hypertrophy. *Eur J Nucl Med 1998;25:69-78.*
25. Elhendy A, van Domburg RT, Bax JJ, Ibrahim MM, Roelandt JRTC. Myocardial perfusion abnormalities in treated hypertensive patients without known coronary artery disease. *J Hypertens 1999;17:1601-1606.*
26. Kao CH, Wang SJ, Ting CT, Chen YT. Tc-99m sestamibi myocardial SPECT in syndrome X. *Clin Nucl Med 1996;21:280-283.*
27. Agabiti-Rosei E, Muiesan ML, Rizzoni D. Cardiovascular structural alterations in hypertension: effect of treatment. *Clin Exp Hypertens 1996;18:513-522.*
28. Santana-Boado C, Candell-Riera J, Castell-Conesa J, Aguade-Bruix S, Garcia-Burillo A, Canela T, Gonzalez JM, Cortadellas J, Ortega D, Soler-Soler J. Diagnostic accuracy of technetium-99m-MIBI myocardial SPECT in women and men. *J Nucl Med 1998;39:751-755.*
29. Van Train KF, Garcia EV, Maddahi J, Areeda J, Cooke CD, Kiat H, Silagan G, Folks R, Friedman J, Matzer L. Multicenter trial validation for quantitative analysis of same-day rest-stress technetium-99m-sestamibi myocardial tomograms. *J Nucl Med 1994;35:609-618.*
30. Rubello D, Zanco P, Candelpergher G, Borsato N, Chierichetti F, Saitta B, Minello S, Ferlin G. Usefulness of 99mTc-MIBI stress myocardial SPECT bull's-eye quantification in coronary artery disease. *Q J Nucl Med 1995;39:111-115.*
31. Solot G, Hermans J, Merlo P, Chaudron JM, Luwaert R, Cheron P, Bodart F, Beauduin M. Correlation of 99Tcm-sestamibi SPECT with coronary angiography in general hospital practice. *Nucl Med Commun 1993;14:23-29.*
32. Zaret BL, Rigo P, Wackers FJ, Hendel RC, Braat SH, Iskandrian AS, Sridhara BS, Jain D, Itti R, Serafini AN. Myocardial perfusion imaging with 99mTc tetrofosmin. Comparison to 201Tl imaging and coronary angiography in a phase III multicenter trial. Tetrofosmin international trial study group. *Circulation 1995;91:313-319.*
33. Azzarelli S, Galassi AR, Foti R, Mammana C, Musumeci S, Giuffrida G, Tamburino C. Accuracy of 99mTc-tetrofosmin myocardial tomography in the evaluation of coronary artery disease. *J Nucl Cardiol 1999;6:183-189.*

34. Montz R, Perez-Castejon MJ, Jurado JA, Martin-Comin J, Esplugues E, Salgado L, Ventosa A, Cantinho G, Sa EP, Fonseca AT, Vieira MR. Technetium-99m tetrofosmin rest/stress myocardial SPET with a same-day 2-hour protocol: comparison with coronary angiography. A Spanish-Portuguese multicentre clinical trial. *Eur J Nucl Med 1996;23:639-647.*
35. Acampa W, Cuocolo A, Sullo P, Varrone A, Nicolai E, Pace L, Petretta M, Salvatore M. Direct comparison of technetium 99m-sestamibi and technetium 99m-tetrofosmin cardiac single photon emission computed tomography in patients with coronary artery disease. *J Nucl Cardiol 1998;5:265-274.*
36. Flamen P, Bossuyt A, Franken PR. Technetium-99m-tetrofosmin in dipyridamole-stress myocardial SPECT imaging: intraindividual comparison with technetium-99m-sestamibi. *J Nucl Med 1995;36:2009-2015.*

CHAPTER 10

RELATION BETWEEN EXERCISE-INDUCED VENTRICULAR ARRHYTHMIAS AND MYOCARDIAL PERFUSION ABNORMALITIES IN PATIENTS WITH INTERMEDIATE PRE-TEST PROBABILITY OF CORONARY ARTERY DISEASE

Source: A Elhendy, FB Sozzi, RT van Domburg, JJ Bax, R Valkema, JRTC Roelandt. *Eur J Nucl Med 2000;27:327-332.* **Adapted.**

ABSTRACT

Background. The significance of exercise-induced ventricular arrhythmias is largely dependent on the clinical characteristics of the studied population. The relation between exercise-induced ventricular arrhythmias and myocardial perfusion abnormalities has not yet been evaluated in a homogenous patient population with intermediate probability of coronary artery disease.

Methods. We studied 302 patients (mean age 54 ± 9 years, 152 men and 150 women) with intermediate pre-test probability of coronary artery disease (range = 0.25 - 0.80, mean = 0.43 ± 0.20) by upright bicycle exercise stress test in conjunction with 99m-technetium SPECT imaging.

Results. Exercise-induced ventricular arrhythmias (frequent or complex premature ventricular contractions or ventricular tachycardia) occurred in 65 patients (22%). No significant difference was found between patients with and without ventricular arrhythmias regarding the pre-test probability of coronary artery disease (0.45 ± 0.21 vs. 0.43 ± 0.20). Patients with exercise-induced ventricular arrhythmias had a higher prevalence of perfusion abnormalities (52% vs. 26%, $P = 0.002$) and ischemic electrocardiographic changes (31% vs. 16%, $P < 0.05$) compared to patients without ventricular arrhythmias. The higher prevalence of perfusion abnormalities in patients with ventricular arrhythmias was observed in men (67% vs. 35%, $P < 0.01$) as well as in women (38% vs. 16%, $P < 0.05$). However, the positive predictive value of exercise-induced ventricular arrhythmias for the presence of myocardial perfusion abnormalities was higher in men than in women (67% vs. 38%, $P < 0.05$). The presence of abnormal myocardial perfusion was the only independent predictor of exercise-induced ventricular arrhythmias (HR 2.2, 95% CI 1.2 - 4.2) by multivariate analysis of clinical and stress test variables.

Conclusions. It is concluded that in patients with intermediate pre-test probability of coronary artery disease, exercise-induced ventricular arrhythmias is predictive of a higher prevalence of myocardial perfusion abnormalities both in men and in women. However, the positive predictive value of exercise-induced ventricular arrhythmias for perfusion abnormalities is higher in men. Because of the underestimation of ischemia by electrocardiographic changes, exercise-induced ventricular arrhythmias should be interpreted as a marker of a higher probability of coronary artery disease.

INTRODUCTION

The diagnosis of coronary artery disease by exercise stress testing is achieved with the highest accuracy in patients with intermediate pre-test probability of coronary artery disease.[1] The significance of exercise-induced ventricular arrhythmias is largely dependent on the clinical characteristics of the studied population.[2] In healthy asymptomatic subjects, exercise-induced ventricular arrhythmias is not related to functional abnormalities or adverse prognosis,[3,4] whereas in patients with known or high probability of coronary artery disease, there is a controversy regarding the relations among exercise-induced ventricular arrhythmias, extent of functional and anatomical abnormalities and prognostic outcome.[5-11] Few studies have evaluated the relation between exercise-induced ventricular arrhythmias and myocardial perfusion abnormalities in patients with known or suspected coronary artery disease.[12-15] However, this relation has not yet been evaluated in a homogenous group of patients with intermediate probability of coronary artery disease. The aim of this study is to find whether the occurrence of exercise-induced ventricular arrhythmias identifies patients with a higher prevalence of myocardial perfusion abnormalities among patients with intermediate pre-test probability of coronary artery disease.

METHODS

Patient selection

The study population consisted of a series of patients referred to our imaging laboratory for the diagnosis of coronary artery disease by exercise stress testing in conjunction with 99m-technetium-sestamibi or tetrofosmin myocardial perfusion SPECT imaging. Patients were included if they had an intermediate pre-test probability of coronary artery disease (between 0.25 and 0.80). The pre-test probability of coronary artery disease was determined using specific calculations based on age, sex and chest pain characteristics described by Diamond and Forrester.[16] Exclusion criteria were a history or an electrocardiographic diagnosis of previous myocardial infarction, previous revascularisation procedures, coronary artery disease detected by coronary angiography before the test, heart failure, unstable angina, valvular heart disease, cardiomyopathy, left-bundle branch block, ventricular hypertrophy, pre-excitation, abnormal cardiac

rhythm and treatment with digitalis or antiarrhythmic mediation. Patients referred for evaluation of arrhythmias were not included. Three hundred-two patients fulfilled these criteria. Mean age was 54 ± 9 years. There were 152 men and 150 women.

Exercise stress test

All patients underwent a symptom limited upright bicycle ergometry test with stepwise increment of 20 Watts each minute. Blood pressure was measured every 2 minutes by the cuff method. Three electrocardiographic leads were continuously monitored. 12 lead electrocardiography was recorded at rest and every minute during the test until the end of the recovery phase. The level of ST-segment was calculated by averaging the signals using a computerised system (Cardiovet, CSG/12, Schiller, Baar, Switzerland). An ischemic response was defined as ≥ 1 mm horizontal or downsloping ST-segment depression persisting 80 ms after the J point. Electrocardiographic signals during rest, exercise and recovery were stored and a single channel electrocardiogram of the whole study was printed after completion of the test at a paper speed of 6.25 mm/sec using a 5 mm/mV scale. Exercise-induced ventricular arrhythmias were defined as complex or frequent ventricular ectopic activity (≥ 5 premature ventricular contractions per minute, couplets, triplets, bigeminy, trigeminy), non sustained ventricular tachycardia (≥ 3 consecutive premature ventricular contractions of < 30 second duration), sustained ventricular tachycardia or ventricular fibrillation.

SPECT imaging

Approximately 1 minute before the termination of the exercise stress test, an intravenous dose of 370 MBq of 99m-technetium-sestamibi (156 patients) or tetrofosmin (146 patients) was administered. Stress images were acquired 1 hour after termination of the exercise test. For resting studies 370 MBq of the same isotope used for stress imaging was injected at least 24 hours after the stress study. Image acquisition was performed with a Siemens Gammasonics single-head Rota Camera (Orbiter; Siemens Corp., Iselin, N.J) and a low energy, all purpose collimator. Thirty two projections were obtained, from the left posterior oblique to the right anterior oblique over 180 degree, with an acquisition time of 45 seconds for each projection. A Gamma 11 computer was used to process the tomographic data. For each study six oblique (short axis) slices from

the apex to the base and three sagittal (vertical long axis) slices from the septum to the lateral wall were defined. Each of the 6 short axis slices was divided into 8 equal segments. The interpretation of the scan was semiquantitatively performed by visual analysis assisted by the circumferential profiles analysis. Stress and rest tomographic views were reviewed side by side by an experienced observer who was unaware of the patients' clinical or stress test data. A reversible perfusion defect was defined as a perfusion defect on stress images that partially or completely resolved at rest in ≥ 2 contiguous segments or slices. A fixed perfusion defect was defined as a perfusion defect on stress images in 2 or more contiguous segments or slices which persists on rest images. To assess the severity of perfusion abnormalities, 6 major myocardial segments were identified: anterior, inferoposterior, septal anterior, septal posterior, lateral and apical. Each of the 6 major left ventricular segments was scored using a 4 grade score method (0 = normal, 1 = slightly reduced, 2 = moderately reduced, 3 = severely reduced or absent uptake). Perfusion defect score was derived by the summation of the score of the 6 myocardial segments for rest and stress images.

Coronary angiography

Coronary angiography was performed within 3 months from dobutamine stress test in 42 patients. Significant coronary artery disease was defined as a diameter stenosis ≥ 50% in ≥ 1 major epicardial arteries.

Statistical analysis

Unless specified, data are presented as mean values ± standard deviation (SD). The chi-square test was used to compare differences between proportions. The Student *t* test was used for analysis of continuous data. Stepwise logistic regression models were used to identify independent predictors of ventricular arrhythmias. P value < 0.05 was considered statistically significant.

RESULTS

Clinical features and haemodynamic response

There was a significant increase of the heart rate (79 ± 16 vs. 149 ± 25 beats/minute, P < 0.0001), systolic blood pressure (139 ± 20 vs. 191 ± 26 mm Hg, P < 0.0001) and rate-pressure product (10965 ± 2720 vs. 28995

Table 1

Clinical features, symptoms and haemodynamic response of patients with and without exercise-induced ventricular arrhythmias.

Clinical features	Exercise-induced ventricular arrhythmias		
	+	-	
	(n = 65)	(n = 237)	P value
Age (yrs.)	56 ± 9	53 ± 9	0.08
Men	33 (51%)	119 (50%)	0.9
Reasons for referral			
Angina	10 (15%)	28 (12%)	0.6
Atypical chest pain	41 (63%)	173 (73%)	0.2
Non-cardiac chest pain, exertional dyspnea	14 (22%)	36 (15%)	0.3
Pre-test probability of CAD	0.45 ± 0.21	0.43 ± 0.20	0.3
Hypercholesterolemia	19 (29%)	60 (25%)	0.9
Cigarette smoking	20 (31%)	67 (28%)	0.9
Systemic hypertension	31 (48%)	90 (38%)	0.6
Diabetes mellitus	2 (3%)	19 (8%)	0.3
Medications			
Beta-blockers	21 (32%)	58 (24%)	0.3
Calcium channel blockers	17 (26%)	70 (30%)	0.7
Nitrates	9 (14%)	33 (14%)	0.9
Diuretics	10 (15%)	22 (9%)	0.2
Peak heart rate	150 ± 26	149 ± 22	0.9
Peak systolic blood pressure	196 ± 31	190 ± 26	0.1
Peak rate-pressure product	29543 ± 7260	28844 ± 9600	0.3
Maximal work load	147 ± 42	152 ± 39	0.4
Achievement of target heart rate	52 (80%)	187 (79%)	0.9
Angina during the test	8 (12%)	21 (9%)	0.6
Ischemic ECG changes	20 (31%)	38 (16%)	0.01

CAD = coronary artery disease, ECG = electrocardiographic.

± 9505, P < 0.00001) from rest to peak exercise respectively. The mean working capacity was 150 ± 48 Watts. Angina occurred in 29 (10%) patients whereas 38 (13%) patients had atypical chest pain. Dyspnea occurred in 21 (7%) patients. The target heart rate (≥ 85% of the maximal exercise heart rate predicted for age) was reached in 239 (79%) patients. Ventricular arrhythmias occurred in 65 patients during exercise. 2 patients had ventricular tachycardia (< 10 beats) whereas the remaining 63 patients had complex or frequent premature ventricular contractions. There was no incidence of sustained ventricular tachycardia or ventricular fibrillation. The test was not terminated due to arrhythmias in any patient. No difference between patients with and without ventricular arrhythmias was found regarding the proportion of patients who underwent sestamibi (49% vs. 52%) or tetrofosmin imaging (51% vs. 48%) respectively. Table 1 summarises the clinical features and haemodynamic response of patients with and those without exercise-induced ventricular arrhythmias. There was no significant difference between both groups regarding gender, prevalence of risk factors, history of angina, pre-test probability of coronary artery disease, medications, prevalence of angina during the test, peak heart rate, systolic blood pressure or rate-pressure product. Ischemic electrocardiographic changes occurred more frequently in patients with exercise-induced ventricular arrhythmias. A trend was found to an older age in patients with ventricular arrhythmias.

Myocardial perfusion abnormalities

Patients with exercise-induced ventricular arrhythmias had a higher prevalence of stress myocardial perfusion abnormalities (52% [34/65] vs. 26% [61/237], P = 0.002) and reversible abnormalities (29% [19/65] vs. 17% [40/237], P < 0.05) compared to patients without ventricular arrhythmias. The stress myocardial perfusion defect score was higher in patients with than without ventricular arrhythmias (1.73 ± 2 vs. 0.97 ± 2.1 respectively, P < 0.01).

Predictors of exercise-induced ventricular arrhythmias

Variables included in the multivariate analysis model were: age, gender, a history of angina, hypertension, cigarette smoking, medications, angina, ischemic electrocardiographic changes during stress and the presence of abnormal myocardial perfusion. The presence of abnormal myocardial perfusion was the only independent predictor of exercise-induced ventricular arrhythmias (HR 2.2, 95% CI 1.2 - 4.2).

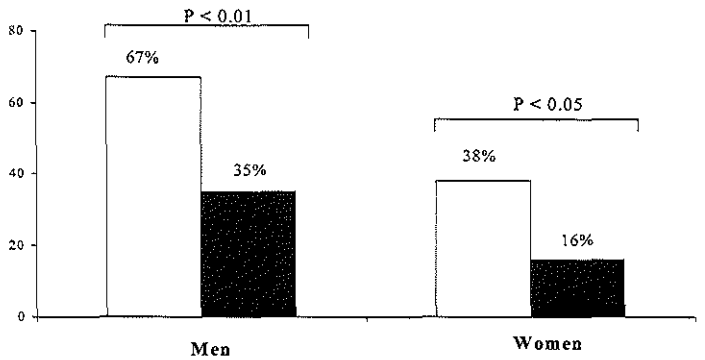


Figure 1

The prevalence of myocardial perfusion abnormalities in men and in women in presence (open bars) and in absence (closed bars) of exercise-induced ventricular arrhythmias.

