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DOBUTAMINE STRESS
ECHOCARDIOGRAPHY:
BEYOND
TRADITIONAL USES

**Dobutamine stress echocardiography:
beyond traditional uses**

**Dobutamine stress echocardiografie:
voorbij traditioneel gebruik**

Thesis

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CHAPTER 1

PREFACE AND OUTLINE OF THE THESIS



PREFACE

Echocardiography is the most attractive and patient-friendly technique for the non-invasive imaging of the heart. Because of the several limitations of standard exercise testing, echocardiography combined with exercise or pharmacologic stress has emerged as a highly feasible, safe, and inexpensive method for the identification of myocardial ischemia and assessment of prognosis.^{1,2}

In patients who either cannot exercise or can exercise submaximally, or when the question is the evaluation of myocardial viability, dobutamine stress echocardiography represents an alternative and exercise-independent stress modality.³ Dobutamine acts on alpha-adrenergic as well as beta-adrenergic receptors of the heart and vessels.^{4,5} The net effect on the heart is an enhanced inotropy and chronotropy. This effect in turn stimulates myocardial oxygen demand and leads to reproduction of ischemia in myocardial regions perfused by severely diseased coronary arteries.^{6,7}

Low rates of dobutamine infusion induce systolic thickening of dyssynergic but viable myocardium.⁸ Resting dyssynergy can be either a sign of subendocardial infarction (scarred tissue), normally perfused but dysfunctional (stunned) myocardium, or chronically hypoperfused (hibernating) myocardium.⁹⁻¹¹ Additionally, an underlying non-ischemic cardiomyopathy may produce diffuse and, less often, segmental dyssynergy.^{12,13} Depending on the cause of resting dyssynergy, myocardium may respond differently after dobutamine challenge. The response can be one of the following: (1) non improvement of systolic thickening when dyssynergic myocardium is not viable (scarred tissue), (2) initial improvement at low-dose infusion and worsening at higher rates of infusion (a response called biphasic), when significantly stenotic coronary arteries lead to myocardial oxygen supply-demand mismatch, and (3) sustained improvement that remains even at high rates of dobutamine infusion, when viable non-ischemic myocardium persists, or when resting dyssynergy is not caused by coronary artery disease (as is the case in idiopathic dilated cardiomyopathy).

Non-traditional applications of dobutamine stress echocardiography

The applicability of dobutamine stress echocardiography can be extended beyond the traditional uses mentioned so far. Low-dose dobutamine infusion has been investigated as a means to reveal myocardial dysfunction that is not obvious at rest. Several cardiotoxic drugs, such as anthracyclines, may produce myocardial damage. Cardiomyopathy caused by these agents is a field in which dobutamine stress echocardiography may have a role.¹⁴⁻¹⁶ Another application is the assessment of the severity of aortic stenosis in patients with low transaortic gradient and poor left ventricular function. In this setting, dobutamine stress echocardiography has been applied to help in decision making, when there is not clear whether left ventricular dysfunction is primary or secondary to severe aortic stenosis.¹⁷⁻¹⁹ Contractile reserve, i.e. the ability of abnormal myocardium to show enhanced contractile response under the influence of stressors such as dobutamine, can be used to correlate certain non-invasive indices with viability of dyssynergic myocardium. Such an example is the correlation of prolonged QT dispersion on surface 12-lead ECG with irreversibly damaged myocardium in patients with ischemic cardiomyopathy.²⁰ Finally, the utility of the recently evolving percutaneous injection of autologous skeletal myoblasts in patients with previous myocardial infarction can be defined by assessing regional contractile reserve induced by low-dose dobutamine challenge.²¹

Quantification of dobutamine stress echocardiography

In spite of its broad use, dobutamine stress echocardiography remains a quite subjective technique. This characteristic affects its diagnostic accuracy and reproducibility, especially during the learning curve of a non-expert operator. A quantitative approach would be able to address some of the limitations of the qualitative approach. Several methods have been proposed to quantify myocardial regional motion, such as the centerline technique, the automated border recognition method, and

the tissue Doppler technique. Tissue Doppler measures myocardial displacement (pulsed-wave and color Doppler tissue imaging) or deformation (strain and strain rate imaging). At the moment, none of these methods has been applied in daily clinical care, with the exception of pulsed-wave and color tissue Doppler imaging. Currently, these modalities are considered quite feasible, as far as data acquisition and evaluation is concerned. In addition, tissue Doppler imaging is available in almost all modern cardiac ultrasound machines, making it easy to apply even in non-specialized echocardiographic departments. Compared to the other quantitative techniques, pulsed-wave tissue Doppler has an additional advantage, i.e. the capability of on-line analysis, thus providing a quick estimation of regional and global myocardial performance.

Utility of pulsed-wave tissue Doppler

Pulsed-wave tissue Doppler allows the measurement of instantaneous regional myocardial velocities with high temporal resolution, and it has been shown quite effective in assessing stress-induced changes of systolic and diastolic regional myocardial velocities.²² It is usually independent of the image quality, hence it can be performed and analyzed even in patients with poor echocardiographic windows. In that way, evaluation of contractility and diastolic relaxation is feasible in the majority of patients (Figure 1).

The change in resting systolic velocity that occurs during low-dose dobutamine infusion has shown a good correlation with the amount of myocardial contractile reserve (Figures 2a and 2b). Low rates of infusion have the potential to enhance contractility of viable regions, whereas higher rates of infusion may produce ischemia with subsequent deterioration of systolic function. Notably, at low-dose dobutamine infusion, induction of ischemia, which is the result of increased myocardial oxygen demand (increased inotropy) and reduced oxygen supply (increased chronotropy), is rarely seen.²³⁻²⁵

Two-dimensional echocardiography allows the assessment of left ventricular function at systole, but does not provide information on the

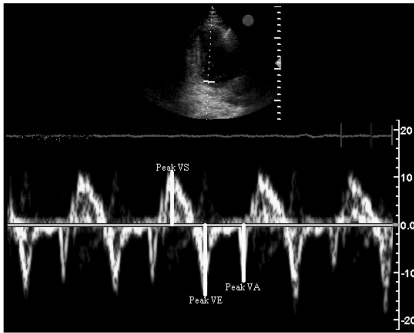


Figure 1. Pulsed-wave tissue Doppler imaging from the apical two-chamber view, with the sample positioned near the mitral annulus. Normal tracing. VS, systolic velocity; VE, early diastolic velocity; VA, atrial-assisted (late) diastolic velocity. Manolis Bountiukos, MD.

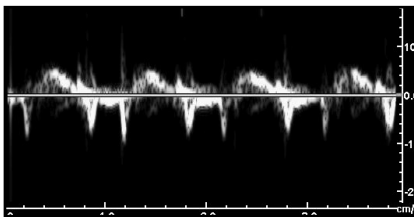


Figure 2a. Pulsed-wave tissue doppler tracing at rest, in a patient with chronic coronary artery disease. Systolic velocity is 6 cm/s.

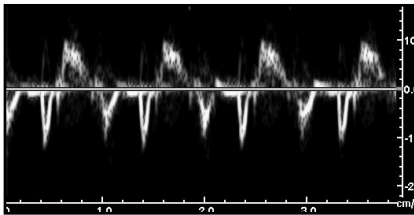


Figure 2b. Pulsed-wave tissue Doppler tracing from the same patient during low-dose dobutamine infusion. Systolic velocity increased (10 cm/s), indicating the presence of myocardial contractile reserve in

that region. Manolis Bountiukos, MD.

diastolic properties of myocardium. Pulsed-wave Doppler of mitral inflow has been used extensively in clinical practice to study diastolic function. However, during the so-called stage of pseudo-normalization of diastolic function, which sometimes follows the stage of abnormal relaxation, the waveform of mitral inflow may mimic the normal mitral inflow pattern. By using tissue Doppler imaging, pseudo-normalization can be differentiated from normal diastolic function (Figures 3a and 3b).

Figure 3a. Pulsed-wave Doppler of the mitral inflow in a hypertensive patient. The early (E) to late (A) velocity ratio of mitral inflow indicates normal diastolic relaxation ($E>A$).

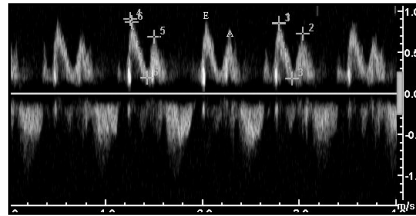
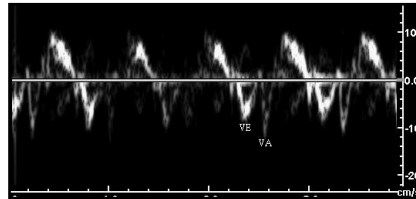


Figure 3b. Pulsed-wave tissue Doppler from the same patient. Diastolic myocardial velocities reveal an abnormal relaxation pattern ($VE<VA$). Manolis Bountiukos, MD.



Quantification of myocardial velocities allows the detection of even minor alterations in myocardial function that could otherwise be undetectable by simple visual estimation of two-dimensional echocardiogram. An example of this application is the evaluation of the influence of statins in patients with a probably diseased endothelium (patients with hypercholesterolemia and peripheral vascular disease), but without known heart disease. This influence can be assessed by the comparison of regional systolic myocardial velocities at rest and during low-dose dobutamine infusion, before and after the treatment with statins.²⁶ Visual estimation of two-dimensional echocardiography would be unable to detect minor changes in patients with normal global contractility of the left ventricle at rest. Likewise, the study of contractile reserve using pulsed-wave tissue Doppler in patients with ischemic cardiomyopathy has shown the potential to delineate different responses of myocardium during dobutamine-induced stress, depending on whether the myocardium under investigation is stunned (normally perfused but dysfunctional) or hibernating (chronically hypoperfused).²⁷ Similarly, differentiation of functional response to dobutamine-induced stress would not be feasible by visual estimation of contractile reserve in stunned and hibernating regions.

Limitations of pulsed-wave tissue Doppler imaging

From a pathologic-anatomic point of view, it is known that the left ventricular subendocardial and subepicardial fibres are oriented longitudinally, whereas the mid-myocardial fibres are oriented in the circumferential direction. Hence, to assess the vectorial sum of velocities of myocardial fibers oriented longitudinally from base to apex data acquisition has to be performed from the apical position.

Heart is a beating organ that moves globally inside the thoracic cavity. The resulting translational and rotational motion of the heart makes difficult the accurate assessment of myocardial velocities. Data acquisition from the apical views can minimize this limitation, since cardiac apex acts as a relatively stable and fixed reference point. However, it is important to ensure that the myocardial segment under investigation remains within the interrogated sample volume throughout the cardiac cycle.

Another limitation of pulsed-wave tissue Doppler is the dependence of the measurements on the angle of incidence between the ultrasound beam and the myocardium under investigation. When the direction of the interrogating beam is more than 20° apart from the direction of the myocardial movement, assessment of velocities cannot be considered reliable. From the apical views, where the longitudinal motion of the myocardial fibres is measured, ultrasound beam can be directed almost in parallel to the basal and mid myocardial segments. However, ultrasound beam cannot be positioned in parallel with the apical segments, and these segments are usually excluded.

A major limitation of tissue Doppler imaging is the dependence of measurements on the tethering effects of adjacent myocardial segments. When an akinetic segment is in close proximity to normally contracting myocardium, velocity in the latter may be underestimated. Inversely, dyssynergic myocardium may show a higher velocity when the adjacent myocardium is normal or hyperkinetic. To overcome this phenomenon, the six-segment model approach (consisted of the six myocardial walls, i.e. anterior, inferior, lateral and posterior wall, and anterior and posterior septum) is preferable. According to this model, the sample is positioned

at the base of each wall near the mitral annulus, and the sum of the velocities of the myocardial fibres directed along the longitudinal axis is estimated. In that way, the estimation of velocities is not segmental, but rather regional, with each region corresponding to a myocardial wall.

In conclusion, the present thesis refers to some alternative utilities of dobutamine stress echocardiography in clinical practise and research, and investigates the value of pulsed-wave tissue Doppler imaging to ameliorate the major disadvantages of dobutamine stress echocardiography, that is qualitative nature and subjectivity of interpretation.

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OUTLINE OF THE THESIS

In Part 1 of the present thesis, applications of dobutamine stress echocardiography in several different clinical aspects are studied.

Anthracyclines are very effective drugs for the treatment of malignant diseases, especially leukaemias and lymphomas. However, cardiotoxicity is a major adverse effect of this medication. Chapter 2 investigates whether repetitive assessment of myocardial wall motion and mitral inflow pattern at rest and during low-dose dobutamine infusion in patients receiving anthracyclines can early predict the development of cardiotoxicity.

Chapters 3 and 4 deal with aortic stenosis. Aortic stenosis is a debilitating condition that is accompanied by severe morbidity and mortality. Perioperative complications and risk for cardiac events and death were studied in patients with aortic stenosis who underwent non-cardiac surgery (chapter 3).

Assessment of the severity of aortic stenosis is not clear in case that

poor left ventricular function coexists, since a low transvalvular gradient does not exclude the presence of severe aortic stenosis. Dobutamine stress echocardiography can be a valuable tool in such patients, since it can discriminate between fixed stenosis demanding valve replacement, and non-significant stenosis, which is treated conservatively. In addition, dobutamine stress echocardiography is a commonly used tool to investigate ischemia and to assess prognosis in patients with mild or moderate aortic stenosis. The safety of dobutamine stress echocardiography in these settings is studied in chapter 4.

The number of patients treated with percutaneous or surgical coronary revascularization is continuously growing. As a result, an increasing number of patients having been revascularized undergo non-invasive stress imaging. Chapter 5 deals with the prognostic value of dobutamine stress echocardiography after surgical or percutaneous coronary revascularization.

QT dispersion on surface ECG is prolonged in numerous cardiac diseases, representing a generalized repolarization abnormality. The hypothesis that non-viable myocardial regions in patients with ischemic cardiomyopathy correspond to increased QT dispersion on surface 12-lead electrocardiogram is tested in chapters 6 and 7. In chapter 6 dobutamine stress echocardiography is used as a reference to assess viability, whereas nuclear scan is used for the same purpose in a similar population in chapter 7.

Transcatheter ablation of the atrio-ventricular (AV) node followed by ventricular pacing has shown to improve symptoms and quality of life of patients with permanent atrial fibrillation. In a considerable number of patients, cardiac function deteriorates after AV node ablation. Dobutamine stress echocardiography was used to determine whether the absence of contractile reserve could identify those patients whose left ventricular function deteriorates after AV node ablation (chapter 8).

Part 2 of the thesis deals with the quantitative analysis of dobutamine stress echocardiography by pulsed-wave tissue Doppler imaging.

Chapter 9 describes the effect of atorvastatin on myocardial

contractile reserve in patients with moderate hypercholesterolemia and peripheral arterial disease. Previous studies have shown that the beneficial effects of statins extend beyond their cholesterol-lowering action. Reversal of endothelial dysfunction may lead to an improvement of flow-dependent coronary vasomotion and enhanced contractile reserve. According to this, contractile reserve was assessed by pulsed-wave tissue Doppler imaging in 26 consecutive patients with normal cardiac function and diseased endothelium, before, six and twelve months after therapy with atorvastatin.

It is well known that the decision to revascularise patients with ischemic cardiomyopathy is based on the existence and extent of viable myocardium. Moreover, stunned myocardium has shown to be more likely to recover after revascularization than hibernating myocardium. Hence, differentiating between stunning and hibernation is of big clinical importance. In chapter 10, pulsed-wave tissue Doppler imaging was used to differentiate between stunned, hibernating, and scarred myocardium in 70 patients with chronic coronary artery disease and low mean left ventricular ejection fraction. Assessment of perfusion (with ^{99m}Tc -tetrofosmin SPECT) and glucose utilization (with ^{18}F fluorodeoxyglucose SPECT) were used to classify dysfunctional regions (assessed by resting two-dimensional echocardiography) as stunned, hibernating or scarred. Subsequently, myocardial systolic velocities were measured in these regions by pulsed-wave tissue Doppler.

Assessment of diastolic function by tissue Doppler is relatively preload-independent. Diastolic dysfunction generally precedes systolic dysfunction in patients with coronary artery disease. Chapter 11 deals with the potential of pulsed-wave tissue Doppler to discriminate between viable and non-viable myocardium in 93 consecutive patients with ischemic cardiomyopathy, by assessing systolic as well as diastolic regional myocardial velocities.

The traditional assumption that Q waves on surface 12-lead ECG indicate the presence of scarred, non-viable myocardium, whereas dysfunctional myocardium that does not correspond to Q waves is always viable, was tested in chapter 12. Eighty-one patients with

previous myocardial infarction were studied using pulsed-wave tissue Doppler imaging. Myocardial velocities were compared in dysfunctional regions with and without Q waves.

Contractile recruitment of myocardium after a premature extrasystolic beat is a well-known phenomenon, based on the Frank-Starling mechanism. According to this mechanism, the strength of myocardial shortening during systole is directly related to the end-diastolic volume of the left ventricle. In chapter 13, the contractile reserve after combined dobutamine infusion and post-extrasystolic potentiation was quantified by pulsed-wave tissue Doppler imaging in a patient with severely depressed left ventricular dysfunction. Nuclear scan assessing glucose utilisation was the reference technique.

Autologous skeletal myoblast transplantation is currently under investigation as a means to improve left ventricular function and to delay remodelling in patients with injured myocardium caused by extensive myocardial infarction. Dobutamine stress echocardiography was one of the means (along with left ventricular angiography, nuclear radiography, and magnetic resonance imaging) to assess left ventricular function in five patients before and after skeletal myoblast transplantation (chapter 14).

CHAPTER 2

REPETITIVE DOBUTAMINE STRESS ECHOCARDIOGRAPHY FOR THE PREDICTION OF ANTHRACYCLINE CARDIOTOXICITY



Source: M Bountiukos, JK Doorduijn, JRTC Roelandt, EC Vourvouri,
JJ Bax, AF Schinkel, MD Kertai, P Sonneveld, D Poldermans
Eur J Echocardiogr 2003 Dec;4(4):300-5. **Adapted**

ABSTRACT

Aims: To evaluate whether repetitive assessment of systolic and diastolic cardiac function by dobutamine stress echocardiography (DSE) can predict anthracycline cardiotoxicity.

Methods and results: Thirty-one patients (age, 57 ± 13 years, 22 male) were studied before chemotherapy, with follow-ups during, at the end, and six months after chemotherapy. Left ventricular (LV) function was assessed by two-dimensional (2D) echocardiographic wall motion score index (WMSI) and by Doppler echocardiography of mitral valve inflow at rest and during DSE. Radionuclide ventriculography was used as an independent reference for ejection fraction (EF). A reduction of $EF \geq 5\%$ occurred in 17 patients (group A) at the last follow-up. Patients without decreased EF comprised group B. Early/late diastolic velocity of mitral inflow (E/A ratio) at rest was lower in group A (0.91 ± 0.2 vs 1.28 ± 0.3 , $P < 0.001$), and it was an independent predictor of cardiotoxicity (adjusted for baseline patient characteristics and parameters of systolic and diastolic function). At follow-up, WMSI at rest paralleled radionuclide EF. Contractile reserve at low-dose DSE was preserved in group A.

Conclusions: WMSI measured by 2D echocardiography parallels radionuclide EF at follow-up. Assessment of contractile reserve has no incremental value for the early detection of cardiotoxicity. A baseline abnormal E/A ratio is an independent predictor of anthracycline cardiotoxicity.

INTRODUCTION

Anthracyclines are among the most widely used and effective antineoplastic agents. A growing number of patients treated with anthracyclines may have the potential for substantial morbidity and mortality owing to anthracycline cardiotoxicity. Patients younger than 75 years and without heart failure or pulmonary disease are more likely to receive chemotherapy.¹ The main manifestations of acute cardiotoxicity are cardiac rhythm disturbances and the pericarditis/myocarditis syndrome,^{2,3} while early (several days to months following therapy) and late (years to decades after treatment) cardiotoxicity is mainly characterized by deterioration of myocardial function.⁴ Subclinical cardiomyopathy is quite more prevalent than symptomatic heart failure.⁵ Various predisposing factors have been proposed, such as total dose of anthracyclines $> 550\text{mg/m}^2$, high rate of administration, previous chest irradiation, young or advanced age, female sex, and coexistent heart disease and/or arterial hypertension.⁶⁻⁹ The early detection of cardiotoxicity may lead to the modification of chemotherapeutic regimen.^{10,11} and to the timely administration of medications for the treatment of cardiomyopathy, such as beta-blockers and ACE inhibitors.^{12,13} Echocardiography during low dose dobutamine infusion (10 mg/kg/min) has the potential to reveal abnormalities of myocardial contractile reserve, while Doppler echocardiography of the mitral valve inflow during diastole has been used for the assessment of left ventricular (LV) diastolic function. This study examines whether the combination of repetitive dobutamine stress echocardiography (DSE) with evaluation of Doppler mitral inflow pattern can be used to predict the development of anthracycline cardiomyopathy.

METHODS

Patient population, study protocol

We studied 31 patients (71% male) with a mean \pm SD age of 57 ± 13

years. All patients had a normal baseline ejection fraction (EF) and none of them had received anthracyclines in the past. Their baseline hematological disorders and clinical characteristics are presented in Tables 1 and 2, respectively. The doses of doxorubicin ranged from 150

Table 1. Haematological disorders of the 31 study patients

Disease	Patients
Acute leukaemia	8 (26)
Hodgkin's disease	5 (16)
Non-Hodgkin lymphoma	14 (45)
Multiple myeloma	3 (10)
Myelodysplastic syndrome	1 (3)

Data are presented as number (%) of patients

Table 2. Clinical characteristics of the two groups of patients

	All patients (n = 31)	Group A (n = 17)	Group B (n = 14)
Age (years)	57 ± 13	59 ± 13	53 ± 13
Gender			
Male	22 (71)	12 (71)	10 (71)
Female	9 (29)	5 (29)	4 (29)
Diabetes ^a	2 (6.5)	1 (5.9)	1 (7.1)
Hypertension ^b	4 (12.9)	2 (11.8)	2 (14.2)
CAD ^c	4 (12.9)	3 (17.6)	1 (7.1)
ACE-inhibitors	3 (9.7)	2 (11.8)	1 (7.1)
Beta-blockers	2 (6.5)	1 (5.9)	1 (7.1)
Nitrates	2 (6.5)	2 (11.8)	0 (0)

Data are presented as number (%) of patients or mean value ± SD. CAD = coronary artery disease; ^aPatients receiving oral antidiabetics or insulin; ^bDefined as blood pressure ≥ 140/90mmHg, or treatment with antihypertensive medication. ^cDefined as one or more of the following: History of myocardial infarction, critical stenosis in coronary angiography, or typical angina.

to 400 mg/m² of body surface area (mean dose, 323 ± 88 mg/m²). Six patients received idarubicin (mean dose, 36 ± 0 mg/m²) and two patients received also mitoxantrone, a cardiotoxic compound that belongs to anthracenediones (mean dose, 40 ± 14 mg/m²). In addition, five patients underwent mediastinal irradiation following chemotherapy. Systolic and diastolic parameters of LV function were evaluated repetitively: before chemotherapy, at the midchemotherapy period, at the end of chemotherapy, and after six months. The local medical ethics committee approved the study protocol. Patients provided informed consent to take part in the study.