Gender differences

Men had a higher prevalence of myocardial perfusion abnormalities than women (42% [64/152] vs. 21% [31/150], P < 0.0001). Exercise-induced ventricular arrhythmias was associated with a higher prevalence of myocardial perfusion abnormalities in men (67% [22/33] vs. 35% [42/119], P < 0.01) as well as in women (38% [12/32] vs. 16% [19/118], P < 0.05) (figure 1). The positive predictive value of exercise-induced ventricular arrhythmias for the presence of myocardial perfusion abnormalities was higher in men than in women (67% vs. 38%, P < 0.05).

Coronary angiography

Coronary angiography was performed in 16 patients with and in 26 patients without exercise-induced ventricular arrhythmias. Patients with exercise-induced ventricular arrhythmias had a higher prevalence of coronary artery disease (12/16 [75%] vs. 10/26 [38%], P < 0.05) and a trend to a higher prevalence of multivessel coronary artery disease (5/16 [32%] vs. 3/26 [12%], P = 0.2) compared to patients without ventricular arrhythmias respectively.

DISCUSSION

This is the first study which evaluates the relationship between exercise-induced ventricular arrhythmias and myocardial perfusion abnormalities in a homogenous population with intermediate pre-test probability of coronary artery disease. In this particular group of patients, stress testing modalities are known to have the highest accuracy for the diagnosis of coronary artery disease.[1] The study design allowed evaluation of the independent association between exercise-induced ventricular arrhythmias and perfusion abnormalities by excluding patients with clinical conditions known to be highly predictive of perfusion abnormalities as those with previous myocardial infarction, known coronary artery disease detected by angiography and revascularisation as well as conditions known to be associated with false positive perfusion studies or to predict worse prognosis on their own like ventricular hypertrophy, left-bundle branch block and paced rhythm. The study showed that exercise-induced ventricular arrhythmias is associated with a higher prevalence of abnormal myocardial perfusion. Stress myocardial perfusion defects were detected in 52% and 26% of patients with and without ventricular arrhythmias respectively ($P < 0.005$). Additionally, ischemic electrocardiographic changes were more frequent in patients with than without ventricular arrhythmias (31% vs. 16%, $P < 0.05$). Since myocardial perfusion abnormalities are highly predictive of coronary artery disease in patients with intermediate probability of coronary artery disease,[17,18] it can be assumed that exercise-induced ventricular arrhythmias is associated with a higher prevalence of coronary artery disease in this particular population. Electrocardiographic changes underestimated the prevalence of perfusion abnormalities in this study and therefore, exercise-induced ventricular arrhythmias should be interpreted as a marker of a higher probability of coronary artery disease in the absence of a sensitive imaging technique such as myocardial perfusion scintigraphy. The association between exercise-induced ventricular arrhythmias and myocardial perfusion abnormalities can be explained by the association between myocardial ischemia and arrhythmias.[19,20] The increase of sympathetic nervous system activity and the circulating catecholamines during exercise is an additional mechanism for inducing myocardial ischemia and for triggering arrhythmias in the ischemic myocardium.[2,20]

Predictors of exercise-induced ventricular arrhythmias

The occurrence of ventricular arrhythmias during exercise was not predicted by a history of angina, age, gender or major risk factors for coronary artery disease. Among the different clinical and stress test parameters included in the multivariate analysis model, the presence of abnormal myocardial perfusion was the only independent predictor of exercise-induced ventricular arrhythmias (HR 2.2, 95% CI;1.2 - 4.2).

Gender differences

Exercise-induced ventricular arrhythmias was associated with a higher prevalence of myocardial perfusion abnormalities in men as well as in women. However, the positive predictive value of exercise-induced ventricular arrhythmias for perfusion abnormalities was higher in men than in women (67% vs. 38%). This may be explained by the higher overall prevalence of perfusion abnormalities in men than in women in this study. Women constituted a larger proportion (65%) of patients with exercise-induced ventricular arrhythmias who demonstrated normal perfusion. This may be explained by a possible gender difference in the prevalence of other conditions associated with chest pain and exercise-induced arrhythmias in absence of coronary artery disease as mitral valve prolapse.[21] Another possibility is the presence of a difference in the diagnostic ability of exercise myocardial perfusion scintigraphy between men and women due to an intrinsic gender difference[22] or a variation of the severity and extent of coronary artery disease between men and women.[23] The trend to an older age in patients with exercise-induced ventricular arrhythmias in our study is consistent with previous reports.[24]

Comparison with previous studies

The significance of exercise-induced ventricular arrhythmias varies markedly among different patient groups. In asymptomatic healthy individuals, exercise-induced ventricular arrhythmias was not a predictor of adverse prognosis.[3,4] However, there is a controversy regarding the relations among exercise-induced ventricular arrhythmias, structural and functional abnormalities and prognosis in patients with known or suspected coronary artery disease. Some investigators have reported a strong association between exercise-induced ventricular arrhythmias [5,9] and increased mortality while other investigators did not find such an association.[6,8]

Few studies have evaluated the relation between exercise-induced ventricular arrhythmias and myocardial perfusion abnormalities.[12-15] Margonato et al[14] reported an association between ventricular arrhythmias and reversible defects in the infarct zone after myocardial infarction. Marieb et al[12] reported that in 383 patients with and without previous myocardial infarction, exercise-induced ventricular arrhythmias was associated with a higher prevalence of reversible 201-thallium defects and provided independent prognostic information beyond that provided by 201-thallium stress test. In contrast, Scheikert et al,[13] reported that exercise-induced ventricular arrhythmias is not associated with short term mortality or angiographic severity of coronary artery disease although it was associated with greater likelihood of thallium perfusion defects. These studies included patients with known coronary artery disease and/or previous myocardial infarction as opposed to the homogenous population of this study.

Limitations of the study

Holter monitoring was not performed and therefore we could not study the relation between spontaneous ventricular arrhythmias and perfusion abnormalities. Patients did not undergo echocardiographic evaluation to rule out the presence of structural cardiac abnormalities. Although, patients were carefully selected with clinical inclusion criteria, it is possible that echocardiography might have detected cardiac abnormalities with known association with arrhythmias that have not been clinically manifest. However, patients presenting with chest pain without a history of heart failure or known coronary artery disease are not usual candidates for echocardiographic studies particularly when they are able to perform exercise stress test as the population of our study. According to the current guidelines for the use of echocardiography, the indication for performing echocardiography in patients with intermediate probability of coronary artery disease is classified as IIb indicating that its usefulness is not well established by evidence or opinion in these patients.[25] Finally, coronary angiography was performed in only 14% of patients. Therefore, the exact prevalence of coronary artery disease in the study group was not defined. Despite that the number of patients who underwent coronary angiography was small, the higher prevalence of coronary artery disease in patients with ventricular arrhythmias was statistically significant. Additionally, exercise myocardial perfusion

scintigraphy is an established accurate method for the diagnosis of coronary artery disease particularly in patients with intermediate pre-test probability of coronary artery disease.

SUMMARY AND CONCLUSION

In patients with intermediate pre-test probability of coronary artery disease, exercise-induced ventricular arrhythmias is associated with a higher prevalence of myocardial perfusion abnormalities. This finding was observed in both men and women. However, the positive predictive value of exercise-induced ventricular arrhythmias for perfusion abnormalities is higher in men than in women. Because of the underestimation of ischemia by electrocardiographic changes, exercise-induced ventricular arrhythmias should be interpreted as a marker of a higher probability of coronary artery disease.

REFERENCES

1. Gibbons RJ, Balady GJ, Beasley JW, et al. Gibbons RJ, Balady GJ, Beasley JW, Bricker JT, Duvernoy WF, Froelicher VF, Mark DB, Marwick TH, McCallister BD, Thompson PD Jr, Winters WL, Yanowitz FG, Ritchie JL, Cheitlin MD, Eagle KA, Gardner TJ, Garson A Jr, Lewis RP, O'Rourke RA, Ryan TJ. ACC/AHA Guidelines for Exercise Testing. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Exercise Testing). *J Am Coll Cardiol 1997;30:260-311.*
2. Candinas RA, Podrid PJ. Evaluation of cardiac arrhythmias by exercise testing. *Herz 1990;15:21-27.*
3. Busby MJ, Shefrin EA, Fleg JL. Prevalence and long-term significance of exercise-induced frequent or repetitive ventricular ectopic beats in apparently healthy volunteers. *J Am Coll Cardiol 1989;14:1659-1665.*
4. Fleg JL, Lakatta EG. Prevalence and prognosis of exercise-induced nonsustained ventricular tachycardia in apparently healthy volunteers. *Am J Cardiol 1984;54:762-764.*
5. Califf RM, McKinnis RA, McNeer JF, Harrell FE Jr, Lee KL, Pryor DB, Waugh RA, Harris PJ, Rosati RA, Wagner GS. Prognostic value of ventricular arrhythmias associated with treadmill exercise testing in patients studied with cardiac catheterization for suspected ischemic heart disease. *J Am Coll Cardiol 1983;2:1060-1067.*
6. Yang JC, Wesley RC Jr, Froelicher VF. Ventricular tachycardia during routine treadmill testing. Risk and prognosis. *Arch Intern Med 1991;151:349-353.*
7. Specchia G, La Rovere MT, Falcone C, campana C, traversi E, caizzi V, de servi S. Cardiac arrhythmias during exercise-induced myocardial ischaemia in patients with coronary artery disease. *Eur Heart J 1986;7 Suppl A:45-52.*
8. Sami M, Chaitman B, Fisher L, Holmes D, Fray D, Alderman E. Significance of exercise-induced ventricular arrhythmia in stable coronary artery disease: a coronary artery surgery study project. *Am J Cardiol 1984;54:1182-1188.*
9. Henry RL, Kennedy GT, Crawford MH. Prognostic value of exercise-induced ventricular ectopic activity for mortality after acute myocardial infarction. *Am J Cardiol 1987;59:1251-1255.*
10. Saunamaki KI, Andersen JD. Post-myocardial infarction exercise testing: clinical significance of a left ventricular function index and ventricular arrhythmias. A prospective study. *Acta Med Scand 1985;218:271-278.*
11. Nair CK, Thomson W, Aronow WS, Pagano T, Ryschon K, Sketch MH. Prognostic significance of exercise-induced complex ventricular arrhythmias

in coronary artery disease with normal and abnormal left ventricular ejection fraction. *Am J Cardiol 1984;54:1136-1138.*

12. Marieb MA, Beller GA, Gibson RS, Lerman BB, Kaul S. Clinical relevance of exercise-induced ventricular arrhythmias in suspected coronary artery disease. *Am J Cardiol 1990;66:172-178.*
13. Schweikert RA, Pashkow FJ, Snader CE, Marwick TH, Lauer MS. Association of exercise-induced ventricular ectopic activity with thallium myocardial perfusion and angiographic coronary artery disease in stable, low-risk populations. *Am J Cardiol 1999;83:530-534.*
14. Margonato A, Mailhac A, Bonetti F, Vicedomini G, Fragasso G, Landoni C, Lucignani G, Rossetti C, Fazio F, Chierchia SL. Exercise-induced ischemic arrhythmias in patients with previous myocardial infarction: role of perfusion and tissue viability. *J Am Coll Cardiol 1996;27:593-598.*
15. Tsuji H, Iwasaka T, Sugiura T, Shimada T, Nakamori H, Kimura Y, Inada M. Relationship between redistribution on exercise thallium-201 scintigraphy and repetitive ventricular premature beats in patients with recent myocardial infarction. *Am Heart J 1991;121:1679-1684.*
16. Diamond G, Forrester J. Analysis of probability as an aid in the clinical diagnosis of coronary artery disease. *N Engl J Med 1979;300:1350-1358.*
17. Iskandrian AS, Heo J. Technetium-labelled myocardial imaging agents. Int J Card Imaging 1992;8:277-287.
18. Berman DS, Kiat H, Van Train K, Garcia E, Friedman J, Maddahi J. Technetium 99m sestamibi in the assessment of chronic coronary artery disease. *Semin Nucl Med 1991;21:190-212.*
19. Sung RJ, Huycke EC, Lai WT, Tseng CD, Chu H, Keung EC. Clinical and electrophysiologic mechanisms of exercise-induced ventricular tachyarrhythmias. *Pacing Clin Electrophysiol 1988;11:1347-1357.*
20. Reinke A, Michel D, Mathes P. Arrhythmogenic potential of exercise-induced myocardial ischaemia. *Eur Heart J 1987;8 Suppl G:119-124.*
21. Swartz MH, Teichholz LE, Donoso E. Mitral valve prolapse: a review of associated arrhythmias. *Am J Med 1977;62:377-389.*
22. Hansen CL, Crabbe D, Rubin S. Lower diagnostic accuracy of thallium-201 SPECT myocardial perfusion imaging in women: An effect of smaller chamber size. *J Am Coll Cardiol 1996;28:1214-1219.*
23. Cerqueira MD. Diagnostic testing strategies for coronary artery disease: special issues related to gender. *Am J Cardiol 1995;75:52D-60D.*
24. Mayuga R, Arrington CT, O'Connor FC, Fleg JL. Why do exercise-induced ventricular arrhythmias increase with age? Role of M-mode echocardiographic

aging changes. *J Gerontol A Biol Sci Med Sci 1996;51:M23-28.*

25. Cheitlin MD, Alpert JS, Armstrong WF, Aurigemma GP, Beller GA, Bierman FZ, Davidson TW, Davis JL, Douglas PS, Gillam LD. ACC/AHA Guidelines of the Clinical Application of Echocardiography. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Clinical Application of Echocardiography). Developed in collaboration with the American Society of Echocardiography. *Circulation 1997;95:1686-1744.*

CHAPTER 11

RELATION AMONG EXERCISE-INDUCED VENTRICULAR ARRHYTHMIAS, MYOCARDIAL ISCHEMIA, AND VIABILITY LATE AFTER ACUTE MYOCARDIAL INFARCTION

Source: A Elhendy, FB Sozzi, RT van Domburg, JJ Bax, ML Geleijnse, JRTC Roelandt. *Am J Cardiol 2000;86:723-729.* **Adapted.**

ABSTRACT

Objective. The aim of this study is to assess the relation between exercise-induced ventricular arrhythmias and scintigraphic markers of myocardial ischemia and viability in patients referred for exercise stress testing late after acute myocardial infarction.

Methods. We studied 171 patients (144 men, age 57 ± 10 years) with resting wall motion abnormalities by exercise stress testing in conjunction with methoxyisobutyl isonitrile (MIBI) single-photon emission computed tomography at a mean of 4.1 years after myocardial infarction. Ischemia was defined as reversible perfusion abnormalities. Myocardial viability was considered in myocardial segments with resting wall motion abnormalities in the presence of normal perfusion, a reversible defect or a fixed defect with regional MIBI uptake 50% of maximal uptake.

Results. Exercise-induced ventricular arrhythmias occurred in 46 patients (27%). Patients with ventricular arrhythmias had a higher prevalence of infarct-related artery stenosis (43 [93%] vs. 93 [74%], $P < 0.01$), peri-infarction ischemia (32 [70%] vs. 54 [43%], $P < 0.005$), and ischemia in 2 vascular regions (20 [43%] vs. 27 [22%], $P < 0.01$) than patients without ventricular arrhythmias. Reversible defects were detected in 39 of 97 dyssynergic segments (40%) in patients with ventricular arrhythmias vs. 40 of 248 dyssynergic segments (16%) in patients without ventricular arrhythmias ($P < 0.0001$). In dyssynergic segments without reversible perfusion abnormalities, the percent resting MIBI uptake was 50% in 39 of 58 segments (67%) in patients with vs. 63% in 131 of 208 segments in patients without ventricular arrhythmias (P = NS). The percentage of viable segments was 80% and 69% in patients with and without ventricular arrhythmias, respectively ($P < 0.05$).

Conclusions. It is concluded that patients with exercise-induced ventricular arrhythmias late after myocardial infarction have a higher prevalence of ischemia in the peri-infarction zone and in multivessel distribution. Myocardial ischemia in the dyssynergic myocardium appears to be a major mechanism underlying the occurrence of ventricular arrhythmias in these patients.