Two- dimensional echocardiography

A Hewlett Packard Sonos-5500 imaging system (Andover, Mass.) equipped with a 1.8 MHz transducer using second harmonic imaging to digitize endocardial border visualization was used to record two-dimensional (2D) echocardiograms. Four standard views were recorded, and two experienced reviewers blinded to the clinical data visually scored the digitized echocardiograms. Regional wall motion and systolic wall thickening were scored using a 16-segment model and a five-point grading scale: 1, normal; 2, mildly hypokinetic; 3, severely hypokinetic; 4, akinetic; 5, dyskinetic.¹⁴ For each patient, a wall motion score index (WMSI, total score divided by the number of segments scored) was calculated.

Dobutamine stress echocardiography

DSE was performed as described previously.¹⁵ The baseline, low dose, peak stress and recovery images were displayed as a cineloop format. In addition, we assessed the change in myocardial contractile reserve by subtracting WMSI at low dose dobutamine infusion from WMSI at rest (delta WMSI). Reduction of wall thickening and new wall motion abnormalities during the stress test were considered to be hallmarks of ischemia, with the exception of the transition of akinesia to dyskinesia, which was considered a mechanically induced

phenomenon. The inter- and intra-observer concordances of resting WMSI were 94 and 97%, respectively, while the inter- and intra-observer agreements for the response of WMSI during dobutamine infusion were 92 and 94%, respectively.

Radionuclide ventriculography

Measurements of LV EF were performed by radionuclide ventriculography (RNV), which is the established non-invasive standard for monitoring anthracycline cardiomyopathy. We used this method as an independent reference for the assessment of EF before the performance of every echocardiographic examination. A small field-of-view gamma camera system (Orbiter, Siemens, Erlangen, Germany), oriented in a 45° left anterior oblique position with a 5 to 10° caudal tilt, was used. After injection of ^{99m}Tc (740 MBq), RNV was performed at rest with the patient in the supine position. The LV EF was calculated by standard methods (Odyssey VP, Picker, Cleveland, Ohio).

Pulsed-wave Doppler of mitral valve inflow

Pulsed-wave Doppler echocardiography was used to evaluate diastolic LV function. Doppler studies were recorded from the apical four-chamber view, with the Doppler sampler positioned within the inflow portion of the left ventricle, midway between the annular margins of the mitral valve. Mitral velocity profiles were digitized from the modal velocity of the Doppler tracings. The peak E (early rapid ventricular filling) and peak A (atrial assisted filling) wave velocities were computed to calculate the E/A velocity ratio. The isovolumic relaxation period (IRP) was assessed with the transducer angulated into the apical five-chamber view and the sample volume placed within the LV outflow truck, but in proximity to the anterior mitral valve leaflet, to record both inflow and outflow signals. Measurements of the deceleration time (DT) were made by the computer software, by placing the caliper to the peak of the E wave, and by following the deceleration slope of the E wave down to the intersection with the A

wave. The mean value of five consecutive normal beats was calculated. Pulsed-wave Doppler signals were measured at rest and at low dose (10 mg/kg/min) dobutamine infusion.

Statistical analysis

Data are presented as mean \pm standard deviation. Logistic regression including all clinical, radionuclide and echocardiographic parameters was used to investigate the existence of independent predictors for cardiotoxicity. Analysis of variance (ANOVA) for repeated measurements was used to compare means of parameters of systolic and diastolic function over time. Continuous variables in the same group were compared with the Student's paired *t*-test. A *P* value ≤ 0.05 was considered statistically significant.

RESULTS

Six months after the end of treatment, 17 patients (group A) had a worsening of the EF $\geq 5\%$ ($P < 0.001$). Fourteen patients (group B) preserved their initial EF at the end of the study. No significant differences existed between the two groups in the doses of chemotherapeutic agents and previous irradiation received. During the study, there was a gradual worsening of WMSI at rest in group A that paralleled the decline of radionuclide EF (Figure 1). In the same group, two patients (6%) manifested signs and symptoms of congestive heart failure two months and one year after the first dose of anthracyclines, respectively. No ischemia was detected in both groups during the serial testing. Early/late diastolic velocity of mitral inflow (E/A ratio) at rest was lower in group A (0.91 ± 0.2 vs 1.27 ± 0.3 , $P < 0.001$). Logistic regression analysis of baseline patient characteristics (age, hypertension, diabetes, coronary artery disease) and baseline parameters of systolic (radionuclide EF, WMSI) and diastolic (E/A ratio, DT, IRP) function revealed that E/A ratio was an independent predictor for cardiotoxicity.

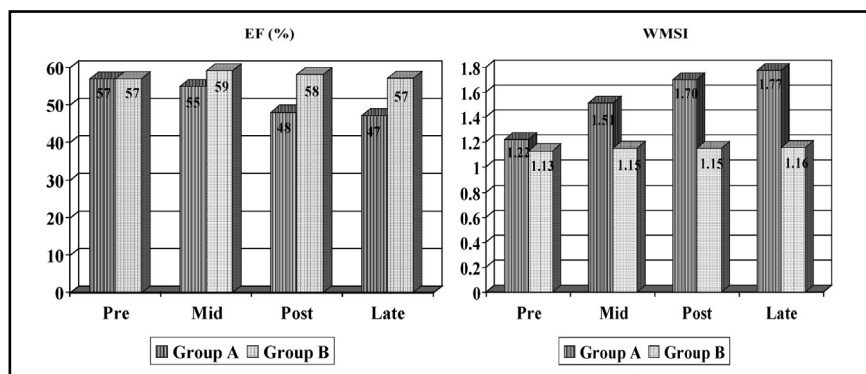


Figure 1. Changes in radionuclide EF (%) and WMSI in groups A and B during follow-up

At midchemotherapy testing, delta WMSI did not indicate any decrease in myocardial contractile reserve in group A, since there was an improvement of segmental contractility from rest to low dose dobutamine infusion in both group. Midchemotherapy E/A ratio at rest and during low dose dobutamine infusion was also significantly lower in group A compared with group B ($P < 0.001$ and $P = 0.017$, respectively), but it did not change afterwards. DT and IRP increased significantly at follow-up. Table 3 summarizes the changes that occurred in systolic and diastolic parameters over time in groups A and B.

Table 3. Changes in parameters of systolic and diastolic function in Groups A and B

	Group A					Group B				
	Pre	Mid	End	Late	<i>P</i> value*	Pre	Mid	End	Late	<i>P</i> value*
WMSI rest	1.22	1.51	1.70	1.77	<0.001	1.13	1.15	1.15	1.16	0.986
WMSI low dose	1.09	1.16	1.28	1.26	0.004	1.01	1.05	1.06	1.03	0.277
E/A ratio rest	0.91	0.77	0.76	0.77	0.128	1.28	1.16	1.16	1.16	0.491
E/A ratio low dose	1.02	0.95	0.89	0.90	0.194	1.22	1.20	1.19	1.20	0.980
DT rest (ms)	219	249	232	237	0.028	194	205	206	209	0.632
DT low dose (ms)	185	227	216	220	0.001	191	199	203	207	0.339
IRP rest (ms)	89	92	95	90	0.803	80	81	82	83	0.972
IRP low dose (ms)	52	64	68	69	0.012	70	73	76	78	0.739

Data are expressed as mean values \pm SD. **P* value was calculated by analysis of variance for repeated measurements (ANOVA). E/A ratio = early diastolic filling velocity/atrial assisted diastolic velocity ratio; DT = deceleration time; IRP = isovolumic relaxation period; WMSI = wall motion score index

DISCUSSION

Main findings

Myocardial contractile reserve, assessed by low-dose DSE does not predict the systolic LV function after chemotherapy, since patients with a reduction in EF at rest preserve their ability to improve LV contractility during low-dose dobutamine infusion. Also, an abnormal E/A velocity ratio at rest, measured prior to chemotherapy, independently predicts patients prone to develop anthracycline cardiomyopathy.

Previous studies of systolic LV function

The study of Gottdiener et al.¹⁶ in 1981 showed that 20 of the 32 patients demonstrated asymptomatic LV dysfunction one to nine months after treatment with anthracyclines. This is consistent with the present findings, since 17 of the 31 patients in our study had a decrease in LV EF, while only two of them developed symptomatic heart failure during follow-up.

Gottsauer-Wolf et al.¹⁷ compared RNV and 2D echocardiography for the assessment of EF in 339 consecutive patients and found that echocardiography was of limited value compared to RNV, especially in patients with slight or moderate reduction in EF. The current findings suggest that the 16-segment evaluation of LV function at rest by WMSI may be superior to global 2D echocardiographic measurement of EF. Autopsy studies have shown that the cardiac injury caused by anthracyclines is patchy, and at times is limited to one or more walls of a ventricle.¹⁸ Therefore, segmental abnormalities can be detected before any global systolic LV dysfunction is apparent.

In 1996, De Wolf et al.¹⁹ performed DSE in 23 childhood cancer survivors who had undergone chemotherapy more than two years previously. They found that 85% of these patients showed an abnormal response, both systolic and diastolic, to dobutamine infusion. In contrast, in the present study, all patient with deterioration of EF six

months after the end of study showed a substantial improvement of systolic LV function at low-dose dobutamine infusion. The relatively short follow-up may explain our findings. It is known that patients with mild and subclinical deterioration of systolic LV function can compensate for a decreased cardiac output with a number of adaptive mechanisms, i.e. increasing preload, heart rate, and contractility during stress.²⁰ After this period of compensation, LV starts thinning and working against high systolic stress. The latter is a finding of late cardiotoxicity, usually observed several years after the completion of chemotherapy.²¹ Our results are also in agreement with that of Bae et al.²² who, in 1988, studied 18 patients under therapy with anthracyclines. These patients underwent RNV at rest and during exercise. The study concluded that regional wall motion abnormalities were more readily detectable at rest, while exercise did not increase the diagnostic accuracy for the detection of cardiotoxicity.

Studies of diastolic LV function

In 1998, Cittadini et al.²³ studied 21 patients before and after treatment with anthracyclines and reported impaired diastolic LV filling compared with the control group. Furthermore, Marchandise et al.²⁴ in 1989, included 45 patients under chemotherapy and showed a prolongation of the IRP (32%) and a reduction of the E/A ratio (23%). These changes preceded systolic LV dysfunction.

To the best of our knowledge, this is the first study to find that a parameter used for the assessment of diastolic function, the E/A velocity ratio, might have predictive value prior to chemotherapy. A baseline E/A velocity ratio less than unity indicates increased LV stiffness and abnormal relaxation, resulting in impaired LV filling. Patients with this baseline diastolic abnormality seem to be more sensitive to the deleterious effects of anthracyclines on myocytes, by a mechanism that still remains unclear. An issue that has to be addressed in the future is the optimal length of follow-up, since it is unclear whether these patients will also show a higher incidence of late cardiotoxicity at longer term follow-up.

Limitations

This study has several limitations. First, the number of patients studied was relatively small. Second, RNV and DSE were not always performed on the same day. Although these tests were performed in the same week, minor alterations in the hemodynamic status of these patients might have occurred. Finally, quantitative information on wall motion was not available in this study.²⁵

Conclusions

At early stages of anthracycline administration, assessment of myocardial contractile reserve during low dose DSE does not give additional information for the early detection of anthracycline cardiomyopathy. Patients who are candidates for treatment with anthracycline agents and found to have an abnormal baseline E/A velocity ratio require an even more careful monitoring during chemotherapy and for at least six months after the last dose of anthracyclines. Repetitive measurements of radionuclide EF and echocardiographic evaluation of systolic and diastolic function at rest seem to be equally effective in detecting cardiotoxicity. If any further worsening of LV function occurs, then modification of chemotherapy regimen and/or the use of cardioprotective agents (i.e. dexrazoxane) and agents indicated for the treatment of heart failure, can be life saving.

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CHAPTER 3

AORTIC STENOSIS: AN UNDERESTIMATED RISK FACTOR FOR PERIOPERATIVE COMPLICATIONS IN PATIENTS UNDERGOING NONCARDIAC SURGERY



Source: MD Kertai, M Bountiukos, E Boersma, JJ Bax,
IR Thomson, F Sozzi, J Klein, JRTC Roelandt, D Poldermans.
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ABSTRACT

Purpose: To determine the incidence of perioperative events in patients with aortic stenosis undergoing noncardiac surgery.

Methods: We studied 108 patients with moderate (mean gradient, 25 to 49 mmHg) or severe (mean gradient, ≥ 50 mmHg) aortic stenosis and 216 controls who underwent noncardiac surgery between 1991 and 2000 at Erasmus Medical Center. Controls were selected based on calendar year and type of surgery. Details of clinical risk factors, type of surgery, and perioperative management were retrieved from medical records. The main outcome measure was the composite of perioperative mortality and nonfatal myocardial infarction.

Results: There was a significantly higher incidence of the composite endpoint in patients with aortic stenosis than in patients without aortic stenosis (14% [15/108] vs. 2% [4/216], $P < 0.001$). This rate of perioperative complications was also substantially higher in patients with severe aortic stenosis compared with patients with moderate aortic stenosis (31% [5/16] vs. 11% [10/92], $P = 0.04$). After adjusting for cardiac risk factors, aortic stenosis remained a strong predictor of the composite endpoint (odds ratio = 5.2; 95% confidence interval: 1.6 to 17.0).

Conclusions: Aortic stenosis is a risk factor for perioperative mortality and nonfatal myocardial infarction, and the severity of aortic stenosis is highly predictive of these complications.

INTRODUCTION

Aortic stenosis is the most common valvular heart disease affecting 2% to 9% of adults over 65 years of age.^{1,2} Aortic stenosis is also considered to be a risk factor for perioperative cardiac complications in patients undergoing noncardiac surgery. The study by Goldman et al. in 1977 was the first to show that patients with aortic stenosis were at increased risk of life-threatening or fatal cardiac complications,³ and this characteristic was also reported in the subsequent study by Detsky et al.⁴ Although three later studies reported that selected patients with aortic stenosis who were not candidates for, or refused, aortic valve replacement could undergo noncardiac surgery with a reasonably low event rate of 0% to 7%,⁵⁻⁷ Rohde et al.⁸ recently reported that increased peak instantaneous aortic gradients were associated with increased cardiovascular morbidity. The present study was designed to determine the incidence of perioperative mortality and nonfatal myocardial infarction over time in a large group of patients with moderate to severe aortic stenosis who were undergoing elective noncardiac surgery.

METHODS

Study design

Between January 1991 and December 2000, a total of 123,802 consecutive patients over 18 years of age underwent noncardiac surgery at the Erasmus Medical Center, Rotterdam, The Netherlands. The hospital electronic database was reviewed for medical records of patients with a diagnosis of aortic stenosis who had undergone elective noncardiac surgery. One hundred and eight patients were identified as having moderate or severe aortic stenosis and as having undergone elective noncardiac surgery. From the same database, two controls were selected for each patient with aortic stenosis; controls had to have undergone surgery immediately before or after the patients with aortic

stenosis, and were stratified according to the type of elective surgery.⁹ We studied a 10-year period with a strict control for the calendar year as surgical and anesthesiological techniques may have changed over this time.

Data collection

For all patients with aortic stenosis and controls, medical records, anesthesiological charts, and discharge letters were manually reviewed for information on cardiac risk factors, chronic medication use, type of noncardiac operation, and cause and type of perioperative complications. The medical records of patients with aortic stenosis were also reviewed for the most recent echocardiogram and signs of symptomatic aortic stenosis, such as syncope or presyncope, angina, and dyspnea.

Details of intraoperative course included the American Society of Anesthesiologists classification,¹⁰ choice of anesthetic technique, intraoperative hemodynamic changes, and the management of those changes. The duration of anesthesia, intraoperative blood loss, intraoperative fluid administration, and use of invasive pressure monitors were recorded. Each anesthetic technique was classified as follows: balanced or intravenous general anesthesia, central neural blockade or intravenous general anesthesia, central neural blockade, combination of general anesthesia and central neural blockade, and conscious sedation. Postoperative admission to the intensive care unit and duration of stay were also noted.

Elective noncardiac operations were classified as follows: major vascular (infrarenal abdominal aortic and infrainguinal procedures), other vascular (carotid endarterectomy, peripheral vascular embolectomy), abdominal (gastrointestinal and renal surgery), orthopedic (total hip or knee arthroplasty, arthroscopy, or lower limb amputation), genitourinary (hysterectomy and operations involving the urinary bladder), head and neck surgery (thyroidectomy, procedures involving the larynx), and other (ear, eye, nose, throat, or breast surgery).

Definition of perioperative events

The study outcome was a composite of perioperative death and nonfatal myocardial infarction, occurring before discharge or within 30 days after surgery, whichever came first. Two of the investigators (MDK, DP) reviewed all available medical records, laboratory values, electrocardiograms, echocardiograms, and clinical events. The cause of perioperative death was obtained from hospital records or autopsy results. The diagnosis of myocardial infarction was made by measurement of a serum creatine kinase level > 110 U/L with a myoglobin isoenzyme fraction of more than 10% or troponin T level > 0.1 $\mu\text{g/L}$, and by new electrocardiographic Q waves ≥ 1 mm or > 30 ms.

Evaluation of the aortic valve

In patients with documented aortic stenosis, the transvalvular aortic gradient and severity of aortic stenosis were determined by continuous-wave Doppler echocardiography. Patients were included in the study if echocardiography was performed within three months before noncardiac surgery, and if patients had moderate aortic stenosis on echocardiography defined as an aortic valve area between 0.7 and 1 cm^2 or a mean gradient between 25 and 49 mmHg, or severe aortic stenosis defined as an aortic valve area index < 0.7 cm^2 or a mean gradient ≥ 50 mmHg.

Statistical analysis

Continuous variables are presented as means (\pm SD) or medians (interquartile range), and categorical variables are presented as percent frequencies. Comparisons were made using the *t* test, Mann-Whitney test, or chi-squared test, as appropriate. The number of outcome events in the study was limited. Therefore, to avoid overfitting and to enable assessment of the relation between clinical risk factors and the composite endpoint, we used the Revised Cardiac Risk Index.¹¹

Univariable logistic regression analyses were used to study the relation between aortic stenosis and the composite endpoint. Multivariable logistic regression analysis was also performed to evaluate the additional predictive value of aortic stenosis, adjusting for baseline clinical characteristics. Odds ratios and corresponding 95% confidence intervals are reported. In order to reveal possible heterogeneity between aortic stenosis and clinical risk factors, an interaction term was evaluated. For all tests, a P value < 0.05 was considered significant. All analyses were performed using SPSS statistical software (SPSS Inc., Chicago, Illinois).

RESULTS

Patients with aortic stenosis were older, and had a higher prevalence of cardiac risk factors, including angina pectoris, myocardial infarction, heart failure, stroke, diabetes mellitus, renal failure, and hypertension, compared with patients without aortic stenosis (Table 1). More patients with aortic stenosis had a cardiac risk index of 1 or more compared with controls. Use of angiotensin-converting enzyme inhibitors, diuretics, and nitrates was also more common among patients with aortic stenosis. There were no differences between the two patient groups with regards to sex, pulmonary disease, and smoking.

Characteristics of patients with aortic stenosis

On two-dimensional echocardiography, 92 patients had moderate aortic stenosis and 16 had severe aortic stenosis. Twenty-two patients (20%) had one or more cardiac symptoms related to aortic stenosis: history of syncope ($n = 2$), angina pectoris ($n = 7$), and exertional dyspnea ($n = 19$). Of these patients, 14 had moderate aortic stenosis and eight had severe aortic stenosis. Aortic valve replacement was not performed for various reasons, including the presence of coexisting medical illness, advanced age, relative emergency of the noncardiac

Table 1. Characteristics of Patients with Aortic Stenosis and Controls

Characteristic	Patients with Aortic Stenosis (n = 108)	Patients without Aortic Stenosis (n = 216)	P Value
	Number (%) or Mean \pm SD		
Age (years)	69.0 \pm 10.3	56.6 \pm 18.0	<0.001
Age >70 years	61 (57)	62 (29)	<0.001
Male sex	55 (51)	119 (56)	0.47
History of angina	26 (24)	24 (11)	<0.01
History of myocardial infarction	27 (25)	29 (13)	0.01
History of heart failure	30 (28)	6 (3)	<0.001
History of cerebrovascular disease	20 (19)	18 (8)	0.01
Diabetes mellitus	26 (24)	20 (9)	<0.001
Renal failure (serum creatinine \geq 2 mg/dL)	22 (20)	13 (6)	<0.001
Revised Cardiac Risk Index \geq 1*	90 (83)	115 (53)	<0.001
Hypertension	66 (61)	66 (31)	<0.001
Pulmonary disease	22 (20)	29 (13)	0.10
Smoking	30 (29)	70 (33)	0.52
Medication			
Aspirin	15 (14)	26 (12)	0.72
ACE inhibitor	55 (51)	51 (24)	<0.001
Beta-blocker	31 (29)	43 (20)	0.09
Diuretic	35 (32)	26 (12)	<0.001
Nitrates	22 (20)	16 (7)	0.001
Statin	18 (16)	21 (10)	0.10

* Derived by assigning 1 point to each of the following characteristics: high-risk type of surgery, ischemic heart disease, history of heart failure, history of cerebrovascular disease, insulin therapy for diabetes, and preoperative serum creatinine level > 2.0 mg/dL.

ACE = angiotensin-converting enzyme inhibitor.

operation, and patient refusal. All patients (n = 93) who survived noncardiac surgery as a routine procedure were seen regularly at the cardiology outpatient clinic at Erasmus Medical Center, of whom 29 underwent aortic valve replacement an average of two years later.

Patients with severe aortic stenosis more often had reduced or severely reduced left ventricular function as compared with patients with moderate aortic stenosis (Table 2). Other hemodynamic parameters such as the mean valve area were lower in patients with severe aortic stenosis, whereas the mean transvalvular aortic velocity and mean derived instantaneous gradient were higher in these patients.

Table 2. Hemodynamic Characteristics of Patients, by Severity of Aortic Stenosis

Variable	Patients with Moderate Aortic Stenosis (n = 92)	Patients with Severe Aortic Stenosis (n = 16)
	Number (%) or Mean \pm SD	
Left ventricular ejection fraction		
$\geq 50\%$	55 (60)	14 (40)
35%–49%	31 (34)	11 (31)
$< 35\%$	6 (6)	10 (29)
Aortic valve gradient (mm Hg)	37.2 \pm 8.1	67.8 \pm 11.3
Valve area (cm ²)	0.9 \pm 0.1	0.6 \pm 0.1
Transvalvular velocity (ms)	3.0 \pm 0.4	4.2 \pm 0.6

Of the 108 patients with aortic stenosis, left ventricular hypertrophy on echocardiography was evident in 49 patients (45%), left ventricular dilation was evident in 17 (16%), and left ventricular wall motion abnormality was evident in 29 (27%). Concomitant mild or moderate valve abnormality was detected in 26 patients (24%). Aortic regurgitation was noted in 11 patients, mitral valve regurgitation in eight, mitral valve stenosis in seven, tricuspid valve regurgitation in seven, and pulmonary regurgitation in three.

Perioperative course

Patients with aortic stenosis were more after classified as having an American Society of Anesthesiologists classification score of 2 or higher, as compared with controls, and had slightly lower hemoglobin and hematocrit levels, but higher serum creatinine levels, before surgery (Table 3). There was an overall difference in the type of anesthesia used. Patients with aortic stenosis were more likely to undergo balanced or general anesthesia than were controls. Indeed, only half of patients with aortic stenosis received epidural or spinal anesthesia and only one third underwent general anesthesia combined with central neural blockade. However, after stratified selection of patients without aortic stenosis, no difference in type of surgery was observed between the two groups (Table 3).

Table 3. Perioperative Characteristics of Patients with Aortic Stenosis and Controls

Characteristic	Patients with Aortic Stenosis (n = 108)	Patients without Aortic Stenosis (n = 216)	P Value
	Number (%), Mean \pm SD, or Median (Interquartile Range)		
Preoperative period			
American Society of Anesthesiology score			<0.001
1	9 (8)	64 (30)	
2	72 (67)	119 (55)	
3	27 (25)	33 (15)	
Laboratory values			
Hemoglobin (g/L)	132 (116–141)	137 (124–148)	0.01
Hematocrit (%)	39 (35–42)	41 (37–43)	0.04
Serum creatinine (mg/dL)*	1.0 (0.8–1.3)	0.8 (0.7–1.1)	0.001
Intraoperative period			
Type of anesthesia			<0.01
Balanced or intravenous general	82 (76)	126 (58)	
Central neural blockade	7 (7)	28 (14)	
Combined technique	8 (7)	41 (19)	
Conscious sedation	11 (10)	21 (9)	
Type of surgery			1.0
Major vascular	41 (38)	82 (38)	
Other vascular	9 (8)	18 (8)	
Abdominal	13 (12)	26 (12)	
Orthopedic	23 (21)	46 (21)	
Genitourinary	7 (7)	14 (7)	
Head and neck	2 (2)	4 (2)	
Other	13 (12)	26 (12)	
Swan-Ganz catheter	26 (24)	5 (2)	<0.001
Intra-arterial blood pressure monitoring	15 (14)	25 (12)	0.15
Central venous pressure monitoring	54 (50)	51 (24)	<0.001
Blood pressure drop during induction (mm Hg) [†]	30 (20–40)	20 (10–30)	<0.01
Dose of phenylephrine (bolus) (μ g)	40 (20–50)	40 (30–50)	0.05
Blood loss (mL)	400 (225–1450)	600 (300–1700)	0.22
Number of packed cells given (unit)	2.0 (1.2–5.3)	2.0 (1.3–4.0)	0.90
Total intraoperative fluid administered (mL)	2000 (1000–3500)	2000 (1500–4000)	0.16
Operation time (h)	2.4 (1.2–4.1)	2.0 (1.1–3.3)	<0.01
Anesthesia time (h)	3.0 (1.3–4.1)	2.3 (1.3–4.1)	0.04
Postoperative period			
Intensive care unit admission	24 (22)	59 (27)	0.35
Number of days in intensive care unit (days)	3.0 (2–3)	3.0 (2–4)	0.70

* To convert from mg/dL to mol/L, multiply by 88.4.

[†]Defined as a drop in systolic blood pressure compared with baseline.

There were no differences between patients with aortic stenosis and controls in terms of intraoperative blood loss, number of packed cells received, and total intraoperative intravenous fluid administration (Table 3). However, patients with aortic stenosis were more likely to have undergone invasive hemodynamic monitoring by Swan-Ganz catheter or central venous pressure monitoring. The median operation and anesthesia times were also slightly longer in patients with aortic

stenosis. Similar percentages of patients from both groups were admitted to the intensive care unit, with no substantial differences in the length of stay.

Relation between aortic stenosis and perioperative outcome

Perioperative death or myocardial infarction occurred in 19 patients (6%): 13 cardiac deaths, four noncardiac deaths (two due to sepsis, one renal failure, and one intestinal ischemia), and two nonfatal myocardial infarctions. Autopsy was performed in 15 patients (79%).

Fifteen (79%) of the 19 patients who died or had a myocardial infarction were from the aortic stenosis group. The rate of perioperative complications was substantially higher in patients with severe aortic stenosis than in those with moderate aortic stenosis (31% [5/16] vs. 11% [10/92], $P = 0.04$). Patients with aortic stenosis had an 8.5-fold increased risk of perioperative complications compared with patients without aortic stenosis (95% confidence interval [CI]: 2.8 to 26.5). This association persisted even after adjusting for clinical risk factors (odds ratio [OR] = 5.2; 95% CI: 1.6 to 17.0). A 1-point increase in the cardiac risk index was also associable with adverse perioperative outcomes in both univariable (OR = 2.2; 95% CI: 1.5 to 3.2) and multivariable (OR = 1.8; 95% CI: 1.2 to 2.7) analyses.

Association between aortic stenosis and the cardiac risk index

Based on the number of clinical risk factors and the presence of aortic stenosis, the incidence of perioperative mortality and nonfatal myocardial infarction was estimated. In patients with aortic stenosis and controls who had a risk index of 0, no adverse perioperative outcomes were observed (Figure). However, if patients with aortic stenosis had a risk index of or higher, there was a higher risk of an adverse perioperative outcome, compared with in controls. Test for heterogeneity revealed no association among the number of risk factors, aortic stenosis, and perioperative adverse outcome ($P = 0.78$).

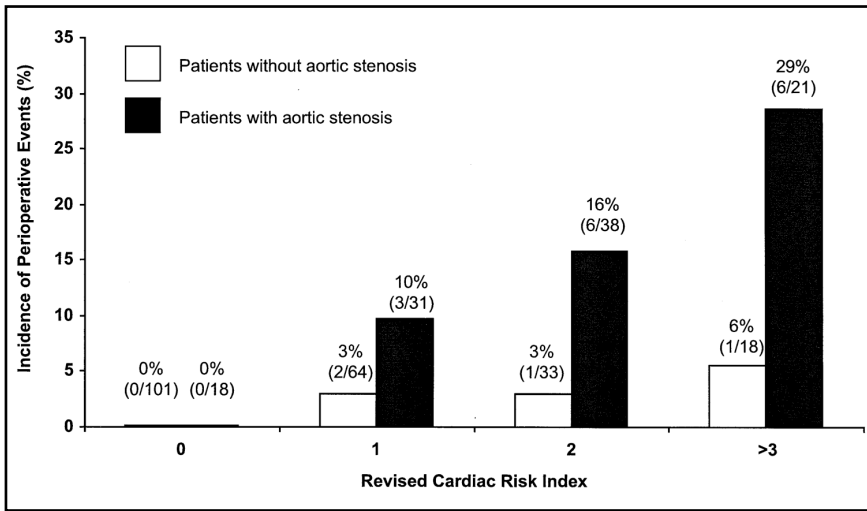


Figure. Incidence of perioperative mortality and nonfatal myocardial infarction in patients with aortic stenosis and controls. Results are based on the absence or presence of aortic valve stenosis, and on the Revised Cardiac Risk Index, which assigns 1 point to each of the following characteristics: high-risk type of surgery, ischemic heart disease, history of heart failure, history of cerebrovascular disease, insulin therapy for diabetes, and preoperative serum creatinine level > 2.0 mg/dL.

DISCUSSION

Our results suggest that patients with aortic stenosis have a fivefold increased risk of perioperative mortality and nonfatal myocardial infarction, regardless of the presence of risk factors for coronary artery disease, such as angina, previous myocardial infarction, heart failure, renal dysfunction, and stroke. The severity of aortic stenosis was also highly predictive of perioperative adverse outcome.

These findings are in agreement with prior research and guidelines, based initially on the study by Goldman et al., who in 1977 reported major cardiac complications in 13% of 23 patients with important aortic stenosis.³ The persistent prognostic value of aortic stenosis was also established by Rohde et al.⁸ in 67 patients with aortic stenosis who

underwent noncardiac surgery and who had a sevenfold increased risk of perioperative cardiac complications. In contrast to these studies and our results, other investigators have found that selected patients with aortic stenosis who were not candidates for, or refused, aortic valve replacement could undergo noncardiac surgery with a reasonably low risk.⁵⁻⁷ However, the 122 patients with aortic stenosis in these studies commonly underwent minor procedures.

Our results showed that cardiac complications were the major cause of perioperative death in all patients (76% [13/17]). Patients with aortic stenosis more often had a clinical history of coronary artery disease than did patients without aortic stenosis. The association between aortic stenosis and coronary artery disease has been confirmed in previous studies.^{12,13} Half of the 123 patients with aortic stenosis studied by Otto et al showed coronary artery disease as assessed by coronary angiography.¹³ Clinical factors that were associated with aortic stenosis were similar to those associated with coronary artery disease, and include advanced age, and a history of angina, previous myocardial infarction, heart failure, or stroke. In addition, the perioperative risk attributed to aortic stenosis is also independent of coronary artery disease. Patients with aortic stenosis are prone to developing hypotension and low cardiac output, which may also increase the risk of perioperative complications.¹⁴

In symptomatic patients with aortic stenosis, valve replacement should be considered before surgery.¹⁵ In patients with aortic stenosis and in those with a history of coronary artery disease, signs of coronary artery disease should be evaluated. Patients without coronary artery disease can be considered candidates for elective surgery provided that strict hemodynamic control is effected and hypotension is recognized early and treated adequately. In patients with signs of both coronary artery disease and aortic stenosis, further evaluation and subsequent coronary revascularization with valve replacement should be considered. In patients who are not candidates for aortic valve replacement or in whom surgery cannot be delayed sufficiently for valve replacement to be performed, the use of balloon aortic valvuloplasty may be more appropriate.

This study has several limitations. The study was retrospective, and adverse events may have been missed. However, we used hard endpoints, such as all-cause mortality and nonfatal myocardial infarction. Additionally, we used a combination of matching and multivariable regression analysis to adjust for potential confounders. We selected and adjusted for clinical characteristics that have been described in the literature as important prognostic factors for perioperative complications. Still, there is always a possibility that unknown clinical risk factors were missed.

In conclusion, patients with aortic stenosis undergoing elective noncardiac surgery remain at an increased risk of perioperative mortality and nonfatal myocardial infarction similar to that during the last few decades. Furthermore, our data showed that the severity of aortic stenosis was also highly predictive of perioperative complications.

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CHAPTER 4

SAFETY OF DOBUTAMINE STRESS ECHOCARDIOGRAPHY IN PATIENTS WITH AORTIC STENOSIS



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ABSTRACT

Background and aim of the study: Aortic valve disease is becoming one of the most important cardiac diseases in western society. Low-dose dobutamine stress echocardiography (DSE) is recommended in patients with low-gradient aortic stenosis (AS) and severe left ventricular (LV) dysfunction. DSE is also used in patients with AS and moderately reduced or normal LV function for diagnostic purposes. The study aim was to assess the safety of DSE in the setting of AS and various degrees of LV dysfunction.

Methods: A total of 75 patients with AS who underwent DSE at the authors' center between 1997 and 2001 was reviewed. Group A patients (n = 20) had severely reduced mean LV ejection fraction of $25 \pm 6\%$, and underwent low-dose DSE; group B patients (n = 55) had moderate to normal LV function (LVEF, $51 \pm 8\%$) and underwent high-dose DSE. The mean pressure gradient, valve area and side effects after DSE were evaluated.

Results: Serious cardiac arrhythmias occurred in 10 patients. In group A, four patients (20%) developed non-sustained ventricular tachycardia. In group B, two patients (4%) had non-sustained ventricular tachycardia (VT), four (7%) had paroxysmal supraventricular tachycardias, and two (4%) severe symptomatic hypotension. Among the 20 patients with evidence of ischemia on DSE, three developed side effects (no difference compared with patients without ischemia; $P = 0.922$). Fourteen patients received atropine during DSE, and 1 of these developed non-sustained VT after atropine administration.

Conclusions: Serious cardiac arrhythmias occur frequently during both low-dose and high-dose DSE in patients with AS. Adverse side effects do not relate to stress-induced ischemia or atropine addition.

INTRODUCTION

Low-dose dobutamine stress echocardiography (DSE) is a recommended investigation in patients with low-gradient aortic stenosis and reduced left ventricular function to assess whether the aortic stenosis is fixed or dynamic (i.e. flow-dependent).¹⁻³ Despite a high number of reported side effects, the test has been claimed to be safe in patients with ‘low gradient’ aortic stenosis.⁴⁻⁶ According to Carabello⁷, “the clinician can be confident that, in a given patient, the symptoms are due to aortic stenosis if the mean aortic-valve gradient exceeds 50 mmHg or if the aortic-valve area is no larger than 1 cm²”.

Patients with aortic stenosis and normal or mildly reduced left ventricular function may be referred for DSE for the diagnosis of coronary artery disease, or for risk stratification before non-cardiac surgery. Currently, few data are available relating to the safety of DSE in these patients.

Hence, the present study was initiated to evaluate retrospectively the current authors’ experience with a patient population with aortic stenosis who underwent either low-dose DSE for the assessment of the severity of aortic stenosis, or a full-dose protocol for diagnostic purposes.

CLINICAL MATERIAL AND METHODS

Patients

The study population comprised 75 consecutive patients with aortic stenosis and a mean gradient ≥ 15 mmHg who had been referred for DSE. Patients with severe aortic insufficiency or severe concomitant valvular heart disease were excluded. All patients were included in an electronic registry accumulated over the course of daily clinical care. Among these patients, 20 (group A) with a poor left ventricular ejection fraction (LVEF) (mean, $25 \pm 6\%$; range: 18 to 35%) and low transvalvular pressure gradient were tested in order to assess the

severity of aortic stenosis. A second group of 55 patients (group B) with mild or moderate aortic stenosis and moderate to normal left ventricular function (LVEF, $51 \pm 8\%$; range: 40 to 69%) underwent high-dose DSE for the diagnosis of coronary artery disease, or for risk stratification before non-cardiac surgery. Group B patients underwent DSE if their LVEF was $\geq 40\%$, and if aortic stenosis was not severe at baseline (mean pressure gradient ≤ 40 mmHg and/or aortic valve area $\geq 1\text{cm}^2$).

Echocardiography

All patients with a suspected aortic stenosis underwent a complete echocardiographic study at rest prior to DSE, using commercially available equipment (Sonos 5500, Andover, Massachusetts, USA). Two-dimensional (2D) images were acquired from three apical views (four-chamber, two-chamber and three-chamber) and two parasternal views (short-axis and long-axis).

Assessment of global left ventricular function

The LVEF was determined off-line using the 2D biplane disk method with the modified Simpson's rule. The endocardial borders of the two- and four-chamber apical views were digitally traced at end-diastole and end-systole. Subsequently, the left ventricular end-diastolic and end-systolic volumes were measured and the LVEF was calculated. Left ventricular hypertrophy was defined as an end-diastolic thickness of the anterior septum ≥ 12 mm when measured by M-mode in the parasternal long-axis view.

Evaluation of the aortic valve

Aortic valves were evaluated off-line for the purpose of the study. Observers were blinded to the development of side effects during dobutamine infusion. A multiwindow approach was used to obtain the maximal transaortic velocity with a continuous-wave Doppler

technique. The peak instantaneous gradient was calculated using the modified Bernoulli equation from three to five consecutive beats. The mean pressure gradient was assessed using appropriate software after tracing the velocity time integral. The diameter of the left ventricular outflow tract was measured from the parasternal long-axis view, in proximity to the aortic valve. The mean pressure gradient of the outflow tract was obtained using pulsed-wave Doppler from the apical three-chamber view, by placing the Doppler sample volume just under the aortic valve and planimetry the signal. Calculations of the aortic valve area were derived using the continuity equation. The measurements of mean pressure gradient and aortic valve area were repeated at the time of the maximum heart rate. Aortic valve insufficiency was qualitatively assessed using a four-grade scale. Left ventricular function, aortic valve area, mean pressure gradient, hemodynamic response to stress, and side effects during dobutamine infusion were evaluated separately in both patient groups.

DSE protocol

DSE was carried out following the acquisition of images at rest. The baseline, low dose, peak stress and recovery images were displayed as a cine loop format. In patients with a severely reduced LVEF and a low transvalvular gradient (group A), dobutamine was infused at a starting dose of 5 $\mu\text{g}/\text{kg}/\text{min}$ for 5 min followed by 10 $\mu\text{g}/\text{kg}/\text{min}$ for 5 min (low-dose stage), up to 20 $\mu\text{g}/\text{kg}/\text{min}$ for a further 3-min period. In patients undergoing high-dose DSE (group B), the dobutamine dose was increased by 10 $\mu\text{g}/\text{kg}/\text{min}$ every 3 min to a maximum dose of 40 $\mu\text{g}/\text{kg}/\text{min}$. Atropine (up to 2 mg) was added at the end of the last stage if the target heart rate had not been achieved. End-points for interruption of the test in group B were: (i) achievement of the target heart rate; (ii) mean pressure gradient > 50 mmHg during the test; and (iii) maximal dose of both dobutamine and atropine. The test end-points for both groups were: (i) extensive stress-induced ischemia (severe new wall motion abnormalities); (ii) horizontal or downsloping ST-segment depression (0.2 mV at 80 ms after the J-point compared

with baseline); (iii) severe angina; (iv) severe and symptomatic reduction in systolic blood pressure > 40 mmHg from baseline; (v) hypertension (blood pressure > 240/120 mmHg); (vi) significant arrhythmias (paroxysmal supraventricular tachycardias, non-sustained ventricular tachycardia (more than three consecutive beats for less than 30 s), sustained ventricular tachycardia (duration of \geq 30 s) and ventricular fibrillation; or (vii) any side effect regarded as being due to dobutamine. Metoprolol was available to reverse the (side) effects of dobutamine and atropine.

Wall motion analysis

A 16-segment model for left ventricular wall motion analysis was used, as recommended by the American Society of Echocardiography,⁸ and visually scored by two experienced reviewers (D.P., M.B.). Each segment was scored as follows: 1 = normal; 2 = mildly hypokinetic; 3 = severely hypokinetic; 4 = akinetic; and 5 = dyskinetic. For each patient, a wall motion score index (total score divided by the number of segments scored) was calculated at rest, at low-dose dobutamine, and at peak heart rate. Reduction of wall thickening and new wall motion abnormalities during the stress test were considered to be hallmarks of ischemia. The transition of akinesia to dyskinesia was considered a mechanically induced phenomenon.⁹

Statistical analysis

Results were expressed as mean \pm SD, and percentages were rounded. The statistical analysis was performed using the SPSS program (version 11.0.1 for Windows). Changes of continuous variables in the same group were tested for significance by a paired two-tailed *t*-test, whilst an independent-samples *t*-test was used to compare continuous variables in different groups. Significant differences in categorical variables were assessed using the Pearson chi-square test. A *P* value < 0.05 was considered to be statistically significant.

RESULTS

Baseline patient characteristics are shown in Table 1. Left ventricular hypertrophy (assessed echocardiographically) was present in 36 patients (48%), the majority of whom (n = 24; 67%) had preserved left ventricular function (group B). Patients in both groups showed no evidence of cardiac arrhythmias before DSE. Syncope or presyncope were present in 10% and 4% of patients in group A and B, respectively (Table 1). In group A, increases from baseline to peak infusion were seen in both the mean pressure gradient (from 25 ± 11 mmHg to 36 ± 15 mmHg) and aortic valve area (from 0.9 ± 0.3 cm² to 1.1 ± 0.4 cm²). Likewise, in group B, increases from baseline to peak infusion were seen in both the mean pressure gradient (from 23.5 ± 12 mmHg to 31.5 ± 14 mmHg) and aortic valve area (from 1.0 ± 0.2 cm² to 1.1 ± 0.3 cm²). Aortic valve indexes and DSE results are presented in Table 2.

Side effects

The mean rate of dobutamine infusion was 15.5 ± 5.0 µg/kg/min in

Table I: Baseline patient characteristics.

Parameter	Group A (n = 20)	Group B (n = 55)
Male:female ratio	15:5	34:21
Age (years) [†]	64 ± 13	69 ± 12
Prior revascularization	4 (20)	10 (18)
Prior myocardial infarction	6 (30)	20 (36)
Heart failure (NYHA class III/IV)	13 (65)	4 (7)
Syncope/presyncope	2 (10)	2 (4)
LVEF (%) [*]	25 ± 6	51 ± 8
Echocardiographic LVH [‡]	12 (33)	24 (67)
Resting electrocardiogram		
Q-waves	5 (25)	17 (31)
LVH	3 (15)	2 (4)
LBBB	4 (20)	5 (9)

^{*}Values are mean ± SD.

[†]End-diastolic thickness of the anterior septum ≥ 12 mm.

Values in parentheses are percentages.

LBBB: Left bundle branch block; LVEF: Left ventricular ejection fraction; LVH: Left ventricular hypertrophy.

Table 2: Aortic valve indexes and dobutamine stress results in patients of group A (n = 20) and group B (n = 55).

Parameter	At rest			Dobutamine infusion		
	Group A	Group B	p-value	Group A	Group B	p-value
MPG (mmHg)	25 ± 11	23.5 ± 12	NS	36 ± 15	31.5 ± 14	NS
AVA (cm ²)	0.9 ± 0.3	1.0 ± 0.2	NS	1.1 ± 0.4	1.1 ± 0.3	NS
Heart rate (beats/min)	76 ± 11	75 ± 17	NS	87 ± 23	118 ± 23	<0.001
SBP (mmHg)	125 ± 34	138 ± 28	NS	125 ± 31	126 ± 32	NS
DBP (mmHg)	67 ± 16	71 ± 13	NS	65 ± 14	66 ± 15	NS
Rate-pressure product	9542 ± 3295	10310 ± 3010	NS	11013 ± 4789	14958 ± 4938	0.003
WMSI	2.7 ± 1.0	1.5 ± 0.8	<0.001	2.3 ± 1.0	1.4 ± 0.7	<0.001
LVEF (%)	25 ± 6	51 ± 8	<0.001	37 ± 8	75 ± 12	<0.001

Values are mean ± SD.

AVA: Aortic valve area; DBP: Diastolic blood pressure; LVEF: Left ventricular ejection fraction; MPG: Mean pressure gradient;

NS: Not significant; SBP: Systolic blood pressure; WMSI: Wall motion score index.

group A, and $32.0 \pm 11.0 \mu\text{g/kg/min}$ in group B. Serious cardiac arrhythmias occurred in 10 patients (Table 3). Four patients (20%) in group A developed non-sustained ventricular tachycardia, two of which contained more than 10 continuous complexes. In group B, two patients (4%) developed non-sustained ventricular tachycardia with less than 10 continuous complexes, and four experienced paroxysmal supraventricular

Table 3: Significant side effects during dobutamine stress echocardiography in groups A and B.