INTRODUCTION

Controversial reports have been published regarding the relations among exercise-induced ventricular arrhythmias, extent of functional and anatomic abnormalities, and prognostic outcome in patients with known or suspected coronary artery disease.[1-9] Some investigators have described an association with increased mortality for patients with stable coronary artery disease and exercise-induced ventricular ectopy,[1-3] whereas other investigators did not find such association.[6,7] Few studies have evaluated the relation between myocardial perfusion abnormalities and exercise-induced ventricular arrhythmias early after acute myocardial infarction.[10,11] However, this relation has not been studied in patients referred for exercise stress testing late after myocardial infarction. These patients represent a large proportion of patients referred for functional evaluation of coronary artery disease and for consideration of the need for revascularisation. Exercise single-photon emission computed tomographic (SPECT) myocardial perfusion imaging using 99m-technetium-methoxyisobutyl isonitrile (MIBI) is a clinically useful method for the diagnosis and functional evaluation of coronary artery disease.[12-14] The extent of myocardial perfusion abnormalities using this method was shown to be a powerful predictor of future cardiac events.[13,14] This study assesses the relation between exercise-induced ventricular arrhythmias and scintigraphic markers of myocardial ischemia and viability in patients referred for exercise stress testing late after acute myocardial infarction.

METHODS

Patient selection

The study population comprised 171 patients (144 men and 27 women, mean age 57 ± 10 years) referred for evaluation of coronary artery disease by exercise stress testing in conjunction with MIBI SPECT imaging. Patients were included in this study if they fulfilled these criteria: (1) previous myocardial infarction (> 6 months) as diagnosed by the standard criteria of chest pain, cardiac enzymes, and serial electrocardiographic changes in the acute phase; and (2) left ventricular wall motion abnormalities on baseline 2-dimensional echocardiography. Exclusion criteria were referral for evaluation of arrhythmias, intake of antiarrhythmic medications, the presence of left-bundle branch block, left

ventricular hypertrophy, myocardial aneurysm, significant valvular heart disease, or unstable chest pain. Mean time from the acute myocardial infarction to the day of the test was 4.1 ± 3.8 years.

Exercise stress test

All patients underwent a symptom-limited upright bicycle ergometry test with stepwise increment of 20 W each minute. Three electrocardiographic leads were continuously monitored. A 12-lead electrocardiogram was recorded at rest and every minute until the end of recovery phase. The level of the ST segment was calculated by averaging the signals using a computerised system (Cardiovet, CSG/12, Schiller, Baar, Switzerland). An ischemic response was defined as ≥ 1 mm horizontal or downsloping ST-segment depression persisting 80 ms after the J point. Electrocardiographic signals during rest, exercise, and recovery were stored, and a single-channel electrocardiogram of the study was printed after completion of the test at a paper speed of 6.25 mm/s using a 5-mm/mV scale. Exercise-induced ventricular arrhythmias was defined as complex or frequent ventricular ectopic activity (10 ventricular premature complexes per minute, couplets, triplets, bigeminy, trigeminy), nonsustained ventricular tachycardia (≥ 3 consecutive ventricular premature complexes of < 30 seconds duration), and sustained ventricular tachycardia or ventricular fibrillation that occur during exercise or during recovery.

Echocardiographic studies

Two-dimensional echocardiography was performed using a commercially available system (Hewlett-Packard phased-array Sonos 1000, Andover, Massachusetts). Images were acquired at rest from standard views. The left ventricular myocardium was divided into 6 major segments: anterior, septal anterior, septal posterior, posterolateral, inferior, and apical. Wall motion was scored in each segment using a 5-grade scale, where 0 = normal, 1 = mild hypokinesia, 2 = severe hypokinesia, 3 = akinesia, and 4 = dyskinesia.

SPECT imaging

Approximately 1 minute before termination of the exercise stress test, an intravenous dose of 370 MBq of MIBI was administered. Stress images were acquired 1 hour after termination of the exercise test. For resting studies, 370 MBq of MIBI was injected at least 24 hours after the stress

study. Image acquisition was performed with a Siemens Gammasonics single-head Rota Camera (Orbiter; Siemens Corp., Iselin, New Jersey). Thirty-two projections were obtained, from the left posterior oblique to the right anterior oblique scanning through or over 180°. For each study, 6 oblique (short-axis) slices from the apex to the base and 3 sagittal (vertical long-axis) slices from the septum to the lateral wall were defined. Each of the 6 short-axis slices was divided into 8 equal segments. The interpretation of the scan was semiquantitatively performed by visual analysis assisted by the circumferential profiles analysis. Images were reviewed side by side by an experienced observer who was unaware of the patients' clinical, electrocardiographic, or angiographic data. A reversible perfusion defect was defined as a perfusion defect on stress images that partially or completely resolved at rest in ≥ 2 contiguous segments or slices. This was considered diagnostic of ischemia. A fixed perfusion defect was defined as a perfusion defect on stress images in two contiguous segments or slices, which persists on rest images.

Segmental match of single-photon emission computed tomography and echocardiography

Echocardiographic and scintigraphic images were matched into 6 major segments: anterior, septal anterior, septal posterior, posterolateral, inferior, and apical. The location of perfusion abnormalities was defined as peri-infarction if these occurred in the distribution of the infarct-related artery, and remote if they occurred outside the distribution of the infarct-related artery. Myocardial viability in dyssynergic segments was considered present if the corresponding segment at single-photon emission computed tomography demonstrated normal perfusion, a reversible defect, or a fixed defect with regional MIBI uptake ≥ 50% of maximal uptake.[15]

Coronary angiography

Coronary angiography was performed within 3 months from the exercise stress test. Lesions were quantified as previously described.[16] Significant coronary artery disease was defined as a diameter stenosis ≥ 50% in ≥ 1 major epicardial artery. The infarct-related artery was identified by the location of Q waves on the baseline electrocardiogram. Q waves in the anterior precordial leads (V1 to 4) were assigned to the left anterior descending coronary artery. Q waves in the inferior leads (II,

III, aVF) were assigned to the right coronary artery, and Q leads in the lateral and high lateral leads (V5 to 6, I, and aVL) were assigned to the left circumflex coronary artery. In patients without Q waves, the infarct location was determined by the location of wall motion abnormalities on echocardiography. The anterior, apical, septal, and anteroseptal walls were assigned to the left anterior descending coronary artery. The posterior and lateral walls were assigned to the left circumflex artery. The inferior and basal posterior septal segments were assigned to the right coronary artery.

Statistical analysis

Unless specified, data are presented as mean values ± standard deviation (SD). The chi-square test was used to compare differences between proportions. The Student's *t* test was used for analysis of continuous data. Stepwise logistic regression models were used to identify independent predictors of ventricular arrhythmias. P value < 0.05 was considered statistically significant.

RESULTS

Clinical features and hemodynamic response

There was a significant increase in heart rate (71 ± 16 vs. 131 ± 23 beats/min, P < 0.0001), systolic blood pressure (132 ± 20 vs. 172 ± 24 mm Hg, P < 0.0001), and rate-pressure product (9441 ± 2541 vs. 22662 ± 5432, P < 0.00001) from rest to peak exercise. The mean working capacity was 143 ± 34 W. Exercise-induced ventricular arrhythmias occurred in 46 patients (27%). Three patients had nonsustained ventricular tachycardia, whereas the remaining 43 patients had complex and frequent ventricular premature beats. There was no incidence of sustained ventricular tachycardia or ventricular fibrillation. The test was terminated due to arrhythmias in 1 patient. Table 1 summarises the clinical features and hemodynamic response of patients with and without exercise-induced ventricular arrhythmias. There was no significant difference between both groups regarding prevalence of risk factors, history of angina, medications, prevalence of angina during the test, peak heart rate, systolic blood pressure, or rate-pressure product. Patients with ventricular arrhythmias were significantly older and had a higher baseline systolic blood pressure

Table 1

Clinical features, symptoms, and hemodynamic response of patients with and without exercise-induced ventricular arrhythmias.

Clinical features	Exercise-induced ventricular arrhythmias		P value
	Yes (n = 46)	No (n = 125)	
Age (yrs.)	60 ± 10	56 ± 9	0.01
Men	42 (91%)	102 (82%)	0.06
Reason for referral			
Angina	23 (50%)	53 (42%)	0.5
Atypical chest pain	23 (50%)	72 (57%)	0.5
Hypercholesterolemia*	15 (33%)	41 (33%)	0.9
Cigarette smoking	11 (24%)	37 (30%)	0.6
Systemic hypertension	16 (35%)	37 (30%)	0.6
Diabetes mellitus	4 (9%)	8 (6%)	0.9
Infarct location			
Anterior or anterolateral	22 (48%)	58 (46%)	0.8
Inferior or inferolateral	19 (41%)	55 (44%	0.7
Combined anterior and inferior	5 (11%)	12 (10%)	0.9
Medications			
Beta-blockers	29 (63%)	84 (67%)	0.8
Calcium channel blockers	18 (39%)	60 (48%)	0.4
Diuretics	8 (17%)	14 (11%)	0.4
Ace Inibitors	10 (22%)	31 (25%)	0.8
Heart rate at rest	71 ± 13	72 ± 16	0.8
Peak heart rate	132 ± 20	131 ± 24	0.8
Systolic blood pressure at rest	139 ± 22	130 ± 20	0.01
Peak systolic blood pressure	173 ± 23	171 ± 24	0.5
Peak rate-pressure product	22297 ± 4914	22538 ± 6203	0.7
Maximal workload	142 ± 36	144 ± 33	0.7
Achievement of target heart rate	25 (54%)	62 (50%)	0.7
Angina during the test	13 (28%)	29 (23%)	0.6
ST-segment depression	10 (22%)	29 (23%)	0.9

* *Defined as serum cholesterol level ≥ 240 mg/dl. ACE = angiotensin converting enzyme*

Table 2

Angiographic data of patients with and without exercise-induced ventricular arrhythmias.

Coronary angiography variables	Ventricular arrhythmias		P value
	Yes (n = 46)	No (n = 125)	
Significant coronary artery disease	45 (98%)	98 (78%)	0.005
1-vessel coronary artery disease	18 (39%)	43 (34%)	0.7
2-vessel coronary artery disease	18 (39%)	29 (23%)	0.06
3-vessel coronary artery disease	9 (20%)	26 (21%)	1
Normal coronary arteries or 50% lesion	1 (2%)	27 (22%)	0.005
Mean number of stenotic arteries	1.8 ± 0.9	1.4 ± 1	0.08
Infarct-related arteries stenosis	43 (93%)	93 (74%)	0.01
Infarct-related arteries occlusion	16 (35%)	36 (29%)	0.6
Angiographic ejection fraction	47 16%	46 13%	0.8

Table 3

Myocardial perfusion abnormalities in patients with and without exercise-induced ventricular arrhythmias.

Perfusion Patterns	Ventricular arrhythmias		P value
	Yes (n = 46)	No (n = 125)	
Normal perfusion	0	7 (6%)	0.2
Completely or partially reversible defects	32 (70%)	72 (58%)	0.2
Fixed perfusion defects	14 (30%)	46 (37%)	0.6
Peri-infarction reversible defects	32 (70%)	54 (43%)	0.004
Reversible defects in dyssynergic regions	30 (65%)	49 (32%)	0.0001
Remote perfusion defects	22 (48%)	49 (39%)	0.4
Reversible defects in ≥ 2 vascular regions	20 (43%)	27 (22%)	0.008

Coronary angiography

Coronary angiographic findings in patients with and without exercise-induced ventricular arrhythmias are demonstrated in Table 2. Patients with ventricular arrhythmias had a higher prevalence of significant coronary artery disease and infarct-related artery stenosis. No significant difference was found regarding ejection fraction as assessed by contrast ventriculography.

Myocardial perfusion abnormalities

The prevalence of myocardial perfusion abnormalities in patients with and without ventricular arrhythmias is shown in Table 3. Patients with ventricular arrhythmias had a higher prevalence of reversible perfusion abnormalities in the peri-infarction zone and in ≥ 2 vascular regions than patients without ventricular arrhythmias. No significant difference was detected regarding the prevalence of reversible perfusion abnormalities in remote myocardial regions (Figure 1).

Wall motion abnormalities

No significant difference was detected between patients with and without ventricular arrhythmias regarding the mean number of segments with resting wall motion abnormalities (2.1 ± 1.5 vs. 2.0 ± 1.6) or the mean wall motion score (3.7 ± 4.1 vs. 4.5 ± 4.3, P = 0.3). Reversible perfusion abnormalities were detected in 39 of 97 dyssynergic segments (40%) (wall motion score 2 to 4) in patients with vs. 40 of 248 dyssynergic segments (16%) in patients without ventricular arrhythmias (P < 0.0001). Reversible perfusion abnormalities were detected in 40 of 179 segments (22%) with normal contractility in patients with ventricular arrhythmias and in 100 of 502 segments (20%) with normal contractility in patients without ventricular arrhythmias (P = NS) (Figure 2).

Assessment of viability

Percent rest MIBI uptake in dyssynergic regions was not different in patients with and without ventricular arrhythmias (62 ± 32% vs. 60 ± 35%). In dyssynergic segments without reversible perfusion abnormalities, the percent resting MIBI uptake was 50% in 39 of 58 segments (67%) in patients with ventricular arrhythmias and in 131 of 208 segments (63%) in patients without ventricular arrhythmias (P = NS). Therefore, the total number of segments considered viable (ischemia and/or MIBI

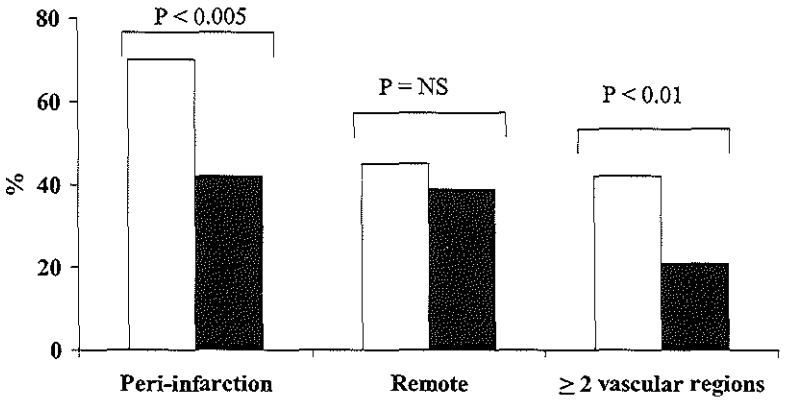


Figure 1

Prevalence of peri-infarction ischemia, remote ischemia, and ischemia in 2 vascular regions in patients with (empty bars) and without (filled bars) exercise-induced ventricular arrhythmias.

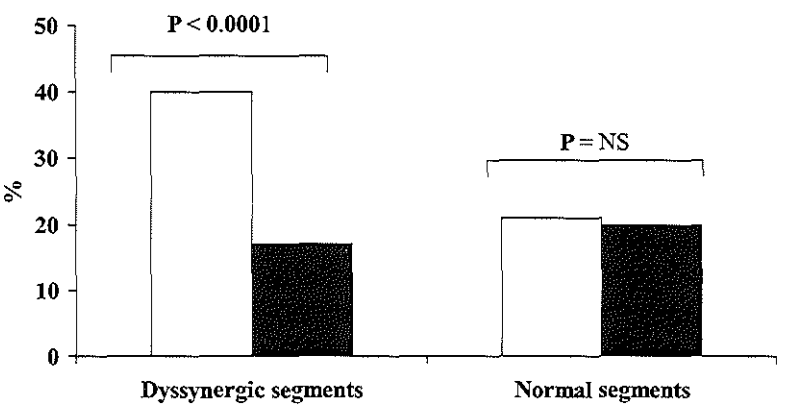


Figure 2

Percentage of segments demonstrating reversible perfusion abnormalities in dyssynergic and in normally contracting myocardium in patients with (empty bars) and without (filled bars) exercise-induced ventricular arrhythmias.

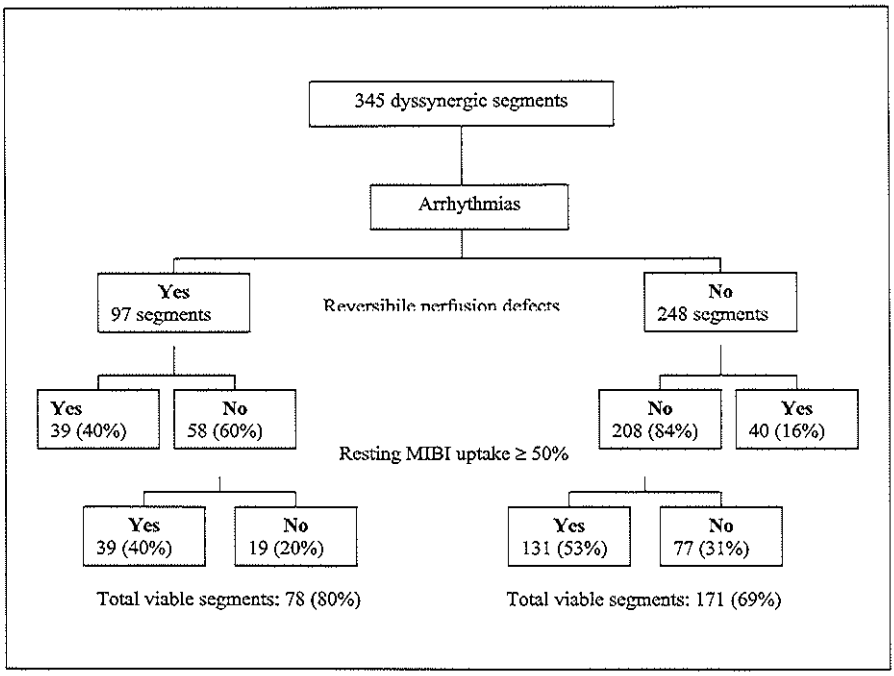


Figure 3

A chart demonstrating the patterns of viability and ischemia assessed by MIBI SPECT in dyssynergic segments in patients with and without exercise-induced ventricular arrhythmias.

uptake 50%) was 78 (80%) in patients with vs. 171 (69%) in patients without ventricular arrhythmias ($P < 0.05$, Figure 3). The exercise electrocardiogram and myocardial perfusion images of a patient with exercise-induced ventricular arrhythmias are presented in Figure 4.