Side effect	Group A n (%)	Group B n (%)
Arrhythmias		
NSVT		
>10 complexes	2 (10)	-
≤10 complexes	2 (10)	2 (3.6)
SVT	-	4 (7.2)
Hypotension*	-	2 (3.6)

*Symptomatic decrease of systolic blood pressure $\geq 40 \text{ mmHg}$ compared to resting value.

NSVT: Non-sustained ventricular tachycardia; SVT: Supraventricular tachycardia.

tachycardia (7%), including one patient with atrial fibrillation. All patients who developed non-sustained ventricular tachycardia in group A had fixed aortic stenosis and a LVEF $\leq 30\%$. The two patients with non-sustained ventricular tachycardia in group B developed arrhythmias at peak dose dobutamine infusion. At that time, stress-induced ischemia

was evident echocardiographically in both patients. In group B, two patients had severe stress-induced hypotension; both developed dizziness and nausea, but the symptoms resolved after intravenous fluid administration and passive leg elevation. The characteristics of the 12 patients who developed serious side effects are listed in Table 4.

Interestingly, patients with stress-induced ischaemia did not differ with respect to the incidence of side effects, compared to patients without ischaemia on DSE (three patients with side effects out of 20 with stress-induced ischemia vs. nine patients with side effects out of 55 patients without ischemia, $P = 0.922$). In addition, among patients in group B that received atropine in order to reach the target heart rate, only one patient developed non-sustained ventricular tachycardia ($P = 0.637$ for the comparison with patients without atropine administration). Medical treatment, cardioversion or hospitalization were unnecessary as all side effects completely resolved within minutes after cessation of dobutamine infusion.

Table 4. Patients with serious side effects.

Patient no.	Age (years)	At rest			Maximum dobutamine rate			Side effect
		MPG (mmHg)	AVA (cm ²)	LVEF (%)	MPG (mmHg)	AVA (cm ²)	LVEF (%)	
Group A								
1	57	16	1.2	25	27	1.3	32	NSVT
2	66	35	0.8	23	42	0.7	28	NSVT
3	70	15	0.8	15	24	0.9	19	NSVT
4	64	35	0.9	28	47	0.9	34	NSVT
Group B								
1	77	18	1.2	66	25	1.2	78	SVT
2	80	18	1.1	62	20	1	80	SVT
3	68	28	1	56	35	1.1	69	SVT
4	72	24	1.3	58	29	1.7	76	SVT
5	69	21	1.2	60	20	1.2	78	HT*
6	79	15	1.3	50	23	1.5	72	HT*
7	56	22	1	40	24	1	68	NSVT
8	60	23	1.2	40	35	1.3	60	NSVT

*Symptomatic decrease of systolic blood pressure ≥ 40 mmHg compared to resting value.

AVA: Aortic valve area; HT: Hypotension; LVEF: Left ventricular ejection fraction; MPG: Mean pressure gradient; NSVT: Nonsustained ventricular tachycardia; SVT: Supraventricular tachycardia.

DISCUSSION

In the present study, a high number of incidents of cardiac arrhythmia and symptomatic hypotension developed in the patients. The high incidence of potentially life-threatening arrhythmias -especially in those patients with a low LVEF- suggests that poor left ventricular function and a fixed aortic stenosis can further lead to sustained ventricular tachycardia or ventricular fibrillation. Hence, these patients should be closely observed and there must be advanced cardiac life support-trained personnel available in close proximity.

Because of the aging population and degenerative changes in the aortic valve, aortic stenosis is currently the third most important cardiac disease in western society.¹⁰ Although low-dose DSE is recommended and is claimed to be safe in patients with aortic stenosis and reduced left ventricular function to distinguish a fixed from a flow-dependent stenosis, cardiac arrhythmia is frequently induced.^{5,6} The mechanisms responsible for cardiac arrhythmia in patients with aortic stenosis are complex. Stress increases cardiac output by both positive inotropic and chronotropic effects, whilst peripheral vascular resistance decreases. The resulting vasodilation is discordant to the fixed stroke volume in patients with aortic stenosis.¹¹ Cardiac output at rest usually remains within normal limits, but often fails to increase sufficiently during stress, resulting in an acute elevation of pulmonary pressure. This mechanism can cause dyspnea and a drop in systolic arterial blood pressure, leading to symptomatic hypotension which, together with the increase in wall stress, results in subendocardial hypoperfusion and ischemia.¹² However, subendocardial ischemic foci may be present and missed by visual wall motion scoring. These foci may serve as a substrate for arrhythmia, especially in the presence of epicardial coronary artery disease and ischemic cardiomyopathy. In the present study, a number of patients had known coronary artery disease (prior revascularization, and/or myocardial infarction). In group A (the low LVEF group), three of the patients had undergone previous coronary artery bypass surgery, and revascularization had been performed at least three years before the dobutamine stress test. It is likely that, at

the time of the surgery, there was no indication for simultaneous aortic valve replacement. After the test, five patients in group A underwent coronary angiography, and this revealed two patients with three-vessel disease, one patient with one-vessel disease, and one with significant stenosis in a vein graft. In group B, 18 patients with stress-induced ischemia on dobutamine stress testing underwent coronary angiography; of these patients, two had normal coronary arteries, 13 had severe stenosis in at least one vessel, and three had stenoses in one or more vein grafts.

Previous studies

DSE was found to be quite safe in patients with poor left ventricular function, without aortic stenosis.¹³ However, an increased incidence of serious cardiac arrhythmia and hypotension in patients with aortic stenosis has been reported in previous studies. Lin et al.⁵ studied 27 patients with an aortic valve area $< 1 \text{ cm}^2$ and reported four cases of atrial tachyarrhythmia (15%), four cases of hypotension (15%), and no ventricular tachycardia. In the study of Plonska et al.⁶, symptomatic hypotension occurred in 16 patients (10%), and ventricular and supraventricular tachyarrhythmia (including premature ventricular contractions) in 33 (21%). The present study confirms these observations, as a quite large proportion of the patients in group A (20%) and group B (11%) developed tachycardias. In addition, 4% of the patients in group B had severe symptomatic hypotension. A large study performed at the present authors' center, included 1737 patients with proven or suspected coronary artery disease who underwent DSE between 1989 and 1997. The incidence of cardiac arrhythmias in this large population was 5% (ventricular fibrillation in three patients, sustained ventricular tachycardia in 13, ventricular tachycardia with less than 10 complexes in 44, and atrial fibrillation in 27). Severe symptomatic hypotension occurred in 0.4% of patients, although the total percentage of hypotensive episodes was 4%.¹⁴

In contrast to DSE studies, single-photon emission computed tomography with adenosine, a vasodilator, was not associated with

cardiac arrhythmias in a group of 35 patients with moderate to severe aortic stenosis.¹⁵

Study limitations

In patients studied with low-dose dobutamine (group A), the presence of ischaemia was difficult to assess, and some of the arrhythmias observed may have been ischaemic in origin. Moreover, the mean dobutamine infusion rate in group A exceeded the normally used low-dose rate of 10 $\mu\text{g}/\text{kg}/\text{min}$, and this may have contributed to the high incidence of arrhythmias in these patients.

In conclusion, during DSE, patients with low-gradient aortic stenosis and left ventricular dysfunction are susceptible to potentially life-threatening arrhythmias. When the results of DSE are likely to influence the patient's management, then low dose DSE should be performed under close monitoring. In patients with mild or moderate aortic stenosis, and with normal or mildly reduced left ventricular function, DSE is relatively safe, but arrhythmias and hypotension can occur during a high-dose dobutamine challenge. In these patients an alternative non-invasive test for the diagnosis of coronary artery disease, such as adenosine perfusion scintigraphy, should be considered.

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CHAPTER 5

PROGNOSTIC VALUE OF DOBUTAMINE STRESS ECHOCARDIOGRAPHY IN PATIENTS WITH PREVIOUS CORONARY REVASCULARIZATION



Source: M Bountiukos, A Elhendy, RT van Domburg, AFL Schinkel,
JJ Bax, BJ Krenning, V Rizzello, JRTC Roelandt, D Poldermans
Heart (in press). **Adapted**

ABSTRACT

Objective: to assess the prognostic value of dobutamine stress echocardiography (DSE) in patients with previous myocardial revascularization.

Design: A prospective study.

Setting: Thoraxcenter, Erasmus MC, Rotterdam, The Netherlands..

Patients: A total of 332 consecutive patients with previous percutaneous or surgical coronary revascularization who underwent DSE. Follow-up was successful in 331 (99.7%) patients. Thirty-eight patients who underwent early revascularization (≤ 3 months) after the test were excluded from analysis.

Main outcome measures: Cox proportional-hazards regression models were used to identify independent predictors of the composite of cardiac events (cardiac death, nonfatal myocardial infarction and late revascularization).

Results: During a mean of 24 ± 20 months, $37 \pm 13\%$ patients died, and $89 \pm 30\%$ had at least one cardiac event (21[7%] cardiac deaths, 11[4%] non-fatal myocardial infarctions, and 68 [23%] late revascularizations). In multivariate analysis of clinical data, independent predictors of late cardiac events were hypertension (hazard ratio [HR]: 1.7, 95% confidence interval [CI] 1.1 to 2.6), and congestive heart failure (HR: 2.1, 95% CI 1.3 to 3.2). Reversible wall motion abnormalities (ischemia) on DSE were incrementally predictive of cardiac events (HR: 2.1, 95% CI 1.3 to 3.2).

Conclusions: Myocardial ischemia during DSE is independently predictive of cardiac events in patients with previous myocardial revascularization, after controlling for clinical data.

INTRODUCTION

Over the past decade, advances in the invasive management of patients with chronic coronary artery disease have evolved dramatically. Thus, patients with previous coronary interventions comprise a growing subgroup of patients referred for non-invasive testing to evaluate symptoms or to rule out coronary restenosis, graft occlusion, or progression of coronary artery disease. However, the clinical utility of stress testing in the setting of prior surgical or percutaneous coronary intervention has been questioned.¹⁻³

Dobutamine stress echocardiography (DSE) has been established as a safe, feasible, and accurate technique for the detection of myocardial ischemia and assessment of prognosis in patients with known or suspected coronary artery disease, particularly in those patients who are unable to perform an adequate exercise stress test.⁴⁻⁶ However, the prognostic value of DSE in patients with previous coronary revascularization has not been established. Accordingly, the aim of this study was to assess whether DSE has additive prognostic value relative to clinical variables in patients with previous coronary revascularization.

METHODS

Patient population

The study population consisted of 332 consecutive patients with previous coronary revascularization. Patients were unable to perform an exercise test due to orthopaedic limitations, peripheral arterial or neurological diseases, respiratory insufficiency, or deconditioning, and underwent DSE in our center. In case that patients underwent DSE more than once after revascularisation, only the results of the first test were included in the study. All patients were included in an electronic registry that accumulated in the course of daily clinical care. Informed consent was given before testing. The Hospital Ethics Committee approved the protocol.

Clinical data

Before the dobutamine stress test, a structured interview and clinical history, including assessment of cardiac risk factors, were obtained. Congestive heart failure was assessed as any current or previous signs or symptoms of breathlessness, abnormal fluid retention, or both. Hypertension was defined as a blood pressure of $\geq 140/90$ mmHg or treatment with antihypertensive medication. Diabetes mellitus was defined as a fasting glucose level of ≥ 140 mg/dl or the need for insulin or oral hypoglycaemic agents. Hypercholesterolemia was defined as total cholesterol of ≥ 200 mg/dl or treatment with lipid-lowering medication.

Dobutamine stress protocol

Dobutamine stress testing was performed according to a standard protocol as previously reported.⁶ Dobutamine was administered intravenously, starting at a dose of $10 \mu\text{g}/\text{kg}/\text{min}$ for 3 min ($5 \mu\text{g}/\text{kg}/\text{min}$ in patients with resting left ventricular dysfunction). Incremental dobutamine doses of $10 \mu\text{g}/\text{kg}/\text{min}$ were given at 3 min intervals up to a maximum dose of $40 \mu\text{g}/\text{kg}/\text{min}$. If the test end-point was not reached at a dobutamine dose of $40 \mu\text{g}/\text{kg}/\text{min}$, atropine (up to 2 mg) was given intravenously. Blood pressure, heart rate, and electrocardiography were constantly monitored. Test end-points were achievement of target heart rate (85% of maximum age and gender predicted heart rate), horizontal or downsloping ST-segment depression > 2 mm at an interval of 80 ms after the J-point compared with baseline, severe angina, systolic blood pressure fall > 40 mmHg, blood pressure $> 240/120$ mmHg, or significant cardiac arrhythmia. An intravenous β -blocker was available to reverse the adverse effects of dobutamine/atropine.

Stress echocardiography

Two-dimensional echocardiographic images were acquired at rest,

during dobutamine stress, and during recovery. The echocardiograms were recorded in a quad-screen format. Two experienced observers scored the echocardiograms using a standard 16-segment model as recommended by the American Society of Echocardiography.⁷ Regional wall motion and systolic wall thickening were scored on a 5-point scale (1 = normal, 2 = mild hypokinesia, 3 = severe hypokinesia, 4 = akinesia, 5 = dyskinesia). 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. Ischemia was not considered to be present when akinetic segments at rest became dyskinetic during stress. For each patient, a wall motion score index was calculated at rest and at peak dobutamine stress by dividing the sum of segment scores by the total number of interpreted segments.

Follow-up

Follow-up data were obtained in 2003. The mean follow-up period was 24 ± 20 months. The current status was determined by contacting the patient's general practitioner and by reviewing hospital records. The date of the last review or consultation was used to calculate the follow-up time. An outcome event was the composite of cardiac death, non-fatal myocardial infarction, and late (> 3 months) coronary revascularization. Cardiac death was defined as death caused by acute myocardial infarction, significant cardiac arrhythmias, or refractory congestive heart failure. Sudden death occurring without another explanation was included as cardiac death. Non-fatal myocardial infarction was defined according to the guidelines of the joint European Society of Cardiology/American College of Cardiology Committee.⁸

Statistical analysis

Data were expressed as mean value \pm standard deviation or number (%), and compared using the Student *t* test or χ^2 test. Univariate and multivariate Cox proportional-hazards regression models were used to

identify independent predictors of late cardiac events. The clinical variables that were entered into the model were gender, age, history of previous myocardial infarction, current smoking, hypertension, hypercholesterolaemia, heart failure, angina pectoris, and the use of β -blockers, diuretics, digoxin, calcium antagonists and ACE-antagonists. The echo variables were fixed wall motion abnormalities, reversible wall motion abnormalities or both, achievement of target heart rate, and typical angina and/or ST depression during the stress test. Variables were selected in a stepwise forward selection manner with entry and retention set at a significance level of 0.05. The incremental value of DSE over the clinical variables in the prediction of events was assessed by adding different echocardiographic data to clinical and stress test parameters. The risk of a variable was expressed as a hazard ratio with a corresponding 95% confidence interval (CI). The probability of cardiac event-free survival was calculated using the Kaplan-Meier method, and the resulting curves were compared using the log-rank test.

RESULTS

Clinical and stress test results

Clinical characteristics of patients are presented in Table 1. During DSE there was a significant increase in heart rate (from 74 ± 14 to 132 ± 15 beats per minute, $P < 0.001$), whereas no significant change of systolic blood pressure occurred (131 ± 24 vs. 129 ± 24 mmHg). The mean maximal dobutamine dose was 37 ± 8 $\mu\text{g}/\text{kg}/\text{min}$. Atropine was added in 153 (52%) of patients. Target heart rate was achieved in 252 (86%) patients. Side effects during DSE were: short runs of ventricular tachycardia (< 10 complexes) in 10 (3%) patients, ventricular tachycardia of ≥ 10 complexes in three (1%), transient atrial fibrillation in 3 (1%), and severe hypotension (symptomatic, or decrease in systolic blood pressure of > 40 mmHg) in four (1%). No patient experienced a myocardial infarction or life-threatening rhythm disorders.

Table 1. *Baseline clinical characteristics.*

Age (years)	62 (11)
Males	217 (74%)
Hypertension	119 (40%)
Diabetes mellitus	97 (33%)
Smoking	97 (33%)
Hypercholesterolemia	120 (41%)
Congestive heart failure	46 (16%)
Myocardial infarction	203 (69%)
Coronary angioplasty	174 (59%)
Coronary artery bypass surgery	171 (58%)
1-vessel disease	141 (48%)
2-vessels disease	94 (32%)
3-vessels or left main disease	58 (20%)
Complete revascularisation	202 (69%)
Incomplete revascularisation	91 (31%)
Medication	
Beta-blockers	127 (43%)
Angiotensin converting enzyme inhibitors	128 (44%)
Calcium antagonists	121 (41%)

Values are expressed as mean (standard deviation), or number (%).

Echocardiographic data

The test was abnormal (fixed and/or reversible wall motion abnormalities) in 241 (82%) patients. Ischemia (new or worsening wall motion abnormalities) was detected in 96 (33%) patients. Of these patients, 75 had resting wall motion abnormalities as well.

Follow-up data

Follow-up was successful in 331 (99.7%) patients. The decision for late revascularisation was based on the recurrence of symptomatic coronary artery disease, or on the occurrence of an acute coronary event (unstable angina, acute myocardial infarction) at least three months apart from the first postrevascularisation DSE.

Thirty-eight patients who underwent coronary revascularization within three months of DSE were excluded from analysis, because in these patients the decision to revascularize might have been influenced by test results. In the remaining 293 patients, 37 (13%) deaths from any cause occurred, whilst 89 (30%) patients had at least one cardiac event; 21 (7%) patients had a cardiac death, 11 (4%) had a non-fatal myocardial infarction, and 68 (23%) had a late revascularization.

Predictors of cardiac events

Univariate predictors of the composite of cardiac events were congestive heart failure (hazard ratio [HR]: 2, 95% CI 1 to 3.8), wall motion score index (WMSI) at rest (HR: 2.7, 95% CI 1.4 to 5), WMSI at peak (HR: 2, 95% CI 1.2 to 3.3), reversible wall motion defects (ischemia) on DSE (HR: 2.9, 95% CI 1.7 to 4.8), ST-segment depression (HR: 2.8, 95% CI 1.2 to 6.3) and angina pectoris (HR: 2, 95% CI 1.2 to 3.5) during the test. Multivariate predictors were hypertension (HR: 1.7, 95% CI 1.1 to 2.6), congestive heart failure (HR: 2.1, 95% CI 1.3 to 3.2), ischemia on DSE (HR: 2.1, 95% CI 1.3 to 3.2) (Figure 1), and ST-segment depression on DSE (HR: 2, 95% CI

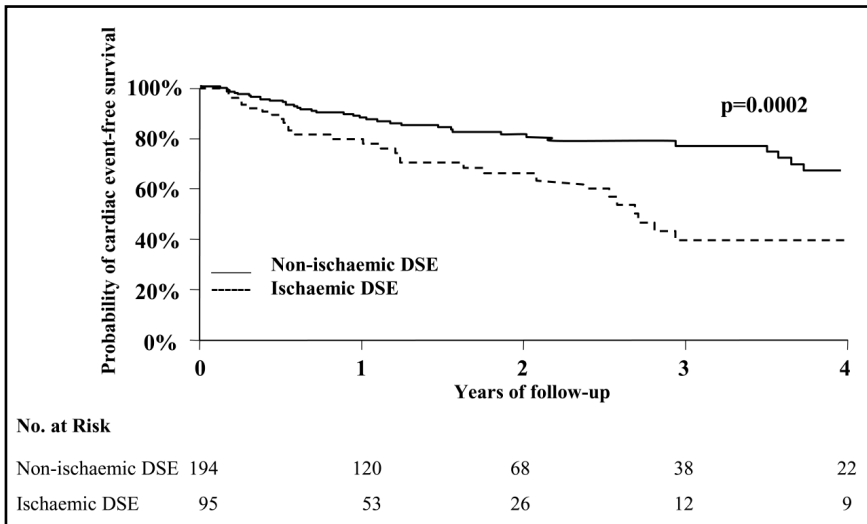


Figure 1. Kaplan-Meier curves for cardiac events (cardiac death/nonfatal myocardial infarction/late revascularisation) as a function of dobutamine stress echocardiography results. A significant difference in event-free survival exists between patients with and without reversible wall motion defects (ischemia).

1.1 to 3.8). Among patients showing ischemia on DSE, those who had a prior coronary intervention less than two years before the test had a trend toward more cardiac events, in comparison with those having been revascularized more than two years before ($P = 0.09$) (Figure 2). The adverse outcome in patients with ischemia did not differ irrespective of the presence or absence of angina before the test (Figure 3).

Predictors of cardiac death

Univariate predictors of cardiac death were diabetes mellitus (hazard ratio [HR]: 3.6, 95% CI 1.2 to 11.4) and congestive heart failure (HR: 6.8, 95% CI 2.8 to 16.3). The same predictors were found after multivariate analysis (HR: 4.9, 95% CI 1.4 to 17.3 for diabetes mellitus, and HR: 10.5, 95% CI 3.8 to 29.3 for congestive heart failure).

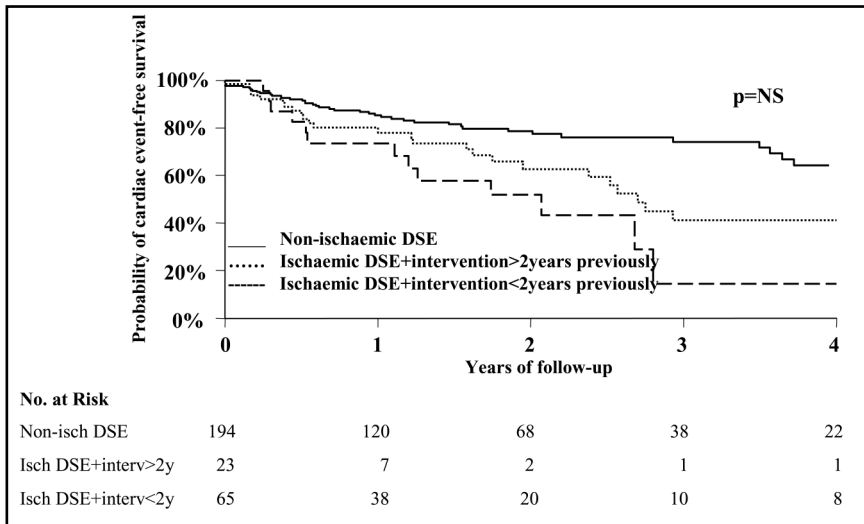


Figure 2. Kaplan-Meier curves for cardiac events (cardiac death/nonfatal myocardial infarction/late revascularisation) as a function of dobutamine stress echocardiography results. Among patients with reversible wall motion defects (ischemia) there is no significant difference in event-free survival between patients who were revascularised > 2 years or < 2 years before the test.

Predictors of heard events

The only predictor of heard events (cardiac death plus myocardial infarction) was congestive heart failure (HR: 4.7, 95% CI 2.3 to 9.6 in univariate analysis, and HR: 8.1, 95% CI 3.5 to 18.5 in multivariate analysis).