Predictors of exercise-induced ventricular arrhythmias

Variables included in the multivariate analysis model were clinical (including the time after infarction), angiographic, and scintigraphic data. Independent predictors of ventricular arrhythmias were older age (chi-square 4, $P < 0.05$), the presence of significant coronary artery disease (chi-square 5, $P < 0.01$), and the presence of reversible perfusion defects in dyssynergic regions (chi-square 9, $P < 0.001$).

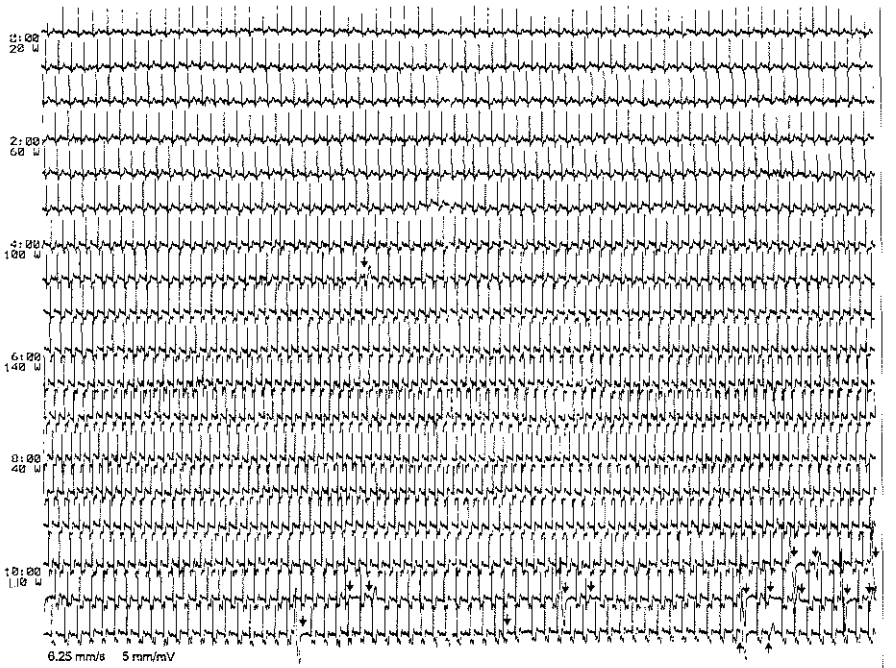


Figure 4A

A single lead (V5) electrocardiogram during exercise and recovery of a 50-year-old male patient with atypical chest pain 18 months after acute anterior myocardial infarction. The tracing demonstrates complex ventricular premature contractions in the recovery period. The echocardiogram of the patient revealed akinesia of the apex and hypokinesia of the anterior wall, septum, and inferior wall.

DISCUSSION

This is the first study evaluating the relation among exercise-induced ventricular arrhythmias, myocardial ischemia, and viability in patients with chronic left ventricular dysfunction late after acute myocardial infarction. This particular group of patients represents a large proportion of patients referred for functional evaluation of coronary artery disease and assessment for possible revascularisation. MIBI SPECT imaging was previously shown to provide an excellent method for tomographic evaluation of myocardial perfusion at rest and during stress. Our study showed that in patients with resting wall motion abnormalities late after acute myocardial infarction, exercise-induced ventricular arrhythmias is associated with findings

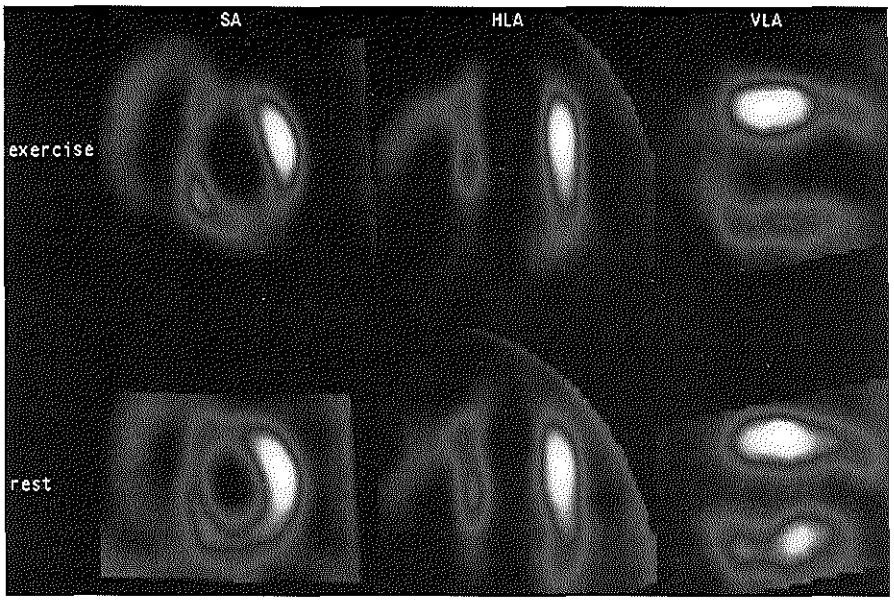


Figure 4B

Exercise stress (upper panel) and rest (lower panel) MIBI SPECT images from the short-axis (SA), horizontal long-axis (HLA), and vertical long-axis (VLA) views of the same patient. The patient had a fixed perfusion defect at the apex and partially reversible defects in the septum, inferior, and posterolateral wall. Coronary angiography revealed 3-vessel coronary artery disease.

known to predict adverse outcome. Patients with exercise-induced ventricular arrhythmias had a higher prevalence of significant coronary artery disease and infarct-related artery stenosis than patients without ventricular arrhythmias. Scintigraphic findings indicative of a high risk of cardiac events[13,14,17] were more frequent in patients with ventricular arrhythmias, because these patients had a higher prevalence of reversible perfusion abnormalities in the peri-infarction area and in ≥ two vascular regions. These findings are consistent with the higher prevalence of significant coronary artery disease and infarct-related artery stenosis in patients with ventricular arrhythmias. The impact of revascularisation on the induction of ventricular arrhythmias and improvement of future outcome needs further evaluation.

Myocardial viability

Myocardial perfusion abnormalities were evaluated by quantitative assessment in myocardial regions with resting wall motion abnormalities. For that purpose we differentiated between the term peri-infarction ischemia (which occurs in the distribution of the infarct-related artery, in segments with or without resting wall motion abnormalities) and the term ischemia confined to the dyssynergic myocardium, because only the latter term of ischemia is an established sign of myocardial viability. This study showed that patients with exercise-induced ventricular arrhythmias have a higher prevalence of ischemia in the dyssynergic myocardium. This can be explained by possible triggering of arrhythmias by the occurrence of ischemia on the substrate of a partially infarcted myocardium in the dyssynergic regions. Another possible explanation for the genesis of arrhythmias in this study is the occurrence of ischemia in ≥ two vascular territories, which may trigger arrhythmias in the regions of vascular overlap. The role of exercise in induction of ventricular arrhythmias may relate to a complex pathophysiologic alteration in patients with coronary artery disease. These include an increase in sympathetic activity, systolic blood pressure, mechanical stretch of the myocardium, and induction of myocardial ischemia.[18,19] These alterations may play a more significant role when they occur. Myocardial viability was considered present in 80% and 69% of dyssynergic segments in patients with and without ventricular arrhythmias, respectively. This difference was mainly due to a higher prevalence of reversible perfusion defects in dyssynergic segments in patients with ventricular arrhythmias. However, the percent rest MIBI uptake and the number of dyssynergic segments demonstrating MIBI uptake of ≥ 50% were not different between patients with and without ventricular arrhythmias. This indicates that the extent of myocardial necrosis is similar in patients with and without ventricular arrhythmias.

Comparison with previous studies

The significance of exercise-induced ventricular arrhythmias varies greatly among different patient groups. In asymptomatic healthy persons, exercise-induced ventricular arrhythmias is not a predictor of adverse prognosis.[20,21] However, there is a controversy regarding the relation among exercise-induced ventricular arrhythmias, structural and functional abnormalities, and prognosis in patients with known or suspected coronary artery disease.[1-11] Some investigators have reported a

strong association between exercise-induced ventricular arrhythmias and increased mortality[1,8] whereas other investigators did not find such an association.[4,6,7]

Few studies have evaluated the relation between exercise-induced ventricular arrhythmias and myocardial perfusion abnormalities.[3,7,8,10,11] Most of these studies included a heterogeneous population with and without previous myocardial infarction or included patients with recent myocardial infarction. Margonato et al[10] reported that patients with exercise-induced ventricular arrhythmias who were studied 3 to 4 weeks after acute myocardial infarction had a higher prevalence of peri-infarction and a lower prevalence of remote reversible MIBI defects than patients without exercise-induced ventricular arrhythmias. Uptake of 18F-fluorodeoxyglucose was observed within the infarcted zone in 10 of 13 patients with, and in 1 of 13 patients without ventricular arrhythmias. Marieb et al[3] reported that in 383 patients with and without previous myocardial infarction, exercise-induced ventricular arrhythmias was associated with a higher prevalence of reversible 201-thallium defects, and provided independent prognostic information beyond that provided by 201-thallium stress testing. In contrast, Schweikert et al[7] reported that exercise-induced ventricular arrhythmias is not associated with short-term mortality or angiographic severity of coronary artery disease, although it was associated with greater likelihood of thallium perfusion defects. The last two studies included patients with and without previous myocardial infarction as opposed to the homogenous population of this study. We have recently shown that exercise-induced ventricular arrhythmias are associated with a higher prevalence and severity of stress myocardial perfusion abnormalities in patients without previous myocardial infarction, who were determined to have an intermediate pre-test probability of coronary artery disease.[22]

Study limitations

Holter monitoring was not performed and therefore we could not study the relation between spontaneous ventricular arrhythmias and perfusion abnormalities. The intake of medications may have an impact on the inducibility of arrhythmias and myocardial ischemia during exercise. However, there was no significant difference in this study between patients with and without arrhythmias regarding the proportion of patients receiving anti-ischemic medications. Finally, the study did

not evaluate the prognostic significance of exercise-induced arrhythmias. However, our patients with ventricular arrhythmias had a higher prevalence of angiographic and scintigraphic abnormalities known to predict a worse prognosis.[13,14,17]

REFERENCES

1. Califf RM, McKinnis RA, McNeer JF, Harrell FE Jr, Lee KL, Pryor DB, Waugh RA, Harris PJ, Rosati RA, Wagner JS. Prognostic value of ventricular arrhythmias associated with treadmill exercise testing in patients studied with cardiac catheterization for suspected ischemic heart disease. *J Am Coll Cardiol 1983;2:1060-1067.*
2. Peduzzi P, Hultgren H, Thomsen J, Angell W. Prognostic value of baseline exercise test. *Prog Cardiovasc Dis 1986;28:285-292.*
3. Marieb MA, Beller GA, Gibson RS, Lerman BB, Kaul S. Clinical relevance of exercise-induced ventricular arrhythmias in suspected coronary artery disease. *Am J Cardiol 1990;66:172-178.*
4. Yang JC, Wesley RC Jr, Froelicher VF. Ventricular tachycardia during routine treadmill testing. Risk and prognosis. *Arch Intern Med 1991;151:349-353.*
5. Specchia G, La Rovere MT, Falcone C, Campana C, Traversi E, Caizzi V, De Servi S. Cardiac arrhythmias during exercise-induced myocardial ischaemia in patients with coronary artery disease. *Eur Heart J 1986;7 suppl A:45-52.*
6. Sami M, Chaitman B, Fisher L, Holmes D, Fray D, Alderman E. Significance of exercise-induced ventricular arrhythmia in stable coronary artery disease: a coronary artery surgery study project. *Am J Cardiol 1984;54:1182-1188.*
7. Schweikert RA, Pashkow FJ, Snader CE, Marwick TH, Lauer MS. Association of exercise-induced ventricular ectopic activity with thallium myocardial perfusion and angiographic coronary artery disease in stable, low-risk populations. *Am J Cardiol 1999;83:530-534.*
8. Henry RL, Kennedy GT, Crawford MH. Prognostic value of exercise-induced ventricular ectopic activity for mortality after acute myocardial infarction. *Am J Cardiol 1987;59:1251-1255.*
9. Nair CK, Thomson W, Aronow WS, Pagano T, Ryschon K, Sketch MH. Prognostic significance of exercise-induced complex ventricular arrhythmias in coronary artery disease with normal and abnormal left ventricular ejection fraction. *Am J Cardiol 1984;54:1136-1138.*
10. Margonato A, Mailhac A, Bonetti F, Vicedomini G, Fragasso G, Landoni C, Lucignani G, Rossetti C, Fazio I, Chierchia SL. Exercise-induced ischemic arrhythmias in patients with previous myocardial infarction: role of perfusion and tissue viability. *J Am Coll Cardiol 1996;27:593-598.*
11. Tsuji H, Iwasaka T, Sugiura T, Shimada T, Nakamori H, Kimura Y, Inada M. Relationship between redistribution on exercise thallium-201 scintigraphy and repetitive ventricular premature beats in patients with recent myocardial infarction. *Am Heart J 1991;121:1679-1684.*

12. Maddahi J, Kiat H, Van Train KF, Prigent F, Friedman J, Garcia EV, Alazraki N, DePuey EG, Nichols K, Berman DS. Myocardial perfusion imaging with technetium-99m sestamibi SPECT in the evaluation of coronary artery disease. *Am J Cardiol 1990;66:55E-62E.*
13. Iskander S, Iskandrian AE. Risk assessment using single-photon emission computed tomographic technetium-99m sestamibi imaging. *J Am Coll Cardiol 1998;32:57-62.*
14. Boyne TS, Koplan BA, Parsons WJ, Smith WH, Watson DD, Beller GA. Predicting adverse outcome with exercise SPECT technetium-99m sestamibi imaging in patients with suspected or known coronary artery disease. *Am J Cardiol 1997;79:270-274.*
15. Bax JJ, Wijns W, Cornel JH, Visser FC, Boersma E, Fioretti PM. Accuracy of currently available techniques for prediction of functional recovery after revascularisation in patients with left ventricular dysfunction due to chronic coronary artery disease: comparison of pooled data. *J Am Coll Cardiol 1997;30:1451-1460.*
16. Elhendy A, van Domburg RT, Roelandt JRTC, Geleijnse ML, Ibrahim MM, Fioretti PM. Safety and feasibility of dobutamine-atropine stress testing in hypertensive patients. *Hypertension 1997;29:1232-1239.*
17. Brown KA, Weiss RM, Clements JP, Wackers F. Usefulness of residual ischemic myocardium within prior infarct zone for identifying patients at high risk late after acute myocardial infarction. *Am J Cardiol 1987;60:15-19.*
18. Sung RJ, Huycke EC, Lai WT, Tseng CD, Chu H, Keung EC. Clinical and electrophysiologic mechanisms of exercise-induced ventricular tachyarrhythmias. *Pacing Clin Electrophysiol 1988;11:1347-1357.*
19. Reinke A, Michel D, Mathes P. Arrhythmogenic potential of exercise-induced myocardial ischaemia. *Eur Heart J 1987;8 suppl G:119-124.*
20. Busby MJ, Shefrin EA, Fleg JL. Prevalence and long-term significance of exercise-induced frequent or repetitive ventricular ectopic beats in apparently healthy volunteers. *J Am Coll Cardiol 1989;14:1659-1665.*
21. Fleg JL, Lakatta EG. Prevalence and prognosis of exercise-induced nonsustained ventricular tachycardia in apparently healthy volunteers. *Am J Cardiol 1984;54:762-764.*
22. Elhendy A, Sozzi FB, van Domburg RT, Bax JJ, Valkema R, Roelandt JRTC. Relation between exercise-induced ventricular arrhythmias and myocardial perfusion abnormalities in patients with intermediate pre-test probability of coronary artery disease. *Eur J Nucl Med 2000;27:327-332.*

SUMMARY

Summary and Conclusions

SUMMARY

In this thesis, we explored new clinical applications for stress imaging techniques in the evaluation of coronary artery disease.