DISCUSSION

We assessed the independent value of DSE for prediction of cardiac events in 331 patients with previous revascularization. During a mean period of 24 ± 20 months, 89 patients had at least one late cardiac event. The presence of congestive heart failure could predict cardiac

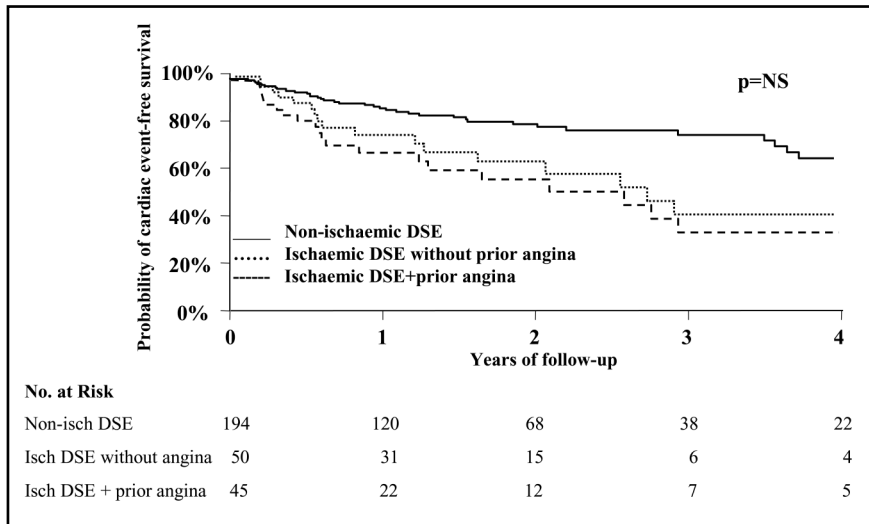


Figure 3. Kaplan-Meier curves for cardiac events (cardiac death/nonfatal myocardial infarction/late revascularisation) as a function of dobutamine stress echocardiography results. Among patients with reversible wall motion defects (ischemia) there is no significant difference in event-free survival between patients with and without history of angina pectoris.

death and/or myocardial infarction, whereas diabetes mellitus was an independent predictor of cardiac death. Clinical predictors of cardiac events were hypertension and congestive heart failure. Ischemia on DSE, indicated by reversible wall motion abnormalities, was associated with increased risk of cardiac events after controlling for clinical parameters. According to the classical ischemic cascade, ST segment changes follow perfusion and wall motion abnormalities on imaging stress testing. However Picano has proposed an alternative ischaemic cascade when endothelial dysfunction and impaired coronary flow reserve are present without significant epicardial coronary artery lesions.⁹ According to this model, ST segment changes come first, perfusion abnormalities second, and echocardiographic changes are usually absent in case of milder, “patchy” degrees of myocardial ischemia. Hence, it is likely that coronary endothelial dysfunction and

impaired flow reserve have an adverse effect on prognosis after coronary revascularisation.

The risk associated with myocardial ischemia was observed in patients who had their revascularization performed within two years as well as in patients who had revascularization more than two years prior to DSE.

Impact of symptoms on the outcome

Currently, restenosis constitutes the major limitation of coronary interventions. It occurs usually within several months after a successful percutaneous coronary intervention, with an incidence as high as 33% in some patient subsets.¹⁰ After coronary bypass surgery, the atherosclerotic process increases over the years, leading to vein graft patency of less than 65% 10 years after surgery.¹¹ According to the guidelines of the American College of Cardiology/American Heart Association, stress testing is recommended after coronary revascularization only in patients with recurrent symptoms that suggest ischemia (Class I), or as part of cardiac rehabilitation (Class IIa).¹² However, symptoms after revascularization are commonly atypical, and they cannot be considered as reliable determinants of restenosis or graft occlusion.

The usefulness of noninvasive imaging in asymptomatic patients after coronary revascularization has been questioned in previous studies. Lauer et al studied by exercise thallium-201 873 symptom-free patients after coronary artery bypass grafting and found that thallium-perfusion defects and impaired exercise capacity were strong and independent predictors of death or nonfatal myocardial infarction.¹³ Sarda et al demonstrated an independent predictive value of thallium-201 myocardial scintigraphy after coronary artery bypass grafting in a patient population consisted of mainly asymptomatic patients before the test.¹⁴ In the present study, the presence of angina pectoris before the test was not associated with more cardiac events in patients with reversible wall motion abnormalities on DSE. Consequently, physicians cannot rely upon symptoms after revascularization in order to determine the risk for future cardiac events. Evidence of reversible

wall motion abnormalities during dobutamine stress predicts patients at high risk to develop late cardiac events, even if they are asymptomatic following a coronary intervention. A more aggressive treatment may be justified in these patients.

Comparison with previous studies

A large number of studies have reported on the incremental prognostic value of DSE in the general population,^{1,2,4-6} as well as in particular patient subsets.¹⁵⁻²⁰ To our knowledge, this is the first study to assess the prognostic value of DSE in patients with prior coronary revascularization. However, exercise echocardiography has been found to be predictive for cardiac events in patients after coronary artery bypass surgery.²¹ In addition, several studies have reported on the prognostic value of nuclear scan in previously revascularized patients. Palmas et al found an incremental prognostic value of thallium-201 in 294 patients \geq 5 years after coronary artery bypass graft surgery.²² Miller et al reported similar prognostic value for thallium-201, within two years after surgical revascularization.²³ In other studies, thallium-201 was predictive of cardiac events in patients one to three years after coronary angioplasty,²⁴ and in patients early (5 ± 2 months) after coronary stenting.²⁴ The present findings indicate that DSE can alternatively be used as a prognostic tool in these patients.

Study limitations

Readers of DSE results were not blinded to clinical information and data concerning previous revascularizations. Additionally, treated physicians were free to modify treatment according to DSE results. Thus, administration of medication that has been proven to reduce cardiac events and improve outcome, such as β -blockers and angiotensin-converting enzyme inhibitors, might have influenced patient prognosis. Finally, our results were obtained in a single center with a high volume and experience on DSE; hence they do not necessarily apply to other less experienced centers.

Conclusions

Dobutamine stress echocardiography provides incremental to the clinical data information on the prognosis of patients after revascularization. Evidence of myocardial ischemia, based on reversible wall motion abnormalities during dobutamine infusion is an independent predictor of cardiac events.

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CHAPTER 6

QT DISPERSION CORRELATES
TO MYOCARDIAL VIABILITY ASSESSED
BY DOBUTAMINE STRESS
ECHOCARDIOGRAPHY IN PATIENTS
WITH SEVERELY DEPRESSED
LEFT VENTRICULAR FUNCTION DUE TO
CORONARY ARTERY DISEASE



Source: M Bountiukos, AFL Schinkel, D Poldermans, V Rizzello,
EC Vourvouri, BJ Krenning, E Biagini, JRTC Roelandt, JJ Bax
Eur J Heart Fail 2004 Mar 1;6(2):187-93. **Adapted**

ABSTRACT

Background: QT dispersion is prolonged in numerous cardiac diseases, representing a general repolarization abnormality.

Aim: To evaluate the influence of viable myocardium on QT dispersion in patients with severely depressed left ventricular (LV) function due to coronary artery disease.

Methods and results: 103 patients with ischemic cardiomyopathy (LV ejection fraction [EF]: $25 \pm 6\%$) were studied. Patients underwent 12-lead electrocardiography to assess QT dispersion, and two-dimensional echocardiography to identify segmental dysfunction. Dobutamine stress echocardiography (DSE) was then performed to detect residual viability. Resting echo demonstrated 1260 dysfunctional segments; of these, 476 (38%) were viable. Substantial viability (≥ 4 viable segments on DSE) was found in 62 (60%) patients. QT dispersion was lower in these patients, than in patients without viability (55 ± 17 ms vs. 65 ± 22 ms, $P = 0.012$). Viable segments negatively correlated to QT dispersion ($r = -0.333$, $P = 0.001$). In contrast, there was no correlation between LVEF and QT dispersion ($r = -0.001$, $P = \text{NS}$).

Conclusions: There is a negative correlation between QT dispersion and the number of viable segments assessed by DSE. Patients with severely depressed LV function and a low QT dispersion probably have a substantial amount of viable tissue. Conversely, when QT dispersion is high, the likelihood of substantial viability is reduced.

INTRODUCTION

A number of prospective studies have assessed the predictive value of QT dispersion for cardiac and all-cause mortality in the general population.^{1,2} QT dispersion has been demonstrated to be prolonged in patients with various cardiac diseases; this is consistent with the concept that QT dispersion represents a general repolarization abnormality.³⁻⁷ A limited number of studies have investigated the value of QT dispersion to predict myocardial viability in the setting of chronic coronary artery disease.⁸⁻¹⁰ However, in most of these studies, patients had a relatively preserved left ventricular function. Current information on the relation of QT dispersion to the amount of viable myocardium in patients with ischemic cardiomyopathy is contradictory.

Accordingly, the aim of this study was to evaluate whether QT dispersion correlates to myocardial viability, assessed by dobutamine stress echocardiography, in a cohort of patients with severely depressed left ventricular (LV) function due to chronic coronary artery disease.

METHODS

Eligibility

A total of 103 consecutive patients were referred for dobutamine stress echocardiography for the assessment of myocardial viability were included in the study. Patients had ischemic cardiomyopathy and a radionuclide LV ejection fraction (EF) \leq 35%. In all patients, a resting 12-lead surface electrocardiogram (ECG) was performed. Exclusion criteria were: (1) recent (< 3 months) myocardial infarction; (2) non-sinus rhythm or left bundle branch block on ECG; (3) antiarrhythmic medication that could influence QT interval (class IA, IC, and III agents); and (4) suboptimal acoustic window. The Hospital Ethics Committee approved the protocol. All patients gave informed consent before the test.

Measurement of QT dispersion

Patients underwent surface electrocardiography with simultaneous 12-lead recordings, in order to avoid the effect of heart rate changes on QT dynamics. A single observer, who was blinded to the dobutamine stress echocardiography results, performed the analysis. A dedicated computer program (Mortara Instruments, Bilthoven, The Netherlands) was used for this purpose. On-screen measurement with electronic calipers and magnification, in order to obtain the maximal electrocardiographic detail, was used. The T wave offset was determined as an interception between a line characterizing the slope of the descending part of the T wave and the isoelectric line. The slope-characterizing line was a tangent to the point of steepest slope. When a U wave was also present, the nadir between the T and the U wave was considered the point of T wave offset.¹¹ QT dispersion was defined as the difference between the maximum and the minimum QT intervals on 12-lead ECG. Rate-corrected (QTc) interval was calculated by dividing QT interval by the square root of RR interval on ECG. Accordingly, QTc dispersion was the difference between the maximum and the minimum QTc interval. Measurements were repeated after a week in 60 randomly selected patients. Intraobserver variability for QT dispersion was 7.4 ± 5.0 ms.

Resting 2D echocardiography, assessment of regional dysfunction

A commercially available imaging system (Hewlett Packard Sonos 5500, Andover, MA, USA) and a 1.8 MHz transducer using second harmonic imaging to optimize endocardial border visualization were used. Two-dimensional imaging was performed with the patient in the left lateral position; standard views were recorded on optical disk (cine loops).¹²

Dobutamine stress echocardiography

To assess myocardial viability in dysfunctional myocardium,

dobutamine stress echocardiography was performed. After the resting echocardiographic study, dobutamine was administered intravenously, starting at a dose of 5 $\mu\text{g}/\text{kg}$ per min for 5 min, followed by a 10 $\mu\text{g}/\text{kg}$ per min dose for 5 min (low dose). Subsequently, the rate of dobutamine infusion was increased by 10 $\mu\text{g}/\text{kg}$ per min every 3 min to a maximum dose of 40 $\mu\text{g}/\text{kg}$ per min. Atropine (up to 2 mg) was added at the end of the last stage if the target heart rate had not been achieved. End points for interruption of the test were: (1) achievement of target heart rate; (2) maximal doses of both dobutamine and atropine; (3) extensive new wall motion abnormalities; (4) new horizontal or downsloping ST-segment depression ≥ 0.2 mV 80 ms after the J point; (5) severe angina; (6) symptomatic reduction in systolic blood pressure > 40 mm Hg from baseline; (7) hypertension (blood pressure $> 240/120$ mm Hg); (8) significant arrhythmia; or (9) any serious side effect regarded as being due to dobutamine infusion.

The baseline, low dose, peak stress and recovery images were displayed as a cine loop format. Two experienced observers, unaware of the clinical and electrocardiographic data, scored the digitised echocardiograms offline. In case of disagreement, a majority decision was achieved by considering the opinion of a third observer. For each study, the LV was divided into 16 segments, as described previously. Regional wall motion and systolic wall thickening were scored using a five-point grading scale: 1 = normal, 2 = mildly hypokinetic, 3 = severely hypokinetic, 4 = akinetic, 5 = dyskinetic. Only severely dysfunctional segments (severe hypokinesia, akinesia or dyskinesia at resting echocardiography) were evaluated for myocardial viability. Segments with improvement, worsening, or a biphasic wall motion response during stress echocardiography were considered viable. Segments with unchanged wall motion were considered nonviable.¹³ A patient was classified as viable in the presence of ≥ 4 dysfunctional viable segments.

Assessment of LVEF

The LVEF was assessed by radionuclide ventriculography as follows: A small field-of-view gamma camera system (Orbiter, Siemens,

Erlangen, Germany) was used, oriented in a 45° left anterior oblique position with a 5-10° caudal tilt. After injection of ^{99m}Tc-pertechnetate labeled autologous erythrocytes (550 MBq), radionuclide ventriculography was performed at rest with the patient in supine position. The LVEF was calculated by standard methods (Odyssey VP, Picker, Cleveland, OH, USA).

Statistical analysis

All continuous data are expressed as mean value ± standard deviation. Percentages are rounded. Differences in continuous variables within groups were compared using the paired Student's *t* test, whereas differences between groups were assessed by Student's *t* test for unpaired samples. The Pearson correlation coefficient was used to estimate correlation between variables. Receiver-operating characteristic (ROC) analysis was used to determine optimal cut-off values of QT dispersion and QTc dispersion to predict myocardial viability. The best cut-off value was defined as the point with the highest sum of sensitivity and specificity. All tests were two-sided, and a *P* value < 0.05 was considered statistically significant. Analyses were performed by an SPSS 10.0 software package (SPSS Inc., Chicago, IL, USA).

RESULTS

Patient characteristics and hemodynamic data

Baseline characteristics of the study patients are presented in Table 1. Patients had a mean age of 59 ± 9 years and a mean LVEF of 25 ± 6% (range: 10 - 35%). Most of the patients were in New York Heart Association Class III or IV (78 patients, 76%). In total, 94 (91%) patients had a previous Q-wave myocardial infarction in at least one region (anterior in 72 patients, septal in 16, lateral in 18, and inferoposterior in 33).

Table 1. Baseline patient characteristics

Age (years)	59±9
Gender	
Male	86 (83%)
Female	17 (17%)
LVEF (%)	25±6
Diabetes ^a	16 (16%)
Hypercholesterolemia ^b	43 (42%)
Hypertension ^c	11 (11%)
Current smoking	32 (31%)
Revascularization	
CABG	20 (19%)
PTCA	15 (15%)
Medication	
ACE-inhibitors	81 (79%)
Beta-blockers	60 (58%)
Diuretics	60 (58%)

Data are presented as number (%) of patients or mean value ± standard deviation. CABG = coronary artery bypass grafting; LVEF = left ventricular ejection fraction; PTCA = percutaneous transluminal coronary angioplasty. ^aPatients receiving oral antidiabetics or insulin; ^bDefined as a total cholesterol ≥ 6.4 mmol/L, or treatment with lipid-lowering medication; ^cDefined as a blood pressure ≥ 140/90 mmHg, or treatment with antihypertensive medication.

Dobutamine stress testing was completed without serious adverse events in all patients. The mean infusion rate of dobutamine was 35.7 ± 7.6 µg/kg per min and atropine was added in 51 patients. Heart rate increased from 76.1 ± 14.0 beats per min at baseline to 133.2 ± 9.0 beats per min at peak ($P < 0.001$). All but 8 patients (92%) reached 85% of the maximal predicted for the age heart rate. Systolic and diastolic blood pressures had no significant changes between baseline and peak dobutamine infusion.

Echocardiographic results

From a total of 1648 segments that were evaluated by 2D echocardiography, 1260 (76%) were dysfunctional at rest; of these, 663 (52%) segments were severely hypokinetic, 588 (47%) akinetic, and nine (1%) dyskinetic. Of the 1260 dysfunctional segments, 476 (38%) were viable and 784 (62%) were non-viable according to dobutamine stress echocardiography. A total of 62 (60%) patients had a substantial amount of viable tissue, whereas the remaining 41 (40%) patients had no or limited (≤ 4 viable segments) viability. The distribution of patients with respect to the number of viable segments is shown in Figure 1.

QT dispersion vs. viability

Measurement of QT interval was feasible in ≥ 8 leads in all patients. The mean number of leads measured was 10.5 ± 1.2 . In total, eight

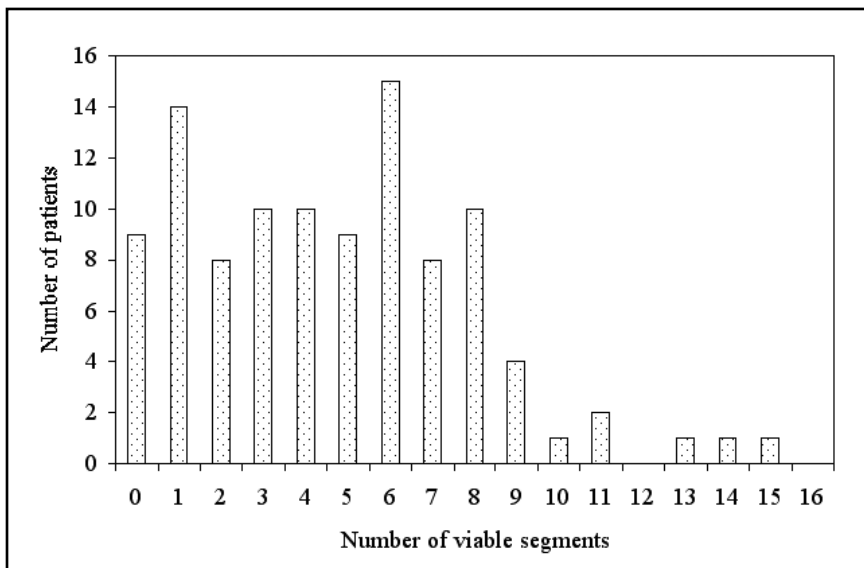


Figure 1. Distribution of study patients ($n = 103$) according to the number of viable segments on dobutamine stress echocardiography

leads were measurable in nine patients (9%), nine leads in 12 (12%), 10 leads in 23 (22%), 11 leads in 32 (31%), and 12 leads in 27 (26%) patients. Mean QT dispersion was 59 ± 20 ms. Heart rate-adjusted QT dispersion (QTc dispersion) was 66 ± 22 ms.

A significant negative correlation was found between QT dispersion and the number of viable myocardial segments on dobutamine stress echocardiography ($r = -0.333$, $P = 0.001$). Similarly, QTc dispersion was negatively correlated to the number of viable segments ($r = -0.303$; $P = 0.002$) (Figure 2). Wall motion score index at rest did not correlate to QT dispersion ($r = 0.033$; $P = 0.739$) or QTc dispersion ($r = 0.126$; $P = 0.204$). In addition, there was no correlation between LVEF and QT dispersion ($r = -0.060$, $P = 0.545$) or QTc dispersion ($r = -0.132$, $P = 0.184$) (Figure 3). Patients with ≥ 4 viable segments on dobutamine stress echocardiography had a significantly lower QT dispersion, compared to patients with < 4 viable segments (55 ± 17 ms vs. 65 ± 22 ms, $P = 0.012$). The difference in QTc dispersion between patients with and without a substantial amount of viable myocardium was also significant (62 ± 21 ms vs. 72 ± 22 ms, $P = 0.032$). A value of QT dispersion ≤ 64 ms had 73% sensitivity and 46 % specificity to predict the presence of viable myocardium (accuracy: 63%). The

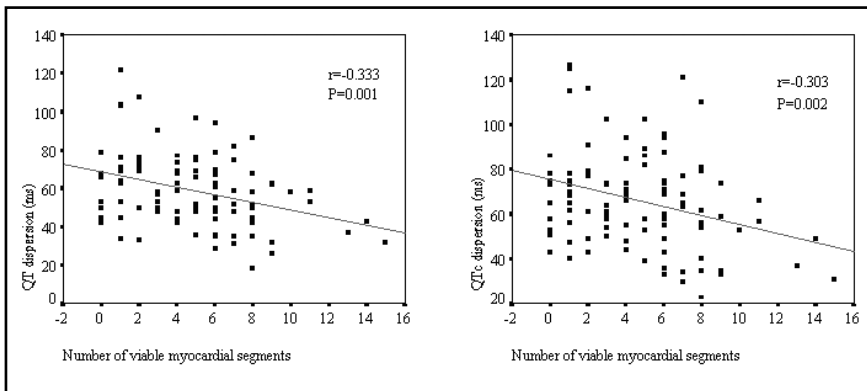


Figure 2. QT dispersion and QTc dispersion are significantly correlated to the number of viable segments on dobutamine stress echocardiography in patients with ischemic cardiomyopathy

corresponding cut-off value for QTc dispersion was 72 ms (sensitivity: 71%, specificity: 46%, accuracy: 61%).

DISCUSSION

Main findings

According to the present study, QT dispersion was negatively correlated to the number of viable myocardial segments, assessed by dobutamine stress echocardiography. Patients with evidence of a substantial amount (≥ 4 segments) of viable myocardium on dobutamine stress echocardiography had significantly lower QT dispersion than patients without viability.