Stress echocardiography and myocardial perfusion imaging are the most widely used non-invasive imaging modalities for the diagnosis and functional assessment of coronary artery disease. These tests are also useful for the evaluation of myocardial viability and the prediction of spontaneous functional improvement after revascularisation procedures.

Each of these imaging modalities has its specific advantages and disadvantages. Echocardiographic machines are smaller, mobile, and widely available at relatively low cost. Echocardiography is capable of accurately defining chamber dimensions, systolic and diastolic volumes, function, and wall thickness. Dobutamine stress echocardiography is a useful non-invasive test, especially for patients with limited exercise capacity. For patients with left ventricular dysfunction, low-dose dobutamine echocardiography is a sensitive method for the assessment of myocardial viability. In addition, dobutamine stress echocardiography has a prognostic merit for post-myocardial revascularisation and peri-operative cardiac risk stratification.

On the other hand, nuclear perfusion imaging is computed and provides quantitative information. The analysis of nuclear imaging results is therefore less subjective compared to stress echocardiography. On patients with a poor acoustic window, nuclear perfusion imaging has a high success rate. It has been demonstrated in several previous studies that nuclear imaging techniques are more sensitive than dobutamine stress echocardiography for the detection of myocardial viability. However, dobutamine stress echocardiography is more specific.

Several stress modalities are available to the clinician for the detection of myocardial ischemia and for risk assessment. The most popular modalities are exercise (bicycle or treadmill) and pharmacological stress testing with a vasodilator (adenosine, dipyridamole) or the sympathomimetic "exercise stimulator." These agents can be used in conjunction with two-dimensional echocardiography or nuclear perfusion imaging.

For the majority of patients capable of performing adequate exercise, exercise electrocardiography is the test of choice because of its widespread availability and experience, low cost, reproducibility of symptoms,

and assessment of both haemodynamic and functional capacity. On patients unable to perform adequate exercise because of deconditioning, neurologic, respiratory, peripheral vascular, or orthopaedic limitations, a pharmacological stress test is performed, because of the lower sensitivity associated with submaximal exercise stress. A pharmacological stress test is also indicated in patients with left-bundle branch block, because of a decrease in specificity associated with exercise electrocardiography. The choice of the stress agent and the imaging modality is dependent on the cost, patient's characteristics, and local expertise.

The addition of an imaging modality is necessary in patients with a high incidence of false positive exercise electrocardiography tests because of hyperventilation syndromes, mitral valve prolapse, and repolarization abnormalities related to left ventricular hypertrophy, conduction disturbances (left-bundle branch block, pre-excitation, ventricular paced rhythm), or digitalis therapy. Stress imaging is extremely helpful when identification of the site of myocardial ischemia or the direct measurement of specific additional information (for example, left ventricular ejection fraction) is necessary for patient management. In addition, dobutamine stress echocardiography is useful in the evaluation of long-term cardiac prognosis, especially in elderly patients referred for complaints of chest pain and for preoperative cardiac risk stratification and evaluation of myocardial viability.

THE CURRENT STUDIES

Clinical Utility of Dobutamine Stress Echocardiography

Imaging quality

Imaging modalities with improved delineation of left ventricular endocardial border are clinically useful because they allow for more accurate assessment of left ventricular global and regional wall function. With second harmonic imaging, the signal returned by the tissue includes not only the transmitted fundamental frequency, but also other frequencies—most notably the harmonic frequency, which is twice the fundamental frequency. The ultrasonographic system separates out the two components and then processes the harmonic signal alone. Ultrasound beams formed with the harmonic signals have interesting properties. One of those properties is that the beam implied by the

space between the dashed lines of focus is narrower than the beam for the conventional narrow aperture technique, and it also involves fewer side lobes. Harmonic imaging provides a double benefit: it produces a narrower beam (which improves resolution), and it produces more energy in the harmonic beam (which benefits imaging). The improvement in beam width and reduction in side lobes will significantly improve grey-scale contrast resolution. In addition, second harmonic imaging eliminates undesirable near-field artefacts and decreases the clutter. For these reasons, the image results are improved. [1,2]

It has been estimated that one or more of 16 segments defined by the American Society of Echocardiography could not be adequately visualised in 30% of patients when fundamental imaging is used.[3,4] The improvement in imaging quality obtained by using second harmonic imaging was shown especially in patients with a traditionally poor acoustic window (obese patients, females, pulmonary disease).[5]

The increased heart rate during dobutamine stress echocardiography causes more technical difficulties in the interpretation of the endocardial border related to increased cardiac motion. Our study (chapter 2) demonstrated that the advantage of second harmonic imaging over fundamental imaging for left ventricle endocardial border delineation at rest is sustained at higher heart rates during dobutamine stress echocardiography. Altogether, the use of second harmonic imaging resulted in a higher feasibility of the left ventricle endocardial border visualisation at rest, at low- and at peak dose dobutamine infusion. The difference between both imaging modalities was more marked during stress. In addition, at peak stress the percentage of patients with invisible endocardial border in ≥ 5 segments, indicating non--feasible dobutamine stress echocardiography results, increased from 4% to 11% with fundamental imaging. This percentage increased only marginally from 3% to 4% with second harmonic imaging. These data indicate that the better image quality at higher heart rates allowed for more segments to be analysed than did fundamental imaging.

The majority of left ventricle segments with invisible borders both at rest and at peak stress were located by fundamental imaging in the anterior and in the lateral walls, which is explained by the fact that these segments are more tangential to the ultrasound beam. The improvement with second harmonic imaging was particularly evident in these walls. We can conclude that second harmonic imaging improves endocardial

border delineation especially during stress and allows for better analysis because the image quality is improved. Therefore, its role is extended, and it is more valuable during stress echocardiography than in rest studies.

One of the major limitations of stress echocardiography using fundamental imaging is the suboptimal segmental endocardial border definition, which interferes with the proper analysis of left ventricular function at rest or during stress. Our study demonstrated that the use of second harmonic imaging resulted in a higher feasibility of the left ventricle endocardial border visualisation at rest, at low- and at peak dose dobutamine infusion. Therefore, its role is extended, and it is more valuable during stress echocardiography than in rest studies.

Accuracy in the diagnosis of coronary artery disease

The diagnostic accuracy of dobutamine stress echocardiography relies on an optimal left ventricular wall visualisation.[6-8]

Our study (chapter 3) showed that the sensitivity of dobutamine stress echocardiography for the diagnosis of coronary artery disease was significantly higher when second harmonic imaging was used. This was most strikingly evident in patients with single-vessel coronary artery disease. Similarly, sensitivity was significantly improved for the analysis of wall function, especially in the territory of the left circumflex coronary artery. The overall specificity and regional specificity produced by both techniques were similar.

The higher sensitivity of second harmonic imaging can be explained by the frequent occurrence of ischemia limited in one segment. Therefore, the increased sensitivity by the use of second harmonic imaging was mostly evident in patients with single-vessel disease, as a result of the smaller magnitude of inducible ischemia in these patients, compared with that in patients with multivessel disease. The lower sensitivity for detection of disease in the left circumflex coronary artery, obtained by fundamental imaging, can be related to the problems with resolution of the endocardium of the lateral wall. The parallel orientation of the wall and the ultrasound beam generates more clutter and near-field artefacts, with consequent loss of lateral resolution. Conversely, second harmonic imaging characterised to reduce these noises produces better imaging quality.

The sensitivity of dobutamine stress echocardiography for the diagnosis of coronary artery disease was significantly higher when second harmonic imaging was used. This was most strikingly evident in patients with single-vessel disease. Similarly, sensitivity was significantly improved for the analysis of wall function, especially in the territory of the left circumflex coronary artery. The overall and the regional specificity produced by both techniques were similar.

Identification of viable myocardium

There is a relationship between the amount of viable myocardium and the expected benefit of myocardial revascularisation.[9-11] In patients with significant left ventricular dysfunction, it is extremely important to estimate the potential of improvement of left ventricular function before considering revascularisation. The most practical tests at present are nuclear testing and stress echocardiography.

It has been shown in a previous study that 201-thallium detected a significantly higher percentage of viable segments than did dobutamine stress echocardiography.[12-14] A similar difference was observed when 19F-fluorodeoxyglucose imaging with positron emission tomography or SPECT was compared with dobutamine stress echocardiography.[16-18] Thus, the nuclear techniques appear to be more sensitive, probably because the detection of myocardial viability by these techniques requires less cellular integrity than is required for eliciting a contractile response during dobutamine stress echocardiography. From a physiological point of view, this can be explained by the fact that more severely damaged myocardium (with less viable tissue and more fibrosis) may still exhibit perfusion and glucose utilisation, but it has lost most of the contractile reserve. Aside from this physiological explanation, technical factors may also contribute to the difference between dobutamine stress echocardiography and nuclear imaging. In fact, imaging quality affects dobutamine stress echocardiography to a greater extent than do nuclear techniques, since a suboptimal acoustic window may limit an accurate conclusion regarding the presence or absence of viable myocardium.

In our study (chapter 4) we evaluated myocardial viability in 30 patients with ischemic left ventricular dysfunction using nuclear imaging (DISA-SPECT) and dobutamine stress echocardiography with both fundamental and second harmonic imaging. In dysfunctional segments, the use of dobutamine stress echocardiography with fundamental

imaging was less accurate than dobutamine stress echocardiography with second harmonic imaging in detecting myocardial viability, considering DISA-SPECT as the test reference. The agreement between dobutamine stress echocardiography with fundamental imaging and DISA-SPECT imaging was 78%, and kappa value was 0.56. When second harmonic imaging was used, the agreement between the two methods significantly increased (agreement 89%, kappa = 0.77). The improvement in sensitivity obtained with second harmonic imaging in dysfunctional segments was mainly due to a reduction in the number of segments that were SPECT viable and dobutamine stress echocardiography nonviable. This was particularly related to better endocardial border visualisation and detection of biphasic responses. Dobutamine stress echocardiography studies were also analysed on an individual patient basis. Using the four segments cut-off level (allowing for optimal identification of patients who would benefit from revascularisation) a difference between fundamental imaging and second harmonic imaging was obtained in six patients. Five of them were classified as having nonviable segments by fundamental imaging but viable by second harmonic imaging. Thus, a substantial number of patients would have been denied revascularisation based on fundamental imaging.

In dysfunctional segments, the use of second harmonic imaging during dobutamine stress echocardiography was more accurate than fundamental imaging in detecting myocardial viability. The agreement between dobutamine stress echocardiography and DISA-SPECT was significantly increased when second harmonic imaging was used, compared with the agreement when fundamental imaging was used.

Impact of beta-blockers on contractile reserve

Dysfunctional but viable myocardium is characterised by a biphasic, ischemic response or sustained improvement during dobutamine stress echocardiography.[19-21] Beta-blockers have both a negative inotropic and chronotropic effect on the heart[22] and are used for the treatment of patients after myocardial infarction and heart failure.[20,23] They adversely affect the ability of dobutamine to elicit myocardial contraction and viability.[24,25] Although it is known that the reduced chronotropic response during dobutamine stress echocardiography in patients on beta-blockers

can be overcome by an increase in dobutamine dose and by the addition of atropine on top of dobutamine, the influence of beta-blockers at low-dose dobutamine stress echocardiography remains uncertain. The question of whether and how beta-blockers affect the result of dobutamine stress echocardiography is important, because it would be an advantage if these agents could be continued to be used in patients with left ventricle dysfunction undergoing dobutamine stress echocardiography for demonstrating viability. Discontinuation of beta-blockers may deprive these patients of the potential benefits of these agents and may lead to rebound tachycardia and worsening of the clinical status. Therefore, we assessed myocardial viability by dobutamine stress echocardiography in the same patients with and without beta-blockers. Nuclear imaging was used as an independent reference test (chapter 5).

We found that in patients on beta-blocker therapy with severe ischemic left ventricular dysfunction, the number of segments identified as viable by dobutamine stress echocardiography was reduced. The kappa value, evaluating the agreement of viability between dobutamine stress echocardiography and nuclear scanning, was 0.71 and 0.78 respectively in patients with and without beta-blockers. When patients were treated with beta-blockers, 15% of the segments considered viable by nuclear imaging showed no viability by dobutamine stress echocardiography. The percentage of segments viable by nuclear imaging but not by dobutamine stress echocardiography were 11% when beta-blockers were stopped. In patients on beta-blocker therapy the resting wall motion score was also significantly higher. Seventeen segments showing mild hypokinesia in patients without beta-blockers worsened to severe hypokinesia when they received a beta-blocker. The worsening of wall motion occurred despite a decrease in afterload and may be due to the direct negative inotropic effects of beta-blockers. Although the worsening of the function of the ischemic myocardium is difficult to explain, it appears that the effect of beta-blockade on wall function of chronically hypoperfused myocardium differs from the effect of beta-blockade on the acutely ischemic myocardium, in which acute beta-blockade causes improved perfusion and wall motion.

Although beta-blocker therapy reduces the number of viable segments in patients, there were no practical implications. In fact, all "viable" patients were scored with and without beta-blocker therapy. If a study on beta-blockers shows only limited viability, it is useful to repeat the test

after discontinuing the beta-blocker therapy, especially when there is a fixed heart rate during low-dose dobutamine. The other approach is to repeat the test using DISA-SPECT. If the latter test is used, one should take into account that a number of viable segments assessed by scan will not recover after revascularisation.

In patients with severe ischemic left ventricular dysfunction, beta-blocker therapy reduced the number of viable segments assessed by dobutamine stress echocardiography when DISA-SPECT was used as a gold standard.

Risk stratification by dobutamine echocardiography

Diabetes mellitus is a major risk factor for cardiovascular morbidity and mortality.[26,27] Coronary artery disease is the leading cause of death in diabetic patients, and the related risk is independent of other conventional risk factors for coronary artery disease.[28-30] Identification of diabetic patients at a high risk for death and myocardial infarction is an essential step in planning the appropriate management strategy. The non-invasive diagnosis and risk stratification of coronary artery disease in diabetic patients is important for the selection and optimisation of therapeutic interventions, which may improve chances for survival and reduce complications of coronary artery disease.[31,32] Exercise stress testing is the most widely used method for the diagnosis and functional evaluation of coronary artery disease.[33,34] However, exercise capacity is frequently impaired in diabetic patients, particularly because of the higher prevalence of peripheral neuropathy and vascular disease in this population.[35-38] Dobutamine stress echocardiography has been reported as a safe and feasible method for evaluation of coronary artery disease in diabetic patients with limited exercise capacity.[39,40] However, data regarding the incremental value of the technique in the risk stratification of diabetic patients are scarce.[26] Additionally, there is currently no outcome data to support the role of stress echocardiography in the prediction of all causes of mortality in diabetic patients.

The aim of this study (chapter 6) was to assess the value of dobutamine stress echocardiography in the prediction of death and hard cardiac events in diabetic patients with known or suspected coronary artery disease and to determine whether this method provides incremental prognostic information relative to clinical data.

Dobutamine stress echocardiography was performed on 396 diabetic patients. During a median follow-up of three years, 97 patients died (55 cardiac deaths) and 27 patients had non-fatal myocardial infarction (82 hard cardiac events). Clinical predictors of hard cardiac events were a history of congestive heart failure and previous myocardial infarction. Clinical predictors of all causes of mortality were age, hypercholesterolemia and history of congestive heart failure. Dobutamine stress echocardiography provided incremental prognostic information for the prediction of both end points. Hard cardiac events were predicted by the presence of resting wall motion abnormalities as well as by the percentage of ischemic segments at stress. These findings demonstrate the importance of resting left ventricular function and the severity of myocardial ischemia in determining the outcome of diabetic patients.

The cumulative hard cardiac event rate was higher in patients with abnormal dobutamine stress echocardiography results as compared with that in patients with normal results (7% vs. 5% at one year, 18% vs. 8% at three years and 23% vs. 10% at five years, overall P = 0.01). Peak dobutamine wall motion score index, which measures the sum of resting and stress-induced wall motion abnormalities, was incremental to clinical data in the prediction of all causes of mortality. The percentage of hard cardiac events increased proportionally to the extension of myocardial ischemia at dobutamine stress echocardiography. The cumulative death rate in patients with abnormal dobutamine stress echocardiography results as compared with that in patients with normal results was 9% vs. 3% at one year, 29% vs. 11% at three years and 31% vs. 24% at five years (overall P = 0.04). From these data it appears that the maximal value of a normal dobutamine stress echocardiography study in the prediction of a lower risk status is obtained at an intermediate term follow-up of three years, where survival curves showed the greatest diversion between patients with normal and abnormal study. At five years, the difference in survival was less significant. As a result, in order to obtain an up-to-date risk status in patients with an initial normal study, it is recommended to repeat the test three years later.