QT dispersion in the setting of heart disease

An increased QT dispersion has been demonstrated in the setting of several cardiac diseases, such as during and after the acute phase of myocardial infarction, in hypertrophic cardiomyopathy, in left

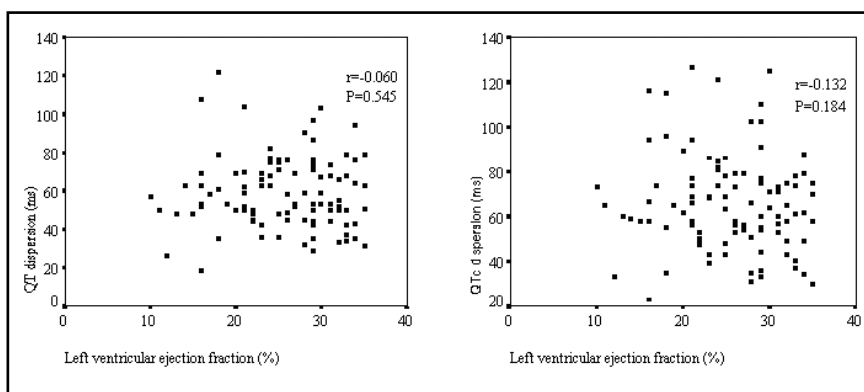


Figure 3. No correlation was found between QT/QTc dispersion and resting radionuclide left ventricular ejection fraction in patients with ischemic cardiomyopathy

ventricular hypertrophy, in idiopathic dilated cardiomyopathy, and in long QT syndrome of various genotypes.³⁻⁷ Prolonged QT dispersion may predict ventricular arrhythmias after myocardial infarction,^{14,15} as well as sudden death in patients with chronic heart failure.¹⁶ In addition, patients with heart failure have a worse outcome when QT dispersion is prolonged,¹⁷ and it has been suggested that one of the mechanisms by which carvedilol improves survival in patients with heart failure may be shortening of QT dispersion.¹⁸

Myocardial viability and QT dispersion

Detection of myocardial viability has become crucial for decision-making in patients with previous myocardial infarction and poor LV systolic function, since several studies have reported on the beneficial effects of revascularization in terms of survival and quality of life in the presence of viable tissue.¹⁹⁻²¹ Moreover, coronary revascularization offers the maximum benefit when a substantial amount of viable myocardium has been detected during non-invasive testing.²²⁻²⁴

The idea of extracting information on the presence of myocardial viability from a simple and inexpensive test, such as the resting surface ECG, is appealing from a clinical point of view. Three studies have reported on the value of QT dispersion to predict viability in patients with chronic coronary artery disease, however the results are conflicting; Ikonomidis et al. studied 75 patients with a previous myocardial infarction and relatively preserved LV function (mean LVEF 34%). QT dispersion was measured at rest and during low dose dobutamine infusion. The authors concluded that the combination of a resting QT dispersion < 65 ms and an increase in QT dispersion > 30% during low dose dobutamine infusion had a sensitivity of 67% and a specificity of 96% to predict viability.⁸ Schneider et al studied 44 patients with chronic Q-wave myocardial infarction using ¹⁸F fluorodeoxyglucose positron emission tomography. As in the present study, patients with viability had low QT dispersion, whereas patients with predominantly nonviable scar tissue had a high QT dispersion. A QT dispersion value ≤ 70 ms had 85% sensitivity and 82% specificity

to predict viability.⁹ Notably, patients in that study had a mildly reduced or preserved LV function. The authors underlined the need for further research in order to establish the applicability of QT dispersion in patients with more severely depressed LV function. Al Mohammad et al used a study with positron emission tomography and ¹⁸F fluorodeoxyglucose to evaluate 42 patients with prior myocardial infarction and poor LV function, and found no correlation between QT dispersion and the presence of viable myocardium.¹⁰ This might be related to the relatively small number of patients enrolled, since there was a trend toward higher QT dispersion in patients without viability.

The present study is the first to report a correlation between QT dispersion and myocardial viability in patients with chronic coronary artery disease and severely depressed LV function. The optimal cut-off values of QT/QTc dispersions found in this study were quite similar to the cut-off values found in previous studies including patients with less severe LV dysfunction. Patients with ischemic cardiomyopathy and a low QT dispersion probably had a substantial amount of viable tissue, whereas in patients with a high QT dispersion the likelihood of substantial viability was low.

Mechanisms of prolongation of QT dispersion in ischemic cardiomyopathy

QT dispersion, when increased, indicates the presence of generalized myocardial electrical instability.¹⁶ In patients with ischemic cardiomyopathy, a large proportion of scarred, fibrous tissue is likely to contribute to an abnormal and inhomogeneous LV repolarization, and thus to increased QT dispersion values.²⁵ Furthermore, ischemic cardiomyopathy is usually accompanied by LV dilatation and increased intracavitary pressures, which can cause load-induced changes in ventricular repolarization.²⁶ In the infarcted LV, dysfunctional segments consist of a combination of fibrotic and hibernating tissue. Infarcted area can be transmural, or localized to subendocardium, with more or less extensive involvement of the exterior myocardial layers. Although dobutamine stress echocardiography has a good accuracy to evaluate

myocardial viability, this variation in the proportion of viable tissue in segments characterized as viable can be responsible for the overlapping QT dispersion values found in viable and non-viable segments in the present study.

Study limitations

Several limitations of this study have to be mentioned. First, measurement of QT intervals is occasionally not accurate, mainly due to inability to assess precisely the offset of T waves. Nevertheless, by measuring only those leads with clear delineation of the end of the T wave, we minimized this limitation. Second, measurement of QT dispersion had a relatively low accuracy to predict viability; therefore QT dispersion currently is not an alternative for non-invasive tests to predict myocardial viability. Further studies are needed to define the clinical role of QT dispersion measurements in the assessment of viable myocardium.

Conclusions

QT dispersion is negatively correlated to the amount of viable myocardium in patients with severely depressed LV function due to chronic coronary artery disease. A low QT dispersion increases the probability that a substantial amount of viable tissue may be found during non-invasive cardiac imaging. Conversely, patients with a high QT dispersion have a low likelihood of substantial viability.

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CHAPTER 7

RELATION BETWEEN QT DISPERSION AND MYOCARDIAL VIABILITY IN ISCHEMIC CARDIOMYOPATHY



Source: AFL Schinkel, M Bountiukos, D Poldermans, A Elhendy,
R Valkema, EC Vourvouri, E Biagini, V Rizzello, MD Kertai,
B Krenning, EP Krenning, JRTC Roelandt, JJ Bax.
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ABSTRACT

The aim of this study was to evaluate the relation between QT dispersion and myocardial viability as assessed by single-photon emission computed tomography. The study population included 97 consecutive patients with severely impaired left ventricular function secondary to chronic coronary artery disease. Patients with a low QT dispersion had a substantial amount of viable myocardium, whereas patients with a high QT dispersion had predominantly nonviable scar tissue.

INTRODUCTION

More than a decade ago, measurement of QT dispersion (the difference between the maximum and minimum QT interval) was proposed as an index of spatial differences in myocardial recovery time.¹⁻³ QT dispersion may be increased in coronary artery disease,^{4,5} and may be associated with increased cardiac and all-cause mortality.⁶⁻⁸ Moreover, a decrease of QT dispersion has been described after medical treatment or myocardial revascularization.^{9,10} Recently, it has been suggested that QT dispersion is related to the amount of dysfunctional but viable myocardium.^{10,11} The aim of this study was to assess the relation between QT dispersion on 12-lead surface electrocardiography and myocardial viability as assessed by single-photon emission computed tomography (SPECT) and ¹⁸F fluorodeoxyglucose (FDG; a marker of cardiac glucose utilization) in a large group of patients with ischemic Cardiomyopathy.

METHODS

The study population included 97 consecutive patients with severely impaired left ventricular (LV) function (LV ejection fraction [EF] < 35%) secondary to chronic coronary artery disease. Patients with left bundle branch block, primary cardiomyopathy, or concomitant significant valvular disease were not included. All patients underwent 12-lead electrocardiography to assess QT dispersion, echocardiography at rest to identify regional wall motion abnormalities, dual-isotope simultaneous acquisition SPECT to assess myocardial viability, and radionuclide ventriculography to assess LVEF. All patients gave informed consent and the hospital medical ethics committee approved the protocol.

An experienced observer, unaware of any other data, read the 12-lead surface electrocardiograms, using a dedicated computer system (Mortara Instruments, Bilthoven, The Netherlands). T-wave offset was determined as an interception between a line characterizing the slope of the descending part of the T wave with the isoelectric line. The slope-

characterizing line was a tangent to the point of steepest slope. When a U wave was also present, the nadir between the T and U waves was considered the point of T-wave offset. QT dispersion was defined as the difference between the maximum and minimum QT.¹² Similarly, QTc dispersion (QT dispersion corrected for heart rate) was calculated.

Two-dimensional echocardiography at rest was performed using a Sonos-5500 system (Hewlett Packard, Andover, Massachusetts). Four standard views were recorded, and two experienced reviewers blinded to the other data scored the echocardiograms. Regional wall motion and systolic wall thickening were scored using a 16-segment model and a five-point scale.¹³

Patients received an intravenous injection of technetium-99m (^{99m}Tc) tetrofosmin (600 MBq) to evaluate perfusion at rest. FDG imaging, to evaluate glucose utilization, was performed after oral administration of Acipimox (500 mg, Byk, The Netherlands).^{14,15} A triplehead gamma camera system (Picker Prism 3000XP, Cleveland, Ohio) with high-energy 511-keV collimators was used for FDG imaging.¹⁶ Energies were centered on the 140-keV photon peak of ^{99m}Tc tetrofosmin with a 15% window and on the 511-keV photo peak of FDG with a 15% window. The ^{99m}Tc tetrofosmin and the FDG data were reconstructed simultaneously, using a similar 16-segment model to that used for the echo data.¹³ Both ^{99m}Tc tetrofosmin and FDG uptake were graded on a four-point scale. Dysfunctional myocardium with a ^{99m}Tc tetrofosmin uptake score of ≤ 1 or a reduction in ^{99m}Tc tetrofosmin uptake score more severe than the reduction in FDG activity by ≥ 1 point (mismatch pattern) was considered viable. Dysfunctional myocardium with concordantly reduced ^{99m}Tc tetrofosmin and FDG uptake was considered nonviable. To assess LVEF, a small field-of-view gamma camera system (Orbiter, Siemens, Erlangen, Germany) was used. After injection of ^{99m}Tc pertechnetate, labeled as autologous erythrocytes (550 MBq), radionuclide ventriculography was performed and the LVEF was calculated (Odyssey VP, Picker, Cleveland, Ohio).

All continuous data are expressed as mean \pm SD; percentages are rounded. Continuous variables were compared using the Student's *t* test for unpaired samples. Differences between proportions were compared

using the chi-square test. Receiver-operating characteristic (ROC) curve analysis was used to identify the QT dispersion and QTc dispersion values that were related to the presence of a substantial amount of viable myocardium. The optimal cut-off value was the QT dispersion that yielded the highest sensitivity and specificity. A *P* value < 0.05 was considered statistically significant.

RESULTS

The clinical characteristics of the 97 patients (81 men, mean age 59 ± 9 years) are listed in Table 1. All patients had heart failure symptoms and severely impaired LV function (LVEF was an average of $26 \pm 9\%$). Two-dimensional echocardiography demonstrated normal contraction in 360 segments (23%) and reduced or absent contractility in 1192 segments (77%). Of the 1192 dysfunctional segments, 639 segments were severely hypokinetic, 540 were akinetic, and 13 were dyskinetic. Patients had an average of 12.3 ± 3.1 dysfunctional segments. In the 1192 dysfunctional segments, FDG SPECT showed viable tissue in 463 segments (39%), whereas the remaining 729 segments (61%) were nonviable. Of the 463 viable segments, 131 (28%) had a blood flow and/or metabolism mismatch pattern and 332 segments (72%) had preserved perfusion and/or metabolism. Patients had an average of 4.8

Table 1. *Clinical Characteristics of the 97 Study Patients*

Men / women	81 (85%) / 16 (16%)
Age (years)	59 ± 9
Systemic hypertension	9 (9%)
Diabetes mellitus	15 (15%)
Hypercholesterolemia	41 (42%)
Smoking	31 (32%)
Family history of coronary disease	63 (65%)
Previous cerebrovascular disease	2 (2%)
No of diseased vessels	2.5 ± 0.6
LVEF (%)	26 ± 6 9range 10 - 35)

Data are presented as number (percentages) of patients or mean value \pm SD.

± 3.8 dysfunctional but viable segments. A total of 52 patients (54%) had a substantial amount of dysfunctional but viable myocardium (≥ 4 viable segments), and 45 patients (46%) had predominantly nonviable tissue. Overall, the QT dispersion averaged 57 ± 18 ms, and QTc dispersion was an average of 64 ± 20 ms^{1/2}. There was no relation between the QT dispersion or QTc dispersion and LVEF, nor was there a relation between QT and QTc dispersion and the number of dysfunctional segments. The QT dispersion in the 52 patients with ≥ 4 viable segments was significantly lower than in the 45 patients with nonviable segments (51 ± 15 vs. 65 ± 17 ms, $P < 0.0001$; Figure 1). Similarly, QTc dispersion in the patients with ≥ 4 viable segments was lower in patients with nonviable segments (56 ± 18 vs. 72 ± 19 ms^{1/2}, P

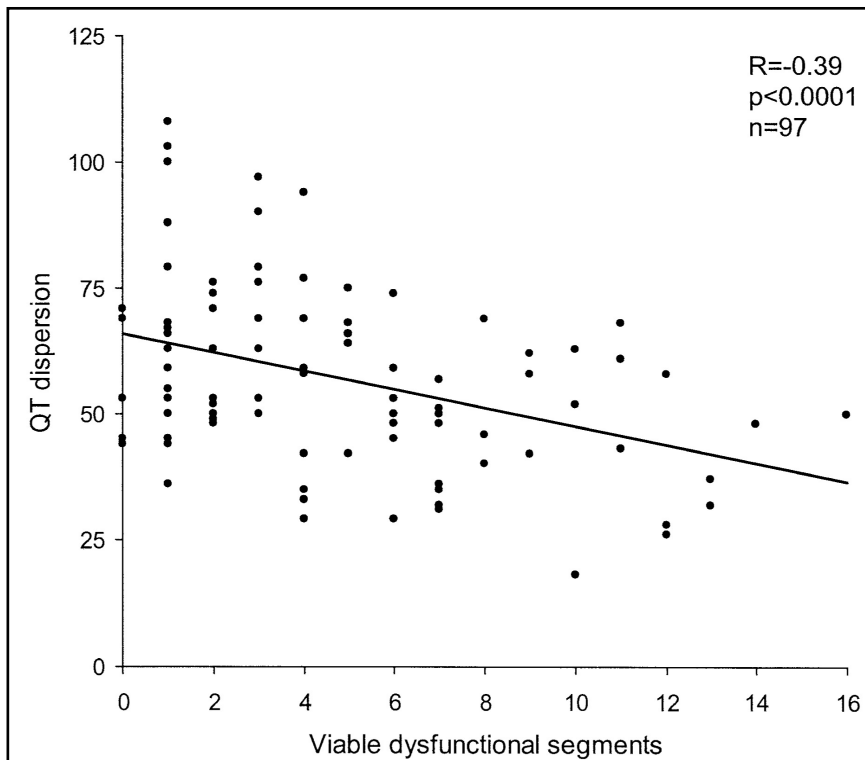


Figure 1. Scatterplot showing that QT dispersion was significantly related to the number of dysfunctional but viable segments ($r -0.39$, $P < 0.0001$, $n = 97$).

< 0.0001). ROC curve analysis demonstrated that QT dispersion \leq 62 ms had the highest sensitivity and specificity to predict the presence of substantial viability (sensitivity 79%, specificity 53%). Similarly, QTc dispersion \leq 67 ms^{1/2} had the highest accuracy to predict viability (sensitivity 73%, specificity 58%). All but two patients who had QT dispersion \geq 75 ms had nonviable segments. In contrast, all but one of the patients with a QT dispersion \leq 40 ms had substantial viability.

DISCUSSION

Metabolic imaging using positron emission tomography or SPECT and FDG is often considered the most accurate method to assess viability.¹⁷ However, these imaging techniques are time consuming and relatively expensive. The surface electrocardiogram is a simple, widely available technique, and thus has the potential to function as a screening for viable myocardium. For many years, chronic electrocardiographic Q waves were believed to reflect irreversibly scarred myocardium. However, chronic Q waves do not necessarily imply irreversible myocardial damage, because residual viability is present in a high proportion of Q-wave regions.¹⁸ Hence, the presence of a Q wave on the electrocardiogram cannot be used as a test to identify viable and/or nonviable myocardium. The present study assessed the relation between QT dispersion on the 12-lead surface electrocardiogram and myocardial viability as assessed by FDG SPECT. Patients with low QT dispersion were likely to have a substantial amount of viable myocardium. Conversely, most of the patients with a high QT dispersion had predominantly nonviable scar tissue. This may be related to abnormalities of ventricular repolarization in irreversibly damaged myocardium. In ischemic cardiomyopathy, myocardial fibrosis may result in abnormal ventricular repolarization.¹⁹ Moreover, abnormal repolarization may be related to increased wall stress due to expansion of the nonviable myocardium in the complex process of ventricular remodeling.²⁰ Only a few studies have evaluated the relation between QT dispersion and

myocardial viability. Schneider et al¹⁰ studied 44 patients with a previous myocardial infarction (mean LVEF $50 \pm 14\%$) using FDG positron emission tomography. QT dispersion was significantly lower in patients with a substantial amount of viability (53 ± 20 vs 94 ± 24 ms, $P < 0.0001$). QT dispersion ≤ 70 ms had a sensitivity of 85% and a specificity of 82% to predict viable myocardium. Al Mohammad et al¹¹ studied 42 patients with impaired LV function due to ischemic heart disease. The patient population was divided in two groups: 26 patients with viable myocardium (mean LVEF $34 \pm 12\%$) and 16 patients without viability (mean LVEF $28 \pm 8\%$). QT dispersion was lower in patients with viable tissue (62 ± 30 ms) than in patients without viable tissue (70 ± 25 ms); however, this difference was not statistically significant. Hence, the current data are limited and inconclusive concerning the relation between QT dispersion and viability, and patients with severely depressed LV function have not been studied extensively.

The present study evaluated the relation between QT dispersion and viability in a large group of patients with ischemic cardiomyopathy. Functional outcome and prognosis after myocardial revascularization were not assessed. In this setting, QT dispersion was significantly lower in patients with viable myocardium than in those with the nonviable myocardium. In correlation with the study of Schneider and colleagues,¹⁰ this present study's cut-off values for QT dispersion of ≤ 62 ms and QTc dispersion of ≤ 67 ms^{1/2} had the highest sensitivity and specificity to predict the presence of substantial viability.

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CHAPTER 8

THE PRESENCE OF CONTRACTILE RESERVE
HAS NO PREDICTIVE VALUE
FOR THE EVOLUTION
OF LEFT VENTRICULAR FUNCTION
FOLLOWING ATRIOVENTRICULAR NODE
ABLATION IN PATIENTS
WITH PERMANENT ATRIAL FIBRILLATION



Source: T Szili-Torok, M Bountiukos, AJQM Muskens,
DAMJ Theuns, D Poldermans, JRTC Roelandt, LJ Jordaens.
Eur J Echocardiogr (in press). **Adapted**

ABSTRACT

Aims: Transcatheter ablation of the atrio-ventricular (AV) node followed by ventricular pacing has been shown to improve symptoms and quality of life (QOL) of patients with permanent atrial fibrillation (AF). In a considerable number of patients, cardiac function deteriorates after AV node ablation. We aimed to determine whether the absence of contractile reserve assessed by low dose dobutamine stress echocardiography (LDDSE) could identify those patients whose left ventricular (LV) function deteriorates after AV node ablation.

Methods: All 25 pts studied had permanent AF for at least 12 months. LVEF was determined six days and three months after AV node ablation by radionuclide ventriculography (RNV), at a paced rate of 80 beats/min. Deterioration in cardiac function was defined as a decrease in LVEF $> 5\%$. LDDSE was performed in all patients before and after ablation. The presence of contractile reserve was defined as an improvement in regional function of ≥ 1 grade at low dose dobutamine in at least 4 segments. QOL measurements were taken using Minnesota, NHBP and MPWB questionnaires.

Results: LVEF showed no improvement in the overall group ($52.8 \pm 11.1\%$ vs. $51.8 \pm 9.8\%$, $P = \text{NS}$). QOL showed significant improvement in all questionnaires (Minnesota: 4.1 ± 2.1 vs. 2.5 ± 2 , $P = 0.001$; NHBP: 54.8 ± 43.3 vs. 34.2 ± 34.3 , $P = 0.002$; MPWB: 22.2 ± 4.6 vs. 19.4 ± 6.2 , $P = 0.03$). There was no significant difference in change of LVEF between patients with and without contractile reserve (-0.4 ± 8.7 vs. 1.6 ± 11.3 , $P = \text{NS}$). However patients with a preserved LVEF at baseline showed more frequently a reduced LVEF after AV node ablation ($62.2 \pm 10.4\%$ vs. $47.5 \pm 7.6\%$, $P = 0.001$).

Conclusions: 1. The absence of contractile reserve does not predict deterioration of cardiac function after AV node ablation. 2. AV node ablation results in a significant improvement in QOL, which is not necessarily associated with improvement of LVEF. 3. Higher baseline LVEF predicts deterioration of cardiac function. These data suggest that although AV node ablation is an excellent way of controlling symptoms, it should be avoided in patients with normal LV function.

INTRODUCTION

Atrial fibrillation (AF) is a common supraventricular arrhythmia, which leads to cardiac dilatation and dysfunction. Theoretically, ablation of the atrio-ventricular (AV) node followed by right ventricular (RV) apical pacing may result in an improvement of the patient's symptoms as well as in cardiac function because of the advantage of a regular ventricular response and adequate rate control¹⁻⁴. Controversial results were reported about the course of patients following AV junction ablation. Quality of life (QOL) and exercise tolerance improved in several studies.³ However, more recent studies indicate that left ventricular (LV) function does not improve or even may deteriorate.⁵⁻⁷ Contractile reserve of the myocardium as determined with echocardiography under pharmacological stress, can be used as a prognostic parameter in patients with LV dysfunction.⁸ The aim of the present investigation was to determine whether the absence of contractile reserve assessed by low-dose dobutamine stress echocardiography (LDDSE) could identify those patients whose LV function deteriorates after AV node ablation and RV apical pacing.

METHODS

Patients were eligible if they had permanent AF, were highly symptomatic and if the ventricular rate could not be adequately controlled by drug therapy. Twenty-five patients with permanent AF underwent ablation of the AV node and insertion of a VVIR pacemaker and RV apical pacing. There were 16 men and 9 women with an age ranging from 44 to 80 years (63 ± 11.4 , mean \pm SD) at the time of ablation. There were no major changes in medication during three months follow up period.

Study protocol

After being informed all patients gave consent for participation in the

study. All patients who met the inclusion criteria had LDDSE, cardiac peptide measurements, QOL measurements and 6-min walk test before the procedure. Four to six days after AV node ablation and PM implantation left ventricular ejection fraction (LVEF) was determined with radionuclide technique. At three-month follow-up all measurements (LDDSE, QOL, cardiac peptides, 6-min walk test and LVEF) were repeated.

Ablation procedure. A temporary pacing electrode was inserted via a femoral vein into the RV before the ablation procedure. One patient had already a permanent pacemaker inserted. Third degree AV block was achieved using a conventional right-sided approach. A permanent cardiac pacemaker was inserted 30 minutes after successful ablation. Neither major nor minor complications related to ablation and pacemaker insertion were observed. Patients were subsequently controlled at the outpatient clinic.

Echocardiographic measurements. M-mode and cross-sectional echocardiograms were obtained at the time of measurement of LVEF by radionuclide ventriculography. Left atrial (LA) size, end left ventricular systolic (LVESD) and end diastolic diameters (LVEDD) were measured according to the recommendations of the American Society of Echocardiography.