Dobutamine stress echocardiography provides data incremental to clinical variables for the prediction of death and cardiac events in diabetic patients with suspected or known coronary artery disease. Resting left ventricular

function and extent of myocardial ischemia during dobutamine stress echocardiography are important predictors of outcome in these patients.

New Clinical Observations in Stress Myocardial Perfusion SPECT Imaging

Diagnosis of single-vessel coronary artery disease

The use of 99m-technetium-labelled radioactive agents improves imaging quality of exercise myocardial perfusion scintigraphy when compared with the use of 201-thallium.[41,42] Therefore, these agents are now widely used in conjunction with exercise and pharmacologic stress testing. However, recent experimental studies demonstrated that sestamibi underestimated flow heterogeneity induced by dobutamine because its uptake plateaus at a lower flow rate than that of vasodilator agents.[43] Additionally, dobutamine may interfere with sestamibi uptake in the normally perfused myocardium, leading to further underestimation of flow heterogeneity.[44] The implication of these experimental studies is that sestamibi scintigraphy may have limited sensitivity in patients with single-vessel coronary artery disease.[43,44] We compared the accuracy of dobutamine stress echocardiography and simultaneous sestamibi SPECT for the diagnosis of single-vessel coronary artery disease and evaluated the agreement between both techniques regarding the presence and the extent of stress induced wall motion and myocardial perfusion abnormalities (chapter 7). The results of the study showed that both echocardiography and sestamibi SPECT have a similar modest sensitivity for the diagnosis of single-vessel coronary artery disease. The mean number of ischemic segments was not different between both techniques. This implied that transient wall motion and myocardial perfusion abnormalities occur with similar frequency and extent in patients with single-vessel coronary artery disease during high dose dobutamine infusion. Despite the modest sensitivity of sestamibi, echocardiography did not provide an advantage in the overall or the regional diagnosis of coronary artery disease in these patients. Sensitivity of both techniques was lower in patients with left circumflex or right coronary artery stenosis. There was no improvement in accuracy by the synergetic use of both techniques for the diagnosis of single-vessel coronary artery disease.

Both echocardiography and sestamibi SPECT had a similar sensitivity for the diagnosis of single-vessel coronary artery disease. The mean number of ischemic segments was not different between both techniques. This implied that transient wall motion and myocardial perfusion abnormalities occur with similar frequency and extent in patients with single-vessel coronary artery disease during high dose dobutamine infusion.

Diagnostic value of tetrofosmin imaging

Previous studies have demonstrated both the feasibility and the accuracy of dobutamine stress myocardial perfusion imaging with 201-thallium and 99m-technetium-sestamibi for the diagnosis of coronary artery disease in patients with limited exercise capacity.[41] 99m-Technetium-tetrofosmin is a newly introduced myocardial perfusion tracer with favourable biokinesis and imaging characteristics. This radiopharmaceutical is distributed within the myocardium in proportion to regional myocardial blood flow. After intravenous injection, a relatively rapid clearance of the tracer from the blood and extracardiac structures occurs, with minimal redistribution from the myocardium. The accuracy of myocardial perfusion scintigraphy with 99m-technetium-tetrofosmin for the diagnosis of coronary artery disease in conjunction with exercise or vasodilator stress echocardiography has been evaluated.[45,46] However, few data are available regarding the use of tetrofosmin with dobutamine stress testing. Although vasodilator stress agents are more widely used for myocardial perfusion imaging than dobutamine, the latter is particularly useful in patients who have contraindications for vasodilator agents.[42,47] As a result, we evaluated the accuracy of dobutamine stress 99m-technetium-tetrofosmin SPECT for the diagnosis of coronary artery disease in patients with limited exercise capacity (chapter 8).

We found that in patients with limited exercise capacity and suspected coronary artery disease, dobutamine tetrofosmin SPECT had a good sensitivity and specificity for the diagnosis of coronary artery disease. The overall sensitivity rate was 80%. The sensitivity rate was higher in patients with multivessel coronary artery disease than in patients with single-vessel coronary artery disease. Additionally, multivessel coronary artery disease was identified in 57% of patients on the basis of perfusion abnormalities in more than one vascular region. The stress myocardial perfusion defect score was higher in patients with multivessel coronary

artery disease than in patients with single-vessel coronary artery disease. This demonstrated the ability of the test to identify extensive coronary artery disease in patients who were known to be at a high risk for cardiac events. The absence of perfusion abnormalities in patients with coronary artery disease was associated with less severe coronary artery stenosis. The lower sensitivity rate under this condition may be explained by means of the early roll-off of tetrofosmin during the high-flow situation. In addition, in this study no significant difference was detected for the accuracy of the detection of individual coronary artery stenosis.

We concluded that dobutamine stress 99m-technetium-tetrofosmin SPECT imaging is a clinically useful method for the diagnosis and localisation of coronary artery disease in patients with limited exercise capacity. The sensitivity and specificity rates of dobutamine tetrofosmin SPECT imaging in this study were fairly comparable with the average sensitivity and specificity rates of exercise tetrofosmin imaging reported in earlier studies. Optimal accuracy of the technique was achieved by using both fixed and reversible abnormalities for the diagnosis of coronary artery disease in patients without an earlier myocardial infarction. False negative test results occurred more frequently in patients with a lower peak stress heart rate, single-vessel coronary artery disease and less severe coronary artery stenosis.

In patients with limited exercise capacity, dobutamine tetrofosmin SPECT imaging had a good sensitivity and specificity for the diagnosis of coronary artery disease. Therefore, it is a clinically useful method for the diagnosis of coronary disease in this category of patients.

Impact of hypertension and left ventricular hypertrophy

Hypertension is a major risk factor for the development of coronary artery disease and a frequent finding in patients referred for stress testing.[48] Patients with hypertension often have left ventricular hypertrophy, a condition that is presumed to potentially cause false positive perfusion defects in the absence of coronary artery disease due to impairment of coronary flow reserve.[49,50]

Although exercise myocardial perfusion scintigraphy has been shown to be more accurate than exercise electrocardiography for the diagnosis of coronary artery disease, myocardial perfusion abnormalities may occur

in hypertensive patients without significant epicardial coronary artery disease. Such abnormalities may not necessarily represent a false positive diagnosis of myocardial ischemia as they may represent the sequelae of microvascular disease, impaired vasodilator reserve, and in a certain subset of hypertensive patients, increased myocardial oxygen demand. Although the occurrence of myocardial perfusion abnormalities in hypertensive patients without epicardial coronary artery disease is well documented, the impact of this observation on the specificity and value of exercise stress myocardial perfusion scintigraphy for diagnosing coronary artery disease in a routine clinical setting remains unclear. It is not known whether myocardial perfusion scintigraphy suffers from particular limitations in hypertensive patients. Such information is important for physicians in deciding whether to refer hypertensive patients for this type of imaging. Therefore, we compared the diagnostic accuracy of exercise stress SPECT with 99m-technetium-labelled agents for diagnosis and localising coronary artery disease in patients with and without hypertension (chapter 9).

We found that exercise SPECT imaging provided a relatively high sensitivity and specificity for the overall diagnosis of coronary artery disease in hypertensive patients. The diagnosis of disease in individual coronary artery territories was accomplished with moderate sensitivity and high specificity, and did not differ among the three vascular regions. This confirms the value of SPECT imaging in the correct diagnosis of regional myocardial perfusion abnormalities.

There was no significant difference between patients with and without hypertension in the sensitivity, specificity or accuracy of exercise SPECT for overall and regional diagnosis of coronary artery disease. Similarly, the accuracy of diagnosing multivessel coronary artery disease on the basis of perfusion abnormalities in more than one vascular region was not significantly different between the two groups. SPECT imaging provided a higher sensitivity and accuracy than electrocardiography irrespective of whether or not there was hypertension. Among hypertensive patients, the presence of left ventricular hypertrophy did not affect the sensitivity or specificity of the diagnosis of coronary artery disease. These data showed that in hypertensive patients without previous myocardial infarction referred for the diagnosis of coronary artery disease, exercise SPECT myocardial perfusion imaging is a useful method for the overall and regional diagnosis of coronary artery disease, with comparable

sensitivity and specificity to those achieved in normotensive patients. The similar specificity in the three vascular regions indicated that false positive results do not tend to involve a particular myocardial segment.

Exercise SPECT imaging provides high sensitivity and specificity for the overall diagnosis of coronary artery disease in hypertensive patients. In our study there was no significant difference between patients with and without hypertension in the sensitivity, specificity or accuracy of exercise SPECT for overall and regional diagnosis of coronary artery disease. Therefore, among hypertensive patients, the presence of left ventricular hypertrophy did not affect the sensitivity.

Exercise-induced ventricular arrhythmias

We studied the relationship between exercise-induced ventricular arrhythmias and myocardial perfusion abnormalities in a homogeneous population with intermediate pre-test probability of coronary artery disease (chapter 10). In this particular group of patients, stress-testing modalities are known to have the highest accuracy for the diagnosis of coronary artery disease.[51] The study design allowed evaluation of the independent association between exercise-induced ventricular arrhythmias and perfusion abnormalities by excluding patients with clinical conditions known to be highly predictive of perfusion abnormalities, such as previous myocardial infarction, known coronary artery disease detected by angiography and revascularisation, as well as conditions known to be associated with false positive perfusion studies or to predict a worse prognosis on their own, such as ventricular hypertrophy, left-bundle branch block and paced rhythm. The study showed that exercise-induced ventricular arrhythmias were associated with a higher prevalence of abnormal myocardial perfusion. Additionally, ischemic electrocardiographic changes were more frequent in patients with than in patients without ventricular arrhythmias. Since myocardial perfusion abnormalities were highly predictive of coronary artery disease in patients with intermediate pre-test probability of coronary artery disease,[52,53] it could be assumed that exercise-induced ventricular arrhythmias were associated with a higher prevalence of coronary artery disease in this particular population. Electrocardiographic changes underestimated the prevalence of perfusion abnormalities in this study, and therefore, exercise-

induced ventricular arrhythmias should be interpreted as a marker of higher probability of coronary artery disease in the absence of a sensitive imaging technique such as myocardial perfusion scintigraphy. The association between exercise-induced ventricular arrhythmias and myocardial perfusion abnormalities is explained by the association between myocardial ischemia and ventricular arrhythmias. The increase in sympathetic nervous system activity and the circulating catecholamines during exercise was an additional mechanism for inducing myocardial ischemia and for triggering arrhythmias in the ischemic myocardium.

Myocardial perfusion abnormalities were highly predictive of coronary artery disease in patients with intermediate pre-test probability. It could be assumed that exercise-induced ventricular arrhythmias were associated with a higher prevalence of coronary artery disease in this particular population.

Exercise-induced ventricular arrhythmias were reported as markers of myocardial viability after acute myocardial infarction.[54,55] We studied the relation between exercise-induced ventricular arrhythmias and scintigraphic markers of myocardial ischemia and viability in patients with chronic left ventricular dysfunction referred for exercise stress testing late after acute myocardial infarction. This particular group of patients represents a large proportion of patients referred for functional evaluation of coronary artery disease and assessment for possible revascularisation. Our study (chapter 11) showed that in patients with resting wall motion abnormalities late after acute myocardial infarction, exercise-induced ventricular arrhythmias were associated with findings known to predict adverse outcome. Patients with exercise-induced ventricular arrhythmias had a higher prevalence of significant coronary artery disease and infarct related artery stenosis than patients without ventricular arrhythmias. Scintigraphic findings indicative of a high risk of cardiac events were more frequent in patients with ventricular arrhythmias, because these patients had a higher prevalence of reversible perfusion abnormalities in the peri-infarction area and in the ≥ 2 vascular regions. These findings were consistent with the higher prevalence of significant coronary artery disease and infarct related coronary artery stenosis in patients with ventricular arrhythmias.[55,56] The data of this study showed that patients with exercise-induced ventricular arrhythmias had a higher prevalence of ischemia in the dyssynergic myocardium. This can be explained by

possible triggering of arrhythmias by the occurrence of ischemia on the substrate of a partially infarcted myocardium in the dyssynergic regions. The role of exercise in induction of ventricular arrhythmias may relate to a complex pathophysiologic alteration in patients with coronary artery disease. These included an increase in sympathetic activity, systolic blood pressure, mechanical stretch of the myocardium and induction of myocardial ischemia.[57,58]

In patients with resting wall motion abnormalities late after acute myocardial infarction, exercise-induced ventricular arrhythmias were associated with findings known to predict adverse outcome. The data of this study showed that patients with exercise-induced ventricular arrhythmias had a higher prevalence of ischemia in the dyssynergic myocardium.

General Conclusions

Second harmonic imaging allows for better left ventricle endocardial border identification at rest and at higher heart rate during dobutamine stress echocardiography. The accuracy of dobutamine stress echocardiography for the diagnosis of significant coronary artery disease and for the assessment of myocardial viability in patients with left ventricular dysfunction is therefore significantly better when second harmonic imaging is used.

The capability of dobutamine stress echocardiography in identifying myocardial viability in patients with left ventricular dysfunction is reduced by the administration of beta-blocker therapy.

Dobutamine stress echocardiography provides incremental data for the prognostic stratification of diabetic patients with suspected or known coronary artery disease.

Both dobutamine stress echocardiography and sestamibi SPECT imaging have a similar moderate sensitivity for the diagnosis of single-vessel coronary artery disease. There is no improvement in diagnostic accuracy by using both techniques.

Dobutamine myocardial perfusion imaging using 99m-technetium-tetrofosmin SPECT is useful for the diagnosis and localisation of coronary artery disease in patients with limited exercise capacity.

Systemic arterial hypertension does not have an impact on the accuracy of exercise stress myocardial perfusion imaging for the diagnosis and localisation of coronary artery disease in patients with and without left ventricular hypertrophy.

In patients with intermediate pre-test probability of coronary artery disease, exercise-induced ventricular arrhythmias are predictive of a higher prevalence of myocardial perfusion abnormalities. Myocardial ischemia in the dyssynergic myocardium appears to be a major mechanism underlying the occurrence of ventricular arrhythmias in patients with exercise-induced ventricular arrhythmias late after myocardial infarction.

REFERENCES

1. Caidahl K, Kazzam E, Lidberg J, Neumann Andersen G, Nordanstig J, Rantapaa Dahlqvist S, Waldenstrom A, Wikh R. New concept in echocardiography: harmonic imaging of tissue without use of contrast agent. *Lancet 1998;352:1264-1270.*
2. Tranquart F, Grenier N, Eder V, Pourcelot L. Clinical use of ultrasound tissue harmonic imaging. *Ultrasound Med Biol 1999;25:889-894.*
3. Broderick TM, Bourdillon PDV, Ryan T, Feigenbaum H, Dillon JC, Armstrong WF. Comparison of regional and global left ventricular function by serial echocardiograms after reperfusion in acute myocardial infarction. *J Am Soc Echocardiogr 1989;2:315-323.*
4. Panza JA, Laurienzo M, Curiel RV, Quyyumi AA, Cannon RO. Transesophageal dobutamine stress echocardiography for evaluation of patients with coronary artery disease. *J Am Coll Cardiol 1994;24:1260-1267.*
5. Kasprzak JD, Paelinck B, Ten Cate FJ, Vletter WB, de Jong N, Poldermans D, Elhendy A, Bouakaz A, Roelandt JR. Comparison of native and contrast-enhanced harmonic echocardiography for visualisation of left ventricular endocardial border. *Am J Cardiol 1999;83:211-217.*
6. Senior R, Soman P, Khattar RS, Lahiri A. Improved endocardial visualisation with second harmonic imaging compared with fundamental two-dimensional echocardiographic imaging. *Am Heart J 1999;138:163-168.*
7. Zaglavara T, Norton M, Cumberledge B, Morris D, Irvine T, Cummins C, Schuster J, Kenny A. Dobutamine stress echocardiography: improved endocardial border definition and wall motion analysis with tissue harmonic imaging. *J Am Soc Echocardiogr 1999;12:706-713.*
8. Spencer KT, Bednarz J, Rafter PG, Korkarz C, Lang RM. Use of harmonic imaging without echocardiographic contrast to improve two-dimensional image quality. *Am J Cardiol 1998;82:794-799.*
9. Schwaiger M, Melin J. Cardiological applications of nuclear medicine. *Lancet 1999;354:661-666.*
10. Rahimtoola SH. Importance of diagnosing hibernating myocardium: how and in whom? *J Am Coll Cardiol 1997;30:1701-1706.*
11. Dilsizian V, Bonow RO. Current diagnostic techniques of assessing myocardial viability in hibernating and stunned myocardium. *Circulation 1993;87:1-20.*
12. Bonow RO, Dilsizian V. Thallium-201 and technetium-99-m-sestamibi for assessing viable myocardium. *J Nucl Med 1992;33:815-818.*
13. Marzullo P, Parodi O, Reisenhofer B, Sambuceti G, Picano E, Distante A, Gimelli A, L'Abbate A. Value of rest thallium-201/technetium-99m sestamibi

scans and dobutamine echocardiography for detecting myocardial viability. *Am J Cardiol 1993;71:166-172.*

14. Qureshi U, Nagueh SF, Afridi I, Vaduganathan P, Blaustein A, Verani, MS, Winters WL, Zoghbi WA. Dobutamine echocardiography and quantitative rest-redistribution 201Tl tomography in myocardial hibernation: Relation of contractile reserve to 201Tl uptake and comparative prediction of recovery of function. *Circulation 1997;95:626-635*
15. Matsunari I, Boning G, Ziegler SI, Nekolla SG, Stollfuss JC, Kosa I, Ficaro EP, Schwaiger M. Attenuation-corrected 99mTc-Tetrofosmin single-photon emission comparison with positron emission tomography using 18F-Fluorodeoxiglucose. *J Am Coll Cardiol 1998;32:927-935.*
16. Bonow RO, Dilsizian V, Cuocolo A, Bacharach SL. Identification of viable myocardium in patients with chronic coronary artery disease and left ventricular dysfunction. Comparison of thallium scintigraphy with reinjection and PET imaging with 18F-fluorodeoxyglucose. *Circulation 1991;83:26-37.*
17. Cornel JH, Visser FC, Fioretti PM, van Lingen A, Huitink JM, Kamp O, Nijland F, Roelandt JR, Visser CA. Prediction of improvement of contractile function in patients with ischemic ventricular dysfunction after revascularisation by Fluorine-18Fluorodeoxyglucose single photon-emission computed tomography. *J Am Coll Cardiol 1997;30:377-383.*
18. Nagueh SF, Mikati I, Weilbaecher D, Reardon MJ, Al-Zaghrini GJ, Cacela D, He ZX, Letsou G, Noon G, Howell JF, Espada R, Verani MS, Zoghbi WA. Relation of the contractile reserve of hibernating myocardium to myocardial structure in humans. *Circulation 1999;100:490-496.*
19. Wijns.W, Vatner SF, Camici PG. Mechanisms of disease: Hibernating myocardium. *N Engl J Med 1998;339:173-181.*
20. Chen L, Ma L, de Prada VA, Chen M, Feng YJ, Waters D, Gillam L, Chen C. Effects of beta-blockade and atropine on ischemic responses in left ventricular regions subtending coronary stenosis during dobutamine stress echocardiography. *J Am Coll Cardiol 1996;28:1866-1876.*
21. Fioretti PM, Poldermans D, Salustri A, Forster T, Bellotti P, Boersma E, McNeill AJ, El-Said ES, Roelandt JRTC. Atropine increases the accuracy of dobutamine stress echocardiography in patients taking beta-blockers. *Eur Heart J 1994;15:355-360.*
22. Marcovitz PA, Armstrong WF. Impact of metoprolol on heart rate, blood pressure, and contractility in normal subjects during dobutamine stress echocardiography. *Am J Cardiol 1997;80:386-388.*
23. Braunwald E. Expanding indications for beta-blockers in heart failure. *N Engl J Med 2001 31;344:1711-1712.*

24. Tendera M, Ochala A. Overview of the results of recent beta-blocker trials. *Curr Opin Cardiol 2001 May;16(3):180-185.*
25. Boersma E, Poldermans D, Bax JJ, Steyerberg EW, Thompson IR, Banga JD, van De Ven LL, van Urk H, Roelandt JR. Predictors of cardiac events after major vascular surgery: Role of clinical characteristics, dobutamine echocardiography, and beta-blocker therapy. *JAMA 2001;285:1865-1873.*
26. Consensus development conference on the diagnosis of coronary heart disease in people with diabetes: 10-11 February 1998, Miami, Florida. American Diabetes Association. *Diabetes Care 1998;21:1551-1559.*
27. Elhendy A, Arruda AM, Mahoney DW Pellikka PA. Prognostic stratification of diabetic patients by exercise echocardiography. *J Am Coll Cardiol 2001;37:1551-1557.*
28. Grundy SM, Benjamin IJ, Burke GL, Chait A, Eckel RH, Howard BV, Mitch W, Smith SC Jr, Sowers JR. Diabetes and cardiovascular disease: a statement for healthcare professionals from the American Heart Association. *Circulation 1999;100:1134-1146.*
29. Haffner SM, Lehto S, Ronnemaa T, Pyorala K, Laakso M. Mortality from coronary heart disease in subjects with type 2 diabetes and in nondiabetic subjects with and without prior myocardial infarction. *N Engl J Med 1998;339:229-234.*
30. Mak KH, Moliterno DJ, Granger CB, Miller DP, White HD, Wilcox RG, Califf RM, Topol EJ. Influence of diabetes mellitus on clinical outcome in the thrombolytic era of acute myocardial infarction. GUSTO-I Investigators. Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries. *J Am Coll Cardiol 1997;30:171-179.*
31. Natali A, Vichi S, Landi P, Severi S, L'Abbate A, Ferrannini E. Coronary atherosclerosis in type II diabetes: angiographic findings and clinical outcome. *Diabetologia 2000;43:632-641.*
32. Kang X, Berman DS, Lewin HC, Cohen I, Friedman JD, Germano G, Hachamovitch R, Shaw LJ. Incremental prognostic value of myocardial perfusion single photon emission computed tomography in patients with diabetes mellitus. *Am Heart J 1999;138(6 Pt 1):1025-1032*
33. Mark DB, Shaw L, Harrell FE Jr, Hlatky MA, Lee KL, Bengtson JR, McCants CB, Califf RM, Pryor DB. Prognostic value of a treadmill exercise score in outpatients with suspected coronary artery disease. *N Engl J Med 1991;325:849-853.*
34. Ellestad MH, Wan MK. Predictive implications of stress testing. Follow-up of 2700 subjects after maximum treadmill stress testing. *Circulation 1975;51:363-369.*
35. May O, Arildsen H, Damsgaard EM, Mickley H. Cardiovascular autonomic neuropathy in insulin-dependent diabetes mellitus: prevalence and estimated

risk of coronary heart disease in the general population. *J Intern Med 2000;248:483-491.*

36. Zarich S, Waxman S, Freeman RT, Mittleman M, Hegarty P, Nesto RW. Effect of autonomic nervous system dysfunction on the circadian pattern of myocardial ischemia in diabetes mellitus. *J Am Coll Cardiol 1994;24:956-962.*
37. Nesto RW, Phillips RT, Kett KG, Hill T, Perper E, Young E, Leland OS Jr. Angina and exertional myocardial ischemia in diabetic and non-diabetic patients: assessment by thallium scintigraphy. *Ann Intern Med 1988;108:170-175.*
38. Schaper NC, Nabuurs-Franssen MH, Huijberts MS. Peripheral vascular disease and type 2 diabetes mellitus. *Diabetes Metab Res Rev 2000;16:S11-S15.*
39. Elhendy A, van Domburg RT, Poldermans D, Bax JJ, Nierop PR, Geleijnse ML, Roelandt JR. Safety and feasibility of dobutamine-atropine stress echocardiography for the diagnosis of coronary artery disease in diabetic patients unable to perform an exercise stress test. *Diabetes Care* 1998;21:1797-1802.
40. Bates JR, Sawada SG, Segar DS, Spaedy AJ, Petrovic O, Fineberg NS, Feigenbaum H, Ryan T. Evaluation using dobutamine stress echocardiography in patients with insulin-dependent diabetes mellitus before kidney and/or pancreas transplantation. *Am J Cardiol 1996;77:175-179.*
41. Hendel RC, Parker MA, Wackers FJ, Rigo P, Lahiri A, Zaret BL. Reduced variability of interpretation and improved imaging quality with a technetium 99m labelled tetrofosmin. *J Nucl Cardiol 1994;1:509-514.*
42. Khattar RS, Hendel RC, Crawley JC, Wackers FJ, Rigo P, Zaret BL, Sridhara BS, Lahiri A. Improved diagnostic accuracy of planar imaging with technetium-99m labelled tetrofosmin compared with thallium-201 for the detection of coronary artery disease. *J Nucl Cardiol 1997;4:291-297.*
43. Wu JC, Yun JJ, Heller EN, Dione DP, DeMan P, Liu YH, Zaret BL, Wackers FJ, Sinusas AJ. Limitation of dobutamine for enhancing flow heterogeneity in the presence of single coronary stenosis: implication for technetium 99m sestamibi imaging. *J Nucl Med 1998;39:417-425.*
44. Calnon DA, Glover DK, Beller GA, Vanzetto G, Smith WH, Watson DD, Ruiz M. Effects of dobutamine stress on myocardial blood flow, 99m Tc sestamibi uptake, and systolic wall thickening in the presence of coronary artery stenosis: implication for dobutamine stress testing. *Circulation 1997;96:2353-2360.*
45. Shanoudy H, Raggi P, Beller GA, Soliman A, Ammermann EG, Kastner RJ, Watson DD. Comparison of technetium 99m tetrofosmin and thallium 201 single photon emission computed tomography imaging for detection of myocardial perfusion defects in patients with coronary artery disease. *J Am Coll Cardiol 1998;31:331-337.*

46. Hays JT, Mahmarian JJ, Cochran AJ, Verani MS. Dobutamine thallium 201 tomography for evaluation patients with suspected coronary artery disease unable to undergo exercise or vasodilator pharmacologic stress testing. *J Am Coll Cardiol 1993;21:1583-1590.*
47. Dakik HB, Vemphaty H, Verani MS. Tolerance, haemodynamic changes and safety of dobutamine stress perfusion imaging. *J Nucl Cardiol 1996;3:410-414.*
48. Joint National Committee. The sixth report of the Joint National Committee on prevention, detection, evaluation and treatment of high blood pressure. *Arch Int Med 1997;157:2413-2446.*
49. Houghton JL, Frank MJ, Carr AA, von Dohlen TV, Prisant LW. Relation among impaired coronary flow reserve, left ventricular hypertrophy and thallium perfusion defects in patients without obstructive coronary artery disease. *J Am Coll Cardiol 1990;15:43-51.*
50. Aguirre JM, Rodriguez E, Ruiz de Azua E, Urrengoetxea J, Faus JM, Caso R, Iriarte M. Segmentary coronary reserve in hypertensive patients with echocardiographic left ventricular hypertrophy, gammagraphic ischemia and normal coronary angiography. *Eur Heart J 1993;14:2:25-31.*
51. Gibbons RJ, Balady GJ, Beasley JW, Bricker JT, Duvernoy WF, Froelicher VF, Mark DB, Marwick TH, McCallister BD, Thompson PD Jr, Winters WL, Yanowitz FG, Ritchie JL, Cheitlin MD, Eagle KA, Gardner TJ, Garson A Jr, Lewis RP, O'Rourke RA, Ryan TJ. ACC/AHA guidelines for exercise testing. A report of the American College of Cardiology/American Heart Association Task Forse of Practice Guidelines/Committee on Exercise Testing. *J Am Coll Cardiol 1997:30;260-311.*
52. Iskandrian AS, Heo J. Technetium-labelled myocardial imaging agents. *Int J Card Med 1992;8:277-287.*
53. Berman DS, Kiat H, Van train K, Garcia E, Friedman J, Maddahi J. Technetium 99m sestamibi in the assessment of chronic coronary artery disease. *Semin Nucl Med 1991;21:190-212.*
54. Margonato A, Mailhac A, Bonetti F, Vicedomini G, Fragasso G, Landoni C, Lucignani G, Rossetti C, Fazio I, Chierchia SL. Exercise-induced ischemic arrhythmias in patients with previous myocardial infarction: role of perfusion and tissue viability. *J Am Coll Cardiol 1996;27:593-598.*
55. Tsuji H, Iwasaka T, Sugiura T, Shimada T, Nakamori H, Kimura Y, Inada M. Relationship between redistribution on exercise-thallium 201 imaging and repetitive ventricular premature beats in patients with recent myocardial infarction. *Am Heart J 1991;121:1679-1684.*

56. Henry RL, Kennedy GT, Crawford MH. Prognostic value of exercise-induce ventricular ectopic activity for mortality after acute myocardial infarction. *Am J Cardiol 1987:59:1251-1255.*
57. Sung RJ, Huycke EC, Lai WT, Tseng CD, Chu H, Keung EC. Clinical and electrophysiologic mechanisms of exercise induced ventricular tachyarrhytmias. *Pacing Clin Electrophysiol 1988;11:1347-1357.*
58. Reinke A, Michel D, Mathes P. Arrhytmogenic potential of exercise induced myocardial ischemia. *Eur Heart J 1987;8 (suppl G):119-124.*

SAMENVATTING

In het eerste deel van dit proefschrift worden toepassingen van een nieuwe echocardiografische techniek, second harmonic imaging geëvalueerd bij patiënten met coronairlijden. Deze nieuwe techniek is bestudeerd tijdens dobutamine stress echocardiografie. Stress echocardiografie wordt steeds vaker gebruikt voor de functionele diagnostiek van coronairlijden en aantonen van myocardvitaliteit. Een van de belangrijkste tekortkomingen van stress echocardiografie, wanneer gebruik wordt gemaakt van fundamental imaging, is de sub-optimale beeld kwaliteit. Dit kan leiden tot een verminderde sensitiviteit alsmede ook een grote variabiliteit in beoordeling van het onderzoek. Second harmonic imaging verbetert de echo kwaliteit. Dit heeft potentiële voordelen bij dobutamine stress echocardiografie. Immers tijdens stress echocardiografie worden wandbewegingen bestudeerd. Hierbij is vooral de verdikking van het endocard van belang. Juist deze verbeterde visualisatie van het endocard is mogelijk van belang voor betere diagnostiek van myocardischemie en myocardvitaliteit.

In het tweede gedeelte van het proefschrift worden toepassingen van myocard scintigrafie besproken, die gebruikt kunnen worden voor de diagnostiek en prognose van coronairlijden.

In hoofdstuk 2 wordt de visualisatie van het endocard van het linker ventrikel bestudeerd tijdens dobutamine stress echocardiografie, zowel met fundamental imaging als second harmonic imaging bij dezelfde patiënten. Tijdens second harmonic imaging trad er een duidelijke verbetering op van de visualisatie van het endocard ten opzichte van fundamental imaging. Dit verschil was aanwezig tijdens de rust opname en werd nog duidelijker tijdens lage dosis dobutamine en tijdens "piek stress". Dit leidde tot een betere detectie van coronairlijden tijdens dobutamine stress echocardiografie. Dit werd in hoofdstuk 3 aangetoond door een dobutamine stress echocardiografie te verrichten gebruik makend van zowel fundamental imaging als second harmonic imaging. Tijdens dobutamine stress echocardiografie met gebruik van second harmonic imaging nam de sensitiviteit voor de detectie van coronairlijden toe, vooral voor één-taks coronairlijden. Dit trad vooral op in het stroomgebied van de circumflex arterie. De specificiteit bleef onveranderd wanneer de dobutamine stress echocardiografie gebruik maakte van second harmonic imaging.

Naast de verbetering van de sensitiviteit voor de detectie van coronairlijden was ook de detectie van myocardvitaliteit verbeterd tijdens

second harmonic imaging. Immers de detectie van vitaliteit berust op de aanwezigheid van een verbeterde contractie en vooral verdikking van het endocard tijdens lage dosis dobutamine en een verslechtering van wandbewegingen tijdens "piekstress". In hoofdstuk 4 werd de detectie van myocardvitaliteit bestudeerd met dobutamine stress echocardiografie bij patiënten met een gestoorde linker ventrikel functie, waarbij een gecombineerde nucleaire perfusie en metabolisme techniek de "gouden standaard" was. De overeenkomst met de nucleaire techniek nam toe tijdens dobutamine stress echocardiografie met second harmonic imaging ten opzichte van fundamental imaging voor het aantonen van vitaal myocardweefsel.

In hoofdstuk 5 werd de invloed van bètablokkers op het aantonen van vitaal myocardweefsel bestudeerd tijdens dobutamine stress echocardiografie. Bètablokkers worden steeds vaker voorgeschreven, ook bij hartfalen patiënten. Juist deze patiënten hebben baat bij het aantonen van dysfunctioneel, maar vitaal myocardweefsel, daar na coronairrevascularizatie een verbeterde functie kan optreden. Bètablokkers beïnvloeden de detectie van vitaal myocardweefsel. De verbeterde contractie response treedt op bij een hogere infusie dosis, 10 µg/kg/minuut in plaats van 5 µg/kg/min bij dezelfde patiënten zonder bètablokkers. Naast een verschuiving van de "dose-response" curve trad ook in een aantal dysfunctionele segmenten geen verbeterde contractie op onder bètablokkers, terwijl een nucleair onderzoek wel vitaliteit liet zien. Bètablokkers beïnvloeden dus de detectie van vitaal myocardweefsel, indien er twijfel is of de individuele patiënt voldoende vitaal myocardweefsel heeft om een revascularizatie uit te voeren, dan dient men dit onderzoek te herhalen nadat de bètablokkers zijn gestopt.