Dobutamine stress echocardiography: Two-dimensional images were acquired from three apical views (four chamber, two chamber and long axis) and one parasternal view (short axis). After the acquisition of rest images, dobutamine was infused at a starting dose of 5 $\mu\text{g}/\text{kg}/\text{min}$ for 5 min, followed by 10 $\mu\text{g}/\text{kg}/\text{min}$ for 5 min (low-dose stage). Dobutamine was then increased by 10 $\mu\text{g}/\text{kg}/\text{min}$ every 3 min to a maximum dose of 40 $\mu\text{g}/\text{kg}/\text{min}$. Atropine (up to 2 mg) was added at the end of the last stage if the target heart rate had not been achieved. The baseline, low dose, peak stress and recovery images were displayed as a cine loop format. A 16-segment model for left ventricular wall function analysis was used, as recommended by the American Society of Echocardiography, and visually scored by two experienced reviewers. Each segment was scored as follows: 1 = normal; 2 = mildly hypokinetic; 3 = severely hypokinetic; 4 = akinetic; 5 = dyskinetic. For each patient,

wall motion score (WMS) was calculated at rest, at low dose dobutamine infusion and at peak heart rate. Reduction of wall thickening and new wall motion abnormalities during the stress test were considered to be hallmarks of ischemia. The transition of akinesia to dyskinesia was considered a mechanically induced phenomenon. The presence of contractile reserve was defined as an improvement in regional function of ≥ 1 grade at low dose dobutamine in at least four segments.

Evaluation of other parameters. LVEF was measured with radionuclide ventriculography (red blood cells, marked with ^{99}Tc pertechnetate, 25 mCi). Imaging was performed in 45 degrees left anterior oblique (LAO) view. The R wave was used for gating, and 16-24 frames per cycle were stored until 400 000 counts per image were acquired. Measurement was made four to six days after and three months after the ablation procedure. For all patients VVI 80 bpm pacing mode was temporarily programmed one hour before LVEF measurements. Deterioration in cardiac function was defined as a decrease in LVEF $> 5\%$.

Cardiac peptide measurements: Before stress echocardiography a blood sample was drawn from a peripheral vein, after the patient had rested for at least 30 minutes in a supine position. Plasma concentrations of ANP, BNP levels were measured with radio-immunoassays using standard commercial kits (Shionoria ANP and BNP kits, Shionogi, Osaka, Japan). The 6 min walk was done according to established methods.⁹

Quality of life (QOL) was measured using the Dutch version of Minnesota living with heart failure, the Dutch version of Nottingham Health Profile, and the MPWB questionnaires.^{10,11}

Statistical analysis

The measured values are expressed as mean \pm SD. Data showing Gaussian distribution were compared using paired (data before and after ablation) and student *t* tests (comparing data in the subgroups). Dichotomous variables were compared using chi-square test. Non-parametric data were compared using Wilcoxon test. The level of significance was set at 0.05.

RESULTS

Patient data (Table 1)

Complete heart block was achieved in all patients, except in one, who was rescheduled and only included for follow-up after a successful redo procedure. Junctional escape rhythm was achieved in 18 patients (72%). The remaining patients had a ventricular escape rhythm. There were no complications related to the ablation and pacing procedures.

Evolution of objective and subjective parameters during the follow-up period

None of the measured objective parameters showed improvement during the follow-up period. QOL showed highly significant improvement in all questionnaires (Table 2). The distribution of deteriorators and stable/improving patients were statistically not significant in subgroups of patients with or without contractile reserve (Table 3).

Table 1. *Clinical characteristics and ablation data of the study patients*

	Overall group
Number of patients (n)	25
Gender (Female/Male)	9/16
Age (years)	63 ± 11.4
Duration of atrial fibrillation	
since permanent (months)	49 ± 11.5
Left atrial dimension (mm)	47.8 ± 8.4
Left ventricular end-diastolic dimension (mm)	48.7 ± 7.2
Left ventricular end-systolic dimension (mm)	34.9 ± 7.8
QRS width after ablation (ms)	95 ± 22.4
Rate of escape rhythm (beats per minute)	41.5 ± 6.9

Data are presented as mean ± SD.

Table 2. Evolution of objective and subjective parameters following AV node ablation in the overall group

	Before ablation	After ablation	P value
Objective parameters			
LVEF (%)	52.8 ± 11.1	51.8 ± 9.8	NS
ANP (pmol/l)	25 ± 22.7	26.7 ± 23.2	NS
BNP (pmol/l)	38.2 ± 55.7	35.1 ± 39	NS
6-min walk test (meters)	353.8 ± 123.4	358.1 ± 160.2	NS
WMS (low dose dobutamine)	22.2 ± 9	21.5 ± 7.6	NS
Subjective parameters			
Minnesota QOL	4.1 ± 2.1	2.5 ± 2	0.001
NHBP	54.8 ± 43.3	34.2 ± 34.3	0.002
MPWB	22.2 ± 4.6	19.4 ± 6.2	0.03

Data are presented as mean ± SD.

ANP, serum level of atrial natriuretic peptide; BNP, serum level of brain natriuretic peptide; LVEF, left ventricular ejection fraction; NS, non-significant; QOL, quality of life; WMS, regional wall motion score.

Table 3. Frequency of deteriorators and stable/ improving patients in the groups with and without contractile reserve

	With CR (n)	Without CR (n)	P value
Deteriorators (n)	4	2	NS
Stable/ improving (n)	9	6	NS
P value	NS	NS	

CR, contractile reserve; NS, non-significant.

Correlation of contractile reserve and changes over time (Table 4)

There was no significant difference in change of LVEF between patients with and without contractile reserve (- 0.4 ± 8.7 vs. 1.6 ± 11.3, $P = NS$). However patients with a preserved LVEF at baseline showed

Table 4. Comparison of baseline objective and subjective parameters following AV node ablation between stable or improvers and deteriorators

	stable/ improving	deteriorator	P value
Objective parameters			
LVEF (%)	47.5 ± 7.6	62.2 ± 10.4	0.001
ANP (pmol/l)	21 ± 10.1	29.6 ± 32	NS
BNP (pmol/l)	25.5 ± 11.3	54.9 ± 81.5	NS
6-min walk test (meters)	385.3 ± 95	297.7 ± 152.5	NS
WMS (low dose dobutamine)	21.1 ± 8.2	24.6 ± 11.5	NS
Subjective parameters			
Minnesota QOL	4.3 ± 2	4 ± 2.4	NS
NHBP	52.1 ± 33.7	59 ± 56.9	NS
MPWB	23.4 ± 4.6	19.7 ± 3.5	NS

Data are presented as mean ± SD.

ANP, serum level of atrial natriuretic peptide; BNP, serum level of brain natriuretic peptide; CR, contractile reserve; LVEF, left ventricular ejection fraction; NS, non-significant; QOL, quality of life; WMS, regional wall motion score.

more frequently a reduced LVEF after AV node ablation ($62.2 \pm 10.4\%$ vs. $47.5 \pm 7.6\%$, $P = 0.001$). There was no other statistically significant difference in baseline values including cardiac peptide serum levels, 6-min walk distances and WMS and QOL scores.

Evolution of subjective and objective parameters in subgroups of patients (Table 5)

In both subgroups QOL showed improvement. Apart from LVEF (which served as a grouping value in this comparison) no objective parameters showed change during the three-month follow-up. LVEF decreased from 62.2 ± 10.4 to $51.4 \pm 13\%$ in the deteriorating group. LVEF showed substantial improvement in the improving group from 47.5 ± 7.6 to $52 \pm 8.1\%$.

Table 5. Evolution of objective and subjective parameters following AV node ablation in subgroups defined as stable or improvers and deteriorators

A, DETERIORATORS			
	Before ablation	After ablation	P value
Objective parameters			
LVEF (%)	62.2 ± 10.4	51.4 ± 13	0.0001
ANP (pmol/l)	29.6 ± 32	20.6 ± 13.4	NS
BNP (pmol/l)	54.9 ± 81.5	37.8 ± 40.5	NS
6-min walk test (m)	297.7 ± 152.5	320.2 ± 187.9	NS
WMS (LDD)	24.6 ± 11	23.6 ± 10	NS
Subjective parameters			
Minnesota QOL	4 ± 2.4	2.4 ± 1.7	0.009
NHBP	59 ± 56.9	41.4 ± 43.7	0.05
MPWB	19.7 ± 3.5	16.8 ± 8	NS
B, STABLE/ IMPROVING			
Objective parameters			
EF (%)	47.5 ± 7.6	52 ± 8.1	0.02
ANP (pmol/l)	21.2 ± 11.3	31.6 ± 28.6	NS
BNP (pmol/l)	24.5 ± 11.8	32.9 ± 39.76	NS
6-min walk test (meters)	385.3 ± 95	379.5 ± 144.5	NS
WMS (LDD)	21.1 ± 8.2	20.5 ± 6.6	NS
Subjective parameters			
Minnesota QOL	4.2 ± 2	2.6 ± 2.2	0.002
NHBP	52.2 ± 34.9	29.8 ± 28.2	0.005
MPWB	23.6 ± 4.7	20.8 ± 4.7	0.008

Data are presented as mean ± SD.

ANP, serum level of atrial natriuretic peptide; BNP, serum level of brain natriuretic peptide; CR, contractile reserve; LDD, low dose dobutamine; LVEF, left ventricular ejection fraction; NS, non-significant; QOL, quality of life; WMS, regional wall motion score.

DISCUSSION

Effect of AV node ablation and RV apical pacing on the function of the heart

Diminished LV function during pacing at the RV apex has been known for decades from numerous animal and human studies.¹²⁻¹⁴ Ventricular pacing results in an abnormal sequence of activation, associated with decreased fiber shortening, contractile work, and myocardial blood flow and oxygen consumption in regions activated early and increases in these parameters in those regions with delayed activation leading to a depressed left ventricular function.¹⁵⁻¹⁷ Experimental animal data have also indicated that RV apical pacing may decrease regional myocardial blood flow within the interventricular septum.^{18,19} These animal data have been confirmed by human studies, where ventricular pacing decreased resting coronary flow velocity in some patients.²⁰ Furthermore, long term RV apical pacing results in a high incidence of myocardial perfusion defects associated with apical wall motion abnormalities and impaired global LV function.²¹ Furthermore, so-called functional mitral regurgitation plays a crucial role in suboptimal hemodynamics. According to these data, abnormal activation of the ventricles by RV apical pacing may result in multiple abnormalities of cardiac function, which may ultimately affect clinical outcome. On the other hand, reports were showing improvement of LV function after AV node ablation and pacing. These are the patients most likely having a tachycardiomyopathy.^{1,2} Unfortunately, there was no available method, which was able to predict which particular patient will improve function after ablation. This can be recognised examining the course of patients with AV node ablation and RV apical pacing. Clinically it is seen, and also shown by most studies that a relatively large proportion of the patients is deteriorating while others are improving.^{2,6,7} To the best of our knowledge this is the first study aiming to determine which patient will deteriorate and which will improve after such a therapy. This question becomes even more important after consideration of the QOL data. Because there is a uniform improvement in QOL life it seems to be

important to recognise patients with a potential deterioration of cardiac function.

Rationale for measuring contractile reserve in patients undergoing AV node ablation and permanent RV pacing

After AV node ablation the chronotropic response of the sinus node is lost and hemodynamic adaptation will be more dependent on changes in contractility than by changes in heart rate. The presence of preserved contractility is hence of vital importance for a good outcome after AV node ablation. Patients with tachycardiomyopathy usually suffer from long lasting fast heart rates and their LV function will likely improve after such intervention.^{1,22,23} It has been shown that in patients with idiopathic dilated cardiomyopathy and long lasting atrial fibrillation (having normal coronary arteries) the LVEF does not improve with low dose dobutamine. However, patients with a tachycardiomyopathy do improve.⁸ This can be the rationale for using LDDSE as a screening test before patients undergoing AV node ablation and pacing. Our data did not confirm that it would be useful for these patients. There was significant difference between the duration of AF between our study patients and the previous study when LDDSE was predictive for improvement. The latter patients had persistent AF, while our patients had permanent long lasting AF regardless their LV ejection function. The fact that almost all patients had symptomatic improvement in our study can be explained by the fact, that circulating catecholamines can no longer accelerate the heart rate, but will only affect the pump function. This will not necessarily improve the outcome of the patients with contractile reserve, but will definitely not influence the ones without contractile reserve.

Left ventricular function after AV node ablation and RV apical pacing for patients with permanent AF: Discordant evolution of subjective and objective parameters

Our data confirm that the functional course of patients following AV

junction ablation is unpredictable. Although noticeable improvement in QOL associated with improved LVEF has been reported in many studies, some other studies reported no improvement or sometimes a decreased LV function.^{1-3,6,7,22-24} An important aspect of these controversial data is that in most available large studies only data on the overall group was reported, despite the obvious fact that some patients deteriorated. After careful analysis of our data and the data extracted from the above-mentioned studies, it seems that during the follow up, objective and subjective parameters show somewhat of a discordant evolution. Correct interpretation of these data may allow us to develop a better understanding of the natural course of these patients and the reasons for this discordance. After AV node ablation numerous factors are influencing LV function. Some of them act in the direction of improvement, but some of them may cause deterioration. Regularisation and ventricular rate control appear to be the most important factors that may have an impact on improvement.⁴ On the other hand RV apical pacing results in disadvantageous cellular changes and worsened hemodynamics.^{5,7,13,16,25,26} It seems so far, that the net effect of interplay between the beneficial and the worsening factors is unpredictable. The almost uniform improvement in quality of life supports the idea that subjective parameters are more influenced by the beneficial factors, however function reacts independently. In some patients, concordant with the QOL, function improves, however in others, despite the improvement in QOL, it may deteriorate. Therefore, in symptom control, regularisation and rate control are important factors, but their role in functional changes is not that clear. This variable outcome is of clinical significance as per the important question of Wood, as to whether AV node ablation is applicable to a wider spectrum of patients.² According to our present data we can conclude that the effect of AV node ablation and RV apical pacing on cardiac function is highly dependent on the baseline LVEF. It seems that patients with preserved LV function will more likely deteriorate their LV function. Therefore, this therapy should be avoided in patients when only symptom control is the goal and when the cardiac function is normal. This is in concordance with the concept of tachycardiomyopathy. It seems, that

AV node ablation and RV apical pacing is the best for patients with tachycardiomyopathy. However, this cannot be predicted with the presence of contractile reserve in these patients.

Conclusions

In this study subjective and objective parameters as obtained at short and midterm after AV node ablation showed discordant evolution. Our data suggest, that the presence of baseline contractile reserve does not predict improvement after AV node ablation. Furthermore, subjective parameters (measurement by QOL questionnaires) are markedly improving in most patients but parameters associated with LV performance are not improving and in a subset of patients these latter parameters even display deterioration. A good baseline LVEF is the best predictor of deterioration.

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CHAPTER 9

EFFECT OF ATORVASTATIN ON MYOCARDIAL CONTRACTILE RESERVE ASSESSED BY TISSUE DOPPLER IMAGING IN MODERATELY HYPERCHOLESTEROLEMIC PATIENTS WITHOUT HEART DISEASE



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ABSTRACT

The effects of statins on myocardial function at rest, as well as on contractile reserve during low-dose dobutamine stress testing, were studied in a cohort of patients with moderate hypercholesterolemia, peripheral arterial disease, and no heart disease. Pulsed-wave tissue Doppler imaging, a relatively new technique for the quantification of segmental myocardial velocities, was used.

An improvement in myocardial longitudinal systolic velocities, assessed by pulsed-wave tissue Doppler imaging during low-dose dobutamine infusion, was observed at six months follow-up after six months of treatment with atorvastatin. Our findings indicate a favorable effect of atorvastatin on contractile reserve, possibly through an enhancement of flow-dependent coronary dilatation during stress.

PATIENTS AND METHODS

Patients were eligible for the study if they had a baseline fasting serum low-density lipoprotein (LDL) cholesterol level between 130 and 230 mg/dl, normal ($\geq 50\%$) left ventricular ejection fraction, and a diagnosis of peripheral arterial disease. Exclusion criteria were: (1) lipid-lowering medication; (2) currently smoking; (3) history of myocardial, pericardial, or valvular heart disease; (4) diabetes mellitus (5) left ventricular hypertrophy (thickness of the interventricular septum at end diastole $> 11\text{mm}$) as documented by echocardiography; (6) cardiac rhythm other than sinus; and (7) evidence of stress-induced ischemia on dobutamine stress echocardiography.

A total of 26 consecutive subjects were studied using two-dimensional echocardiography and pulsed-wave tissue Doppler at rest and during dobutamine infusion. Subsequently, subjects initiated a low-fat (step 1) diet¹ and were randomized to receive either atorvastatin 10 mg daily (13 patients), or 80 mg daily (13 patients). Echocardiographic evaluation was repeated at three and six months. Six patients who met the same inclusion and exclusion criteria -who had been studied in the past, before and at three and six months after the initiation of the step 1 diet -made up the control group. Cardiovascular medication was kept unchanged throughout the study. The Hospital Ethics Committee approved the protocol. All patients gave informed consent before they were enrolled in the study.

A commercially available imaging system equipped with a 1.8 MHz transducer and second harmonic imaging to optimize endocardial border visualization (Sonos-5500, Hewlett Packard, Andover, Massachusetts) was used to record two-dimensional echocardiograms. Patients were examined in the left lateral decubitus position. Three apical views (four-chamber, two-chamber, and long-axis) and one parasternal view (short-axis) were acquired, and two experienced reviewers (D.P, M.B.) visually scored the digitized echocardiograms. Regional wall motion and systolic wall thickening were scored using a 16-segment model, as recommended by the American Society of Echocardiography,² and a five-point grading scale: 1 = normal, 2 =

mildly hypokinetic, 3 = severely hypokinetic, 4 = akinetic, 5 = dyskinetic. Wall motion score index was calculated by dividing the sum of wall motion score of all measurable segments by their total number. Left ventricular ejection fraction was determined off line using the two-dimensional biplane disk method by digitally tracing the endocardial borders at end-diastole and end-systole to calculate left ventricular end-diastolic and end-systolic volumes.

Before treatment was started, patients underwent a complete dobutamine stress test targeting the achievement of 85% of maximal age- and gender-predicted heart rate. Dobutamine was infused at a starting dose of 5 $\mu\text{g}/\text{kg}/\text{min}$ for 5 min, followed by 10 $\mu\text{g}/\text{kg}/\text{min}$ for another 5 min. Dobutamine was then increased by 10 $\mu\text{g}/\text{kg}/\text{min}$ every 3 min to a maximum dosage of 40 $\mu\text{g}/\text{kg}/\text{min}$. Atropine, up to 2 mg, was added at the end of the last stage if the target heart rate had not been achieved. Subsequent tests were performed at low-dose dobutamine infusion and were stopped after data acquisition at 10 $\mu\text{g}/\text{kg}/\text{min}$ dobutamine infusion. Other test end points were horizontal or downsloping ST-segment depression > 2 mm at an interval of 80 ms after the J-point compared with baseline; severe angina; decrease in systolic blood pressure > 40 mm Hg; blood pressure > 240/120 mmHg; and significant cardiac arrhythmia. An intravenous β -blocker was available to reverse the adverse effects of dobutamine and/or atropine.

Pulsed-wave tissue Doppler imaging was performed with a pulse repetition frequency of 45 to 60 KHz and a sample volume of 4 mm³. To minimize the variability induced by respiration,³ the measurement of myocardial velocity was sampled in three apical views (four-chamber, two-chamber, and long-axis) close to the mitral annulus and during a minimum of five consecutive beats. The depth of the sample volume of every region was kept constant during dobutamine stress echocardiography to make sure that left ventricular myocardium was sampled close to the mitral annulus. The Doppler velocity profiles and electrocardiographic tracings were simultaneously stored on optical disk. The velocity values (centimeters per second) were obtained on calibrated still frames by manually measuring the distance between the

zero baselines and the peak Doppler profile of the ejection phase, and of the early and late diastolic phases, in reference to the electrocardiogram. Cardiac cycles with extrasystolic, post-extrasystolic beats, or rhythm disturbance were excluded. Recordings and measurements were performed at baseline and during low-dose (10 μg /kg/min) dobutamine infusion rate. Measurements of tissue Doppler velocities were repeated after two months in 10 randomly selected patients by the same observer who performed the initial analysis. A second observer, blinded to the results of the first observer, measured tissue Doppler velocities of the same patients. The interobserver and intraobserver agreement for systolic velocities were 94% and 98%, respectively; for early diastolic velocities 97% and 97%, respectively; and for atrial assisted velocities 96% and 98%, respectively.

Dichotomous variables are presented as numbers and percentages, and continuous variables are expressed as mean \pm 1SD. Differences in baseline characteristics between the three patient groups (control patients, atorvastatin 10-mg group, and atorvastatin 80-mg group) were evaluated by chi-square test and one-way analysis of variance (ANOVA), as appropriate. Two-way ANOVA with repeated measures was applied to evaluate changes in continuous variables across time as well as differences in these changes between the patient groups. Significance of all statistical tests was stated at $P = 0.05$.

RESULTS

Baseline patient characteristics are listed in Table 1. No patients received β -blockers. During the study, there were no untoward cardiac events that could have altered the status of left ventricle. Compliance with atorvastatin treatment was absolute in all patients receiving the drug. Similarly, compliance with the step-1 diet was high and comparable in all groups. At the end of the study, all patients in the control group, 12 patients in the atorvastatin 10-mg group, and 11 patients in the atorvastatin 80-mg group stated that they had followed the instructions properly.

Table 1. Baseline patient characteristics in study groups

	No statin (n=6)	10 mg atorvastatin (n=13)	80 mg atorvastatin (n=13)
Age (years)	57 ± 9	60 ± 12	56 ± 9
Men	5	5	7
Left ventricular ejection fraction (%)	60 ± 7	58 ± 6	58 ± 3
Systemic hypertension [†]	3	4	4
Total cholesterol (mg/dl)	248 ± 20	240 ± 25	245 ± 27
LDL cholesterol (mg/dl)	169 ± 26	160 ± 23	165 ± 16
HDL cholesterol (mg/dl)	39 ± 7	40 ± 6	39 ± 6
Triglycerides (mg/dl)	204 ± 90	199 ± 59	204 ± 89
Medication			
Calcium-antagonists	2	2	3
Angiotensin converting enzyme-inhibitors	2	3	3
Antiplatelets	2	2	2
Anticoagulants	1	3	2

Values are expressed as mean ± SD.

[†]Defined as a blood pressure ≥ 140/90 mmHg.

After the 6-month follow-up, patients receiving atorvastatin had a significant decrease in total cholesterol and LDL cholesterol values. The effect of atorvastatin on lipids was more prominent in patients receiving high-dose (80 mg) atorvastatin. There was a 33% ± 4% decrease in total cholesterol, a 43% ± 9% decrease in LDL cholesterol, a 19% ± 20% decrease in triglycerides, and a 16% ± 19% increase in high-density lipoprotein (HDL) cholesterol. In patients receiving low-dose (10 mg) atorvastatin, the decrease in total cholesterol, LDL cholesterol and triglycerides was 22% ± 8%, 24% ± 8%, and 16% ± 26% respectively, whereas HDL cholesterol increased by 7% ± 23%.