De prognostische waarde van dobutamine stress echocardiografie bij patiënten met diabetes mellitus is nog onvoldoende onderzocht. In hoofdstuk 6 wordt de aanvullende waarde van dobutamine stress echocardiografie voor het voorspellen van late cardiale complicaties bestudeerd. Klinische risico factoren zoals hartfalen en een oud myocardinfarct zijn gerelateerd aan late cardiale complicaties. Resultaten van dobutamine stress echocardiografie geven extra, onafhankelijke informatie. De aanwezigheid van afwijkingen in rust alsmede de aanwezigheid van stress geïnduceerde ischemie verhogen de kans op late complicaties en identificeert een hoog-risico populatie.

In de volgende hoofdstukken worden studies met perfusie scintigrafie beschreven. In hoofdstuk 7 wordt de vergelijking beschreven tussen echocardiografie en sestamibi SPECT tijdens dobutamine infusie voor de diagnostiek van één-taks coronairlijden. Ischemie tijdens het onderzoek, aangetoond door respectievelijk wandbewegingsstoornissen en perfusie defecten laat een vergelijkbare sensitiviteit zien.

In een volgende studie, hoofdstuk 8, werd 99m-technetium-tetrofosmin SPECT met dobutamine stress, geëvalueerd voor de diagnose van coronairlijden bij patiënten met een verminderde inspannings capaciteit. In deze groep patiënten had de test een uitstekende sensitiviteit voor de detectie van coronairlijden. In een volgend hoofdstuk 9, wordt de invloed van hypertensie op deze test bestudeerd. De aanwezigheid van hypertensie en linker ventrikelhypertrofie, had geen invloed op de test voor het aantonen van coronairlijden.

Tijdens perfusie scintigrafie met inspanning kunnen hartritmestoornissen ontstaan. Deze kunnen gerelateerd zijn aan de aanwezigheid van coronairlijden. Bij patiënten met een lage kans op coronairlijden kan dit een extra aanwijzing zijn naast perfusie defecten voor de aanwezigheid van coronairlijden. Inderdaad laat deze studie zien dat het optreden van hartritmestoornissen vaker voorkomt bij patiënten met coronairlijden. Naast perfusie defecten komen ook ECG afwijkingen tijdens het onderzoek, als maat voor myocardischemie, vaker voor bij patiënten met ritmestoornissen. In hoofdstuk 10 wordt beschreven dat patiënten met een beperkte kans op coronairlijden een hogere kans hebben op een positieve test met perfusie defecten als er hartritmestoornissen optreden. Ook bij patiënten die na een myocardinfarct worden geanalyseerd voor ischemie en myocardvitaliteit, zijn hartritmestoornissen tijdens inspanning gerelateerd aan complicaties op lange termijn als uiting van coronairlijden. Patiënten met hartritmestoornissen hebben dan ook een hogere kans op late cadiale complicaties (hoofdstuk 11).

List of abbreviations

DSE	dobutamine stress echocardiography
FI	fundamental imaging
SHI	second harmonic imaging
MI	myocardial infarction
CAD	coronary artery disease
ECG	electrocardiographic
WMSI	wall motion score index
WMA	wall motion abnormalities
BBL	beta-blockers
ACE	angiotensin converting enzyme
DISA	dual isotope simultaneous acquisition
SPECT	single photon emission computed tomography
MIBI	technetium-methoxyisobutyl isonitrile
PET	positron emission tomography
LAD	left anterior descending artery
LCx	left circumflex artery
RCA	right coronary artery
PTCA	percutaneous transluminal coronary angioplasty
SA	short-axis
HLA	horizontal long-axis
VLA	vertical long-axis
LV	left ventricle
IVS	interventricular septal thickness
LVID	left ventricular internal dimension
PWT	left ventricular posterior wall thickens
NS	non significant
HR	hazard ratio
CI	confidence interval
SD	standard deviation
n	number

ACKNOWLEDGMENTS

The time I have spent at the Thoraxcentre in Rotterdam has been an incomparable and rich experience for me. Back in 1999, when I started the fellowship at the Thoraxcentre, I did not realise that it would change my work—and even my life—so completely. This period of time has been for me an intense one of engaging in research; of learning; of experiencing life, especially life in a different culture; and of speaking a different language. Now, at thirty years of age, I relate to a different reality than that with which my Italian background had endowed me. It has been ultimately a special type of journey: a journey into the scientific world, into life—and inward and toward myself. Here, I would like to take the opportunity to thank all the people who made this experience one of the most exciting and fruitful of my life.

First of all, I am deeply indebted to Professor Jos Roelandt for his support and encouragement for my research. He provided me the opportunity to work at the Thoraxcentre and to pursue a PhD degree; he expanded my vision in clinical research with sharp insight and valuable highlights; and he always guided me with constructive advice. Also, I would like to express deep appreciation to my co-promoter Dr Don Poldermans. His meticulous supervision of the design and presentation of studies was of great importance in accomplishing my research objectives, and his good sense of humour and optimistic outlook created a friendly and positive working atmosphere.

My deep appreciation also goes to Dr Abdou Elhendy, whose collaboration was of great importance in accomplishing my work. I am grateful to Dr Ron van Domburg and Dr. Eric Boersma for their excellent statistical support, and to Dr Jeroen Bax, who deserves my special thanks for his expert scientific opinions.

I also acknowledge gratefully Dr Folkert Ten Cate, chief of the Echolab, for his high scientific criticism of my research. I would like to give my special thanks to Wim Vletter, chief of the echo technicians, and to all the sonographers—Jackie McGhie, Debby van Dongen, Marianne Vaneker, Elly Hagman, Veronica Linkers, Hans Brandeburg, and Mieke Berghout—for their support of my projects

and for creating a friendly atmosphere at work. A heartfelt thanks also goes to Dr Spitaels, Dr Meijbon and Dr. Roos of the congenital cardiology unit, and to Dr Jan Gevers and Dr Tina De Bakker and all the staff members and colleagues at the Thoraxcentre.

I am grateful to Mrs. Virginie Poldermans, who is my paranymph; she cared a lot about me during my stay in Rotterdam. My gratitude also goes to Dr Eleni Vourvouri for the scientific contribution to my research, for being my paranymph, and, moreover, for being a good friend.

To Dr Arend Schinkel and to Dr Yohan De Sutter, deep thanks for the scientific co-operation and the friendly support.

Thanks to Ad van Drunen, Willeke Korpershoek, Arita Orgers and Miranda Broeders for their timely help with the daily administration, and to Rene Frowijn and Jan Tuin for their invaluable technical help with the computer. I owe my thanks to Dr Willelm de Jong and to Mrs. Marianne Einckoz for helping in the management of the bureaucratic aspect of the thesis, and to Dr Nico Bruining for his helpful suggestions related to the issue of printing the thesis.

Thanks also to Dr Simona Boito, Dr Yolanda Del Diego, Dr Maria Daniel, Dr Ingrid Senden, Dr Robert Van Der Helm, Dr Diego Ferone, Dr Evelyn Regar, Dr Alex Wardek, Dr Lubov Koroleva and Dr Georgos Sianos, who have been not only colleagues, but also friends. Thanks to Dr Youssef Nosir, Dr Jiefen Yao, Dr Anita Dall'Agata, Dr Riccardo Rambaldi—all colleagues who achieved this objective before I did.

During my medical school and specialisation studies in Italy, I was lucky to have had many great mentors guiding my way. I would also like to take this special opportunity to express my gratitude to them. My deep thanks go to Professor Alberico Borghetti, who encouraged my research project from the first day; to Professor Ettore Astorri, Professor Federico Raschi and Professor Ettore Lazzeroni, who inspired my interest in cardiology and in echocardiography; and to Professor Diego Ardissino for being a committee member for my thesis defence and for the judgement of my thesis. I would especially like to remember

here the late Professor Giorgio Olivetti, who was the first person who showed me how to do research.

I consider all my achievements the results of the love, support and understanding I received from my family. My father and mother taught my brothers and me perseverance and self-confidence. Above all, we learned to believe that we each had a gift for something and that that gift should be developed. I dedicate this work to my parents and to my brothers, Alessandro, Daniele and Tommaso. They have encouraged me in all my choices and have always been with me and supporting me.

During my stay in Rotterdam I have had the good fortune to realise how people can be so apparently different (in culture, language, education) but so ultimately similar. Here, I would like to thank those real friends I made in the Netherlands who taught me this, giving me their support, trust and help. Many thanks also to the friends I left in Italy, who have been supporting me during this time away.

Last, but definitely not least, I thank God for everything.

CURRICULUM VITAE

FABIOLA ANNA MARGHERITA ALESSANDRA SOZZI

Address: Via Roma 20, Formigara,
26020 Cremona, Italy
E-mail: Fabiola_Sozzi@hotmail.com

Date of birth: 12 December 1970
Place of birth: Italy

Education and Professional Experience

1989 **Secondary School, Cremona, Italy**
High School Diploma (graduated cum laude)

1990 **Conservatory of Music A. Boito, Parma, Italy**
Piano Diploma

1989-1996 **Medical School, Parma University, Parma, Italy**
Doctor of Medicine (graduated cum laude)

1996 **Medical School, Parma University, Parma, Italy**
Licence to practice as a medical doctor (graduated magna cum laude)

1996-2000 **School of Specialisation in Cardiology, Parma University, Parma, Italy**
Master's Degree in Cardiology (graduated magna cum laude)

1999–2001 **Thorax Center, Academisch Ziekenhuis Dijkzigt, Rotterdam, Netherlands**
Research Fellow in Echocardiography Laboratory

Additional Distinctions

2000 Member of the European Society of Cardiology's working group on echocardiography

2000 Doctorate candidate in cardiovascular physiology from the Tor Vergata University, Rome, Italy

Publications

Sozzi FB, Poldermans D, Boersma E, Elhendy A, Bax JJ, Borghetti A, Roelandt JRTC. Does second harmonic imaging improves left ventricular endocardial border identification at higher heart rates during dobutamine stress echocardiography? *J Am Soc Echocard 2000;13:1019-1024.*

Sozzi FB, Poldermans D, Bax JJ, Boersma E, Vletter W, Borghetti A, Roelandt JRTC. Second harmonic imaging improves sensitivity of dobutamine stress echocardiography for the detection of coronary artery disease. *Am Heart Journal 2001,142:153-159.*

Sozzi FB, Poldermans D, Bax JJ, Elhendy A, Vourvouri E, Borghetti A, Roelandt JRTC. Improved identification of viable myocardium using second harmonic imaging during dobutamine stress echocardiography: comparison with Fluorine-18 Fluorodeoxyglucose SPECT. *Heart, in press.*

Sozzi FB, Poldermans D, van Domburg R, Bax JJ, Elhendy A, Borghetti A, Roelandt JRTC. Prognostic value of dobutamine stress echocardiography in patients with diabetes mellitus. *Am J Med 2001, submitted.*

Poldermans D, **Sozzi FB**, Bax JJ, Boersma E, Vletter W, Vourvouri E, Elhendy A, Roelandt JRTC. Does beta-blockade therapy limit the assessment of viable myocardium during dobutamine stress echocardiography in patients with severe left ventricular dysfunction? *Am J Cardiol 2001, 88:68-70.*

Elhendy A, **Sozzi FB**, van Domburg R, Vantripont P, Valkema R, Krenning E, Roelandt JRTC. Accuracy of dobutamine tetrofosmin myocardial perfusion SPECT imaging for the noninvasive diagnosis of transplant coronary artery stenosis. *J Heart Lung Transplant 2000;19:360-366.*

Poldermans D, Bax JJ, Elhendy A, **Sozzi F**, Boersma E, Thomson IR, Jordaens L. Long-term prognostic value of dobutamine stress echocardiography in patients with atrial fibrillation. *Chest 2001;119:144-149.*

Elhendy A, van Domburg R, Bax J, Poldermans D, **Sozzi FB**, Roelandt JRTC. Accuracy of dobutamine 99m-technetium sestamibi SPECT imaging for the diagnosis of single vessel coronary artery disease. Comparison with echocardiography. *Am Heart J 2000;86:723-730.*

Elhendy A, **Sozzi FB**, Valkema R, Bax J, van Domburg R, Krenning E, Roelandt JRTC. Dobutamine 99m-technetium tetrofosmin SPECT imaging for the diagnosis of coronary artery disease in patients with limited exercise capacity. *Am J Cardiol 2000;86:723-729.*

Elhendy A, van Domburg R, **Sozzi FB**, Bax J, Fioretti P, Roelandt JRTC. Impact of hypertension on the accuracy of exercise stress 99m-technetium sestamibi SPECT for the diagnosis of the coronary artery disease. *Heart 2001;85:655-661.*

Elhendy A, **Sozzi FB**, van Domburg R, Bax J, Fioretti P, Roelandt JRTC. Relation among exercise induced ventricular arrhythmias, ischemia and viability late after acute myocardial infarction. *J Nucl Cardiol 2000;7:649-654.*

Elhendy A, **Sozzi FB**, van Domburg R, Bax J, Poldermans D, Valkema R, Roelandt JRTC. Relation between exercise induced ventricular arrhythmias and myocardial perfusion abnormalities in patients with intermediate pre-test probability of coronary artery disease. *Eur J Nuclear Med 2000;27:327-332.*

Elhendy A, **Sozzi FB**, van Domburg R, Valkema R, Bax J, Roelandt JRTC. Accuracy of exercise stress 99m-technetium sestamibi SPECT imaging in the evaluation of the extent and location of coronary artery disease in patients with earlier myocardial infarction. *J Nucl Cardiol 2000;7:432-438.*

Elhendy A, van Domburg R, Vantrimpont P, **Sozzi FB**, Roelandt JRTC, Maat LP, Balk AH. Impact of heart transplantion on the safety and feasibility of dobutamine stress test. *J Heart Lung Transplant 2001;20:399-406.*

Vourvouri E, De Sutter J, Poldermans D, **Sozzi FB**, Roelandt JRTC. Experience with an ultrasound stethoscope. *J Am Soc Echocard 2001, in press.*

Vourvouri E, Poldermans D, Schinkel A, **Sozzi FB,** Bax JJ, Roelandt JRTC. Experience with ultrasound stethoscope for abdominal aneurysm. *Eur J Vasc Endovasc Surg 2001, in press.*

Vourvouri EC, Poldermans D, Bax JJ, Sianos G, **Sozzi FB,** Schinkel AFL, De Sutter J, Parcharidis G, Valkema R, Roelandt JRTC. Evaluation of left ventricular function and volumes in patients with ischemic cardiomyopathy: gated single photon emission computed tomography versus 2D echocardiography. *Eur J Nucl Med 2001, in press.*

Elhendy A, **Sozzi FB**, Poldermans D, Van Domburg R, Bax JJ, Roelandt JRTC. Myocardial ischemia as a predictor of cardiac death in patients with heart failure. *J Am Coll Cardiol 2001, submitted.*

Vourvouri EC, Poldermans D, Schinkel A, Koroleva L, **Sozzi FB**, Bax JJ, Parcharidis G, Roelandt JRTC. Screening for left ventricular hypertrophy using a hand-held ultrasound device. *J Hypertens 2001, submitted.*

Schinkel AFL, Bax JJ, **Sozzi FB,** Boersma E, Valkema R, Elhendy A, Roelandt JRTC, Poldermans D. Prevalence of myocardial viability assessed by single-photon emission computed tomography in patients with chronic ischemic left ventricular dysfunction. *J Am Coll Cardiol 2001, submitted.*

De Sutter J, Poldermans D, Vourvouri E, Domburg R, Elhendy A, Bax J, **Sozzi FB**, Jordaens L, Roelandt JRTC. Long-term prognostic significance of complex ventricular arrhythmias induced during dobutamine stress echocardiography. *J Am Coll Cardiol 2001, submitted.*

Schinkel AFL, Bax JJ, Elhendy A, Valkema R, van Domburg R, Vourvouri EC, **Sozzi FB**, Roelandt JRTC, Poldermans D. Dobutamine induced contractile reserve in stunned, hibernating, and necrotic myocardium in patients with ischemic cardiomyopathy. *Eur J Nucl Med 2001, submitted.*

ABSTRACTS

Thirty abstracts presented at scientific sessions (American Heart Association; American College of Cardiology, European Society of Cardiology, Euroecho, European Association of Nuclear Medicine, International Nuclear Meeting, Italian Society of Cardiology, Greek Society of Cardiology).

WITH THANKS TO:

Pfizer Italy
Medi-Trade
Yamanouchi Pharma
Bayer