Patients not receiving atorvastatin had a mild decrease in lipid levels, probably because of the lipid-lowering diet. Table 2 lists changes in lipid levels at six months in all patient groups.

The subjects experienced no serious side effects from serial dobutamine stress testing. No reversible wall motion abnormalities (i.e., ischemia) were observed. Hemodynamic response to dobutamine infusion is shown in Table 3. Left ventricular ejection fraction at rest and during low-dose dobutamine infusion did not change significantly in any of the three patient groups at the three- and six-month follow-ups (Table 4). Similarly, wall motion score index, which was initially normal or nearly normal in all patients, remained unchanged.

No patient group had a significant change in systolic velocity (V_s) at rest, although a trend toward increase was observed in patients treated with atorvastatin. With low-dose dobutamine, there was a significant increase in V_s in patients receiving atorvastatin. This increase occurred irrespective of the dose of atorvastatin. Control patients did not show any statistically significant change in V_s . Patients receiving atorvastatin had a trend toward an increase in early diastolic velocity (V_E) at six months, which was more prominent in the atorvastatin 80-mg group. A similar nonsignificant increase was observed in atrial-assisted (late) diastolic velocity (V_A) in patients treated with atorvastatin 80 mg. Because of the almost proportional increase in early and late diastolic velocities in these patients, the V_E/V_A ratio remained unchanged. Table 4 lists mean tissue Doppler velocities in all study groups at baseline as well as the three- and six-month follow-ups.

DISCUSSION

Enhanced left ventricular function with time, assessed by pulsed-wave tissue Doppler velocity, was observed during low-dose dobutamine infusion in patients treated with atorvastatin. This increase was not dose-related, because it was present in patients treated with 10 mg and with 80 mg of atorvastatin daily. Patients not receiving atorvastatin had no significant change in tissue Doppler V_s . Considering there was no change in patients' medication during the

Table 2. Change in baseline lipid levels after six months of combined diet and statin therapy, or diet alone

	Baseline				6 months		P value*
	No statin	Atorvastatin 10 mg	Atorvastatin 80 mg	No statin	Atorvastatin 10 mg	Atorvastatin 80 mg	
Total cholesterol (mg/dl)	249 ± 19	240 ± 25	245 ± 27	237 ± 29	187 ± 17	164 ± 20	<0.001
LDL cholesterol (mg/dl)	169 ± 26	160 ± 23	165 ± 16	158 ± 24	120 ± 13	95 ± 17	<0.001
HDL cholesterol (mg/dl)	39 ± 5	40 ± 6	39 ± 6	39 ± 6	42 ± 6	45 ± 4	0.266
Triglycerides (mg/dl)	210 ± 78	199 ± 59	204 ± 89	193 ± 61	155 ± 30	156 ± 62	0.478

All values are expressed as mean value±SD.

*Comparison was performed by repeated measures 2-way ANOVA.

Table 3. Response of systolic and diastolic blood pressure (mm Hg), and heart frequency (beats/min) to dobutamine infusion across time, in study groups

	Baseline			3 months			6 months			P value*
	No statin	10 mg	80 mg	No statin	10 mg	80 mg	No statin	10 mg	80 mg	
SBP (rest)	141 ± 5	146 ± 19	154 ± 24	140 ± 16	144 ± 23	144 ± 16	139 ± 16	141 ± 18	148 ± 15	0.650
SBP (low-dose)	143 ± 15	142 ± 22	153 ± 9	143 ± 12	147 ± 24	146 ± 17	134 ± 9	141 ± 17	146 ± 16	0.460
DBP (rest)	77 ± 10	82 ± 12	86 ± 12	80 ± 5	81 ± 9	81 ± 5	80 ± 5	81 ± 9	85 ± 5	0.570
DBP (low-dose)	81 ± 9	75 ± 10	80 ± 11	73 ± 9	72 ± 9	78 ± 11	74 ± 7	72 ± 9	76 ± 6	0.770
HF (rest)	68 ± 8	69 ± 7	72 ± 13	67 ± 15	72 ± 12	70 ± 13	66 ± 9	69 ± 5	73 ± 12	0.650
HF (low -dose)	72 ± 11	78 ± 8	81 ± 16	80 ± 12	84 ± 9	82 ± 16	78 ± 13	82 ± 6	83 ± 14	0.720
RP product (rest)	9.6 ± 1.1	10.0 ± 1.7	11.1 ± 2.9	9.2 ± 1.3	10.4 ± 2.5	10.1 ± 2.4	9.0 ± 1.4	9.8 ± 1.5	10.8 ± 2.5	0.340
RP product (low-dose)	10.3 ± 2.3	11.0 ± 2.3	12.5 ± 3.8	11.5 ± 2.5	12.4 ± 2.6	12.0 ± 3.1	10.3 ± 1.5	11.6 ± 12.0	12.1 ± 2.7	0.270

Values are expressed as mean ± SD.

DBP, diastolic blood pressure; HF, heart frequency; RP, rate-pressure; SBP, systolic blood pressure.

* Comparison was performed by repeated measures 2-way ANOVA.

Table 4. Changes in left ventricular ejection fraction (%), and systolic and diastolic tissue Doppler velocities (cm/s) across time in study groups

	Baseline		3 months		6 months		P* value
	No statin	Atorvastatin	No statin	Atorvastatin	No statin	Atorvastatin	
		10 mg	80 mg	10 mg	80 mg	10 mg	
LVEF (rest)	57 ± 3	58 ± 6	59 ± 5	58 ± 5	59 ± 6	59 ± 6	0.960
LVEF (low-dose)	66 ± 4	69 ± 7	68 ± 5	71 ± 6	69 ± 7	69 ± 6	0.750
VS (rest)	8.1 ± 1.0	7.8 ± 1.5	7.3 ± 1.3	8.3 ± 1.9	8.2 ± 1.1	8.9 ± 2.4	0.280
VS (low-dose)	11.0 ± 2.2	10.8 ± 3.0	10.1 ± 1.6	11.5 ± 2.8	11.1 ± 1.8	12.5 ± 3.3	0.008
VE (rest)	9.5 ± 2.4	9.2 ± 2.4	8.8 ± 2.1	8.8 ± 2.6	9.4 ± 1.9	9.2 ± 2.9	0.080
VE (low-dose)	10.3 ± 2.3	10.5 ± 3.1	10.0 ± 2.1	10.3 ± 2.7	10.4 ± 2.1	11.2 ± 3.3	0.320
VA (rest)	9.8 ± 2.2	9.5 ± 1.5	9.3 ± 1.4	10.3 ± 0.6	10.1 ± 1.4	10.1 ± 1.5	0.510
VA (low-dose)	11.0 ± 2.8	11.1 ± 1.6	10.3 ± 1.7	12.4 ± 1.6	11.6 ± 1.6	12.0 ± 1.9	0.070
VE/VA (rest)	1.1 ± 0.6	1.0 ± 0.3	1.0 ± 0.2	0.9 ± 0.3	0.9 ± 0.2	0.9 ± 0.3	0.160
VE/VA (low-dose)	1.0 ± 0.6	0.9 ± 0.3	1.0 ± 0.2	0.8 ± 0.2	0.9 ± 0.2	0.9 ± 0.2	0.930

Values are expressed as mean ± SD.

LVEF, left ventricular ejection fraction; VA, atrial-assisted (late) diastolic velocity; VE, early diastolic velocity; VS, systolic velocity.

* Comparison was performed by repeated measures two-way analysis of variance.

study, and no untoward cardiac events occurred, it is likely that the enhanced contractile reserve during low-dose dobutamine infusion was the result of atorvastatin treatment. Notably, no differences were observed in either left ventricular ejection fraction or wall-motion score index during treatment with atorvastatin. Hence, pulsed-wave tissue Doppler revealed changes in myocardial contractility that could not be detected by the conventional methods used to evaluate left ventricular systolic function.^{4,5}

Our results are in line with those of previous studies that reported the positive action of statins on stress test parameters and coronary flow reserve. Ramirez et al.⁶ demonstrated a decrease in exercise-induced ischemia in patients with previously positive exercise test results, coronary stenosis > 70%, and cholesterol levels > 300 mg/dl, as early as 16 weeks after the initiation of treatment with statins. The investigators explained that this decrease in ischemic threshold occurred from an increase in coronary vasodilator capacity in patients with initially decreased coronary blood flow reserve. Baller et al.⁷ studied 18 patients with moderate hypercholesterolemia (LDL cholesterol levels 168 ± 33 mg/dl) who underwent dynamic positron emission tomography with dipyridamole infusion. An improvement in dipyridamole-induced coronary vasodilator capacity after six months of intensive lipid-lowering therapy was found in patients having early-stage coronary atherosclerosis. Similarly, in the study by Huggins et al.,⁸ an increase in the maximal myocardial blood flow of stenotic coronary segments, approaching 45%, was evident after short-term lipid-lowering therapy with simvastatin.

To our knowledge, no previous study has used tissue Doppler imaging to quantify the effect of statin therapy on left ventricular function. Pulsed-wave tissue Doppler from the apical views assesses longitudinal shortening and lengthening. Subendocardial fibers in the left ventricle are oriented longitudinally; hence, subendocardial hypoperfusion caused by impaired coronary flow reserve may result in decreased tissue Doppler velocities.^{9,10} Inversely, tissue Doppler velocities are expected to increase after normalization of subendocardial perfusion. Improvement of endothelial function has

been described as one of the non-lipid-lowering properties of statins.^{11,12} In this investigation, the resulting increase in systolic myocardial velocities during stress could be attributed to the beneficial effect of atorvastatin on flow-dependent coronary dilatation.

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CHAPTER 10

PULSED-WAVE TISSUE DOPPLER IMAGING FOR THE QUANTIFICATION OF CONTRACTILE RESERVE IN STUNNED, HIBERNATING, AND SCARRED MYOCARDIUM



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ABSTRACT

Objectives: To assess whether quantification of myocardial systolic velocities by pulsed-wave tissue Doppler imaging can differentiate between stunned, hibernating, and scarred myocardium.

Design: Observational study.

Setting: Tertiary referral centre.

Patients: 70 with reduced left ventricular function caused by chronic coronary artery disease.

Main outcome measures: Pulsed-wave tissue Doppler imaging was done close to the mitral annulus at rest and during low-dose dobutamine; systolic ejection velocity (V_s) and the difference in V_s between low-dose dobutamine and the resting value (ΔV_s) were assessed using a 6-segment model. Assessment of perfusion (with ^{99m}Tc -tetrofosmin SPECT) and glucose utilization (by ^{18}F -fluorodeoxyglucose SPECT) was used to classify dysfunctional regions (assessed by resting cross sectional echocardiography) as stunned, hibernating, or scarred.

Results: 253 of 420 regions (60%) were dysfunctional. Of these, 132 (52%) were classified as stunned, 25 (10%) as hibernating, and 96 (38%) as scarred. At rest, V_s in stunned, hibernating, and scar tissue was respectively 6.3 ± 1.8 cm/s, 6.6 ± 2.2 cm/s, and 5.5 ± 1.5 cm/s ($P = 0.001$ by ANOVA). There was a gradual decline in V_s during low-dose dobutamine infusion between stunned, hibernating and scar tissue (8.3 ± 2.6 cm/s vs. 7.8 ± 1.5 cm/s vs. 6.8 ± 1.9 cm/s, $P < 0.001$ by ANOVA). ΔV_s was higher in stunned (2.1 ± 1.9 cm/s), than in hibernating (1.2 ± 1.4 cm/s, $P < 0.05$) or scarred regions (1.3 ± 1.2 cm/s, $P = 0.001$).

Conclusions: Quantitative tissue Doppler imaging showed a gradual reduction in regional velocities between stunned, hibernating, and scarred myocardium. Dobutamine-induced contractile reserve was higher in stunned regions than in hibernating and scarred myocardium, reflecting different severities of myocardial damage.

INTRODUCTION

In patients with chronic coronary artery disease, it is important to differentiate between stunned, hibernating and scarred myocardial tissue. Patients with substantial viability (stunned or hibernating myocardium) may be candidates for coronary revascularization, whereas patients with irreversible damaged myocardium will probably not benefit from revascularization.¹⁻³ The development of stress echocardiography and nuclear imaging techniques has enabled us to differentiate viable from non-viable myocardium.⁴⁻⁸ Moreover, the combined assessment of perfusion and glucose utilization permits the differentiation of normally perfused dysfunctional myocardium (stunned myocardium) from chronically hypoperfused dysfunctional myocardium (hibernating myocardium).⁹⁻¹¹ Although it is likely that stunned and hibernating myocardium do not represent different entities, but consist of a continuum of myocardial dysfunction in ascending order of severity, it is clinically relevant to delineate stunning from hibernation. Preliminary data show that hibernating myocardium may need a longer time to recover contractile function fully than stunned tissue.¹² Our aim in this study was to quantify, using pulsed-wave tissue Doppler imaging, the differences in regional systolic wall motion and contractile reserve in stunned, hibernating, and scarred myocardial tissue.

METHODS

Patient population

Seventy patients with chronic coronary artery disease (previous myocardial infarction or angiographically proven coronary artery disease) were studied at least six months after any previous myocardial infarct. Patients with idiopathic dilated cardiomyopathy, significant valvar heart disease, or a suboptimal acoustic window were not included in the study.

The study protocol was performed as follows. First, left ventricular

ejection fraction was assessed by radionuclide ventriculography. Next, regional contractile function was evaluated by resting cross sectional echocardiography. Then low-dose dobutamine (5 and 10 $\mu\text{g}/\text{kg}/\text{min}$) was infused and contractile reserve was assessed. The resting regional wall motion systolic velocities (V_s) and change in velocities during dobutamine infusion (contractile reserve, ΔV_s) were then quantified by pulsed-wave tissue Doppler imaging. Finally, single-photon emission computed tomography (SPECT) imaging was done, and perfusion and glucose utilization were evaluated using $^{99\text{m}}\text{Tc}$ -tetrofosmin and ^{18}F -fluorodeoxyglucose (^{18}F -FDG), respectively. According to the perfusion-metabolism patterns on SPECT imaging, dysfunctional myocardium was categorised as stunned, hibernating, or scar tissue. Quantitative tissue Doppler imaging data were related to the SPECT findings.

All patients gave informed consent, and the local Ethics Committee approved the study protocol.

Radionuclide ventriculography to assess left ventricular ejection fraction

After injection of $^{99\text{m}}\text{Tc}$ (740 MBq), radionuclide ventriculography was done at rest with the patient in the supine position. A small-field-of-view gamma camera (Orbiter; Siemens, Erlangen, Germany) was used, oriented in a 45° left anterior oblique position with a $5 - 10^\circ$ caudal tilt. The left ventricular ejection fraction was calculated using standard methods.¹³

Cross sectional echocardiography to assess resting contractile function and contractile reserve

We used a commercially available imaging system (Sonos 5500; Hewlett Packard, Andover, Massachusetts, USA) and a 1.8 MHz transducer employing second harmonic imaging to optimise visualization of the endocardial border.¹⁴ Cross sectional imaging was done with the patient in the left lateral position. Standard views were

recorded onto an optical disk (cine loop format). For the assessment of contractile reserve in dysfunctional myocardium, we use dobutamine stress echocardiography as described previously.¹⁵ After the resting echocardiographic study, dobutamine was given intravenously, at doses of 5 and 10 $\mu\text{g}/\text{kg}/\text{min}$ for 5 min. Two experienced observers, unaware of the clinical data or the SPECT results, scored the digitised echocardiograms off-line. In cases of disagreement, a third observer reached a majority decision. Six regions were evaluated, including lateral, inferior, infero-septal, antero-septal, anterior, and posterior.¹⁶ Regional wall motion and systolic wall thickening were scored using a five-point grading scale: 1, normal; 2, mildly hypokinetic; 3, severely hypokinetic; 4, akinetic; and 5, dyskinetic. Regions with severe hypokinesia, akinesia, or dyskinesia were considered abnormal; segments with mild hypokinesia were considered normal.

Tissue Doppler imaging to quantify resting contractile function and contractile reserve

The same six-segment model was used for pulsed-wave tissue Doppler imaging. A pulse repetition frequency of 45-60 KHz and a sample volume of 4 mm³ were used. The measurement of myocardial velocity was sampled in three apical views (four-chamber, two-chamber, and three-chamber) close to the mitral annulus and during a minimum of five consecutive beats, in order to minimize the variability induced by respiration. The depth of the sample volume of every region was kept constant during dobutamine stress echocardiography to ensure that left ventricular myocardium was sampled close to the mitral annulus. The Doppler velocity profiles and ECG tracings were simultaneously stored on optical disk. All measurements were done off-line using a computer-assisted drawing system. The velocity values (cm/s) were obtained on calibrated still frames by manually measuring the distance between the zero baselines and the peak Doppler profile of the ejection phase, in reference to the ECG. Cardiac cycles with extrasystolic, post-extrasystolic beats, or rhythm disturbance were excluded. Recordings and measurements were performed at baseline

and during low-dose (10 μg /kg/min) dobutamine infusion rate.

SPECT tissue characterization: assessment of stunning, hibernation and scar

All patients underwent dual-isotope simultaneous-acquisition SPECT. Resting $^{99\text{m}}\text{Tc}$ -tetrofosmin SPECT (600 MBq) was used to assess regional perfusion. Myocardial glucose utilization was evaluated by ^{18}F -FDG SPECT (185 MBq). To optimize cardiac ^{18}F -FDG, 500 mg of Acipimox (Byk, The Netherlands) was given orally to all patients.¹⁷ A triple-head gamma camera (Prism 3000XP; Picker, Cleveland, Ohio, USA) was used. The camera was equipped with commercially available high-energy 511-keV collimators.¹⁸ The energies were centred on the 140-keV photon peak of $^{99\text{m}}\text{Tc}$ -tetrofosmin with a 15% window and on the 511-keV photon peak of ^{18}F -FDG with a 15% window. Data were acquired over 360° (120 sectors of 3°), and total imaging time was 32 min. The data were stored in a 64×64 , 16-bit matrix. The images were reconstructed by filtered backprojection using a Butterworth filter (cut-off frequency, 0.17 cycles per pixel); 6-mm-thick (1 pixel) transaxial slices were obtained. Subsequently, standard short- and long-axis projections perpendicular to the heart axis were reconstructed. The same six regions as for the echocardiographic analysis were used.

Both $^{99\text{m}}\text{Tc}$ -tetrofosmin and ^{18}F -FDG studies were analysed quantitatively (segments normalized to maximum tracer uptake). Dysfunctional segments (identified by resting echocardiography) were evaluated for perfusion and glucose utilization.^{4,19,20} Dysfunctional segments with normal perfusion (normalised $^{99\text{m}}\text{Tc}$ -tetrofosmin uptake of $> 80\%$) were classified as stunned. Dysfunctional segments with a perfusion defect (normalised $^{99\text{m}}\text{Tc}$ -tetrofosmin uptake $< 80\%$) were classified as hibernating when a perfusion- ^{18}F -FDG mismatch was present (relative increase of ^{18}F -FDG uptake $\geq 10\%$, compared with $^{99\text{m}}\text{Tc}$ -tetrofosmin uptake). Dysfunctional segments with a perfusion defect were classified as scar tissue when a perfusion- ^{18}F -FDG match was present ($< 10\%$ difference in tracer activities).^{4, 19, 20}

Statistical analysis

Dichotomous variables are presented as n (%) and continuous variables as mean \pm SD. Comparisons between severely and non-severely dysfunctional regions were made using the Student *t* test. Comparisons between normal, mildly hypokinetic, severely hypokinetic, and akinetic/dyskinetic regions, as well as between stunned, hibernating, and scarred regions were made by one-way analysis of variance (ANOVA). Bonferroni analysis was used to assess significance during multiple comparisons. Significance of all statistical tests was assumed at the 0.05 probability level.

RESULTS

Patient characteristics

The baseline clinical characteristics of the 70 patients are summarised in Table 1. Mean left ventricular ejection fraction was 31 ± 10 % (range 10 - 45%), and New York Heart Association (NYHA) functional class was on average 3.0 ± 1.2 . The majority of patients (53 patients, 76%) were in NYHA class III or IV.

Cross sectional echocardiography to assess resting contractile function and contractile reserve

Resting echocardiography was undertaken in 420 regions. Of these, 167 (40%) had normal contractile function (normokinesia), while 253 (60%) regions were dysfunctional, including 164 severely hypokinetic, and 89 akinetic/dyskinetic regions. Of the 253 dysfunctional regions, 181 (72%) showed contractile reserve during dobutamine infusion (increase in wall motion score index by one grade or more during dobutamine infusion). The hemodynamic response during low-dose dobutamine infusion is shown in Table 2. The administration of dobutamine was well tolerated by all patients.

Table 1. Clinical baseline characteristics of the 70 study patients

Male sex	59 (84%)
Age (years)	62 ± 10
New York Heart Association functional class	3.0 ± 1.2
Left ventricular ejection fraction (%)	31 ± 10
Previous myocardial infarction	62 (89%)
Previous coronary artery bypass graft surgery	15 (21%)
Previous percutaneous transluminal coronary angioplasty	20 (29%)
Hypertension ^a	17 (24%)
Diabetes mellitus ^b	8 (11%)
Hypercholesterolemia ^c	27 (39%)
Current smoking	15 (21%)
Angina pectoris	40 (57%)
Medication	
Aspirin/oral anticoagulants	62 (89%)
Angiotensin-converting enzyme inhibitors	58 (83%)
Diuretics	35 (50%)
Beta-blockers	42 (60%)
Digoxin	12 (17%)

Data are n (%) or mean ± SD.

^aDefined as blood pressure ≥140/90 mmHg, or treatment with anti-hypertensive drugs.

^bPatients receiving oral antidiabetics or insulin.

^cDefined as a total cholesterol ≥6.4 mmol/l or treatment with lipid-lowering drugs.

The protocol was completed in all patients without serious side effects.

Tissue Doppler imaging to quantify resting contractile function and contractile reserve

Myocardial systolic velocity of normal or mildly hypokinetic regions (non-dysfunctional regions) was 6.8 ± 2.0 cm/s at rest and 9.2 ± 3.3

Table 2. Hemodynamic response during dobutamine infusion

	Baseline	10 μ g/kg/min	P value
Heart rate (beats/min)	74 \pm 12	83 \pm 15	<0.001
Systolic blood pressure (mmHg)	125 \pm 22	125 \pm 19	0.960
Diastolic blood pressure (mmHg)	76 \pm 11	73 \pm 11	0.018
Rate-pressure product	9250 \pm 2376	10377 \pm 3017	<0.001
Wall motion score index	2.8 \pm 0.5	2.5 \pm 1.0	<0.001

Values are mean \pm SD.

cm/s during low-dose dobutamine challenge, while ΔV_s was 2.4 ± 2.8 cm/s. Dysfunctional regions had significantly lower velocities: 6.2 ± 1.6 cm/s at rest ($P < 0.001$), and 7.6 ± 2.0 cm/s at low-dose dobutamine ($P < 0.001$), with ΔV_s reaching 1.4 ± 1.5 cm/s ($P < 0.001$). Figure 1 illustrates the systolic velocities at rest and during low-dose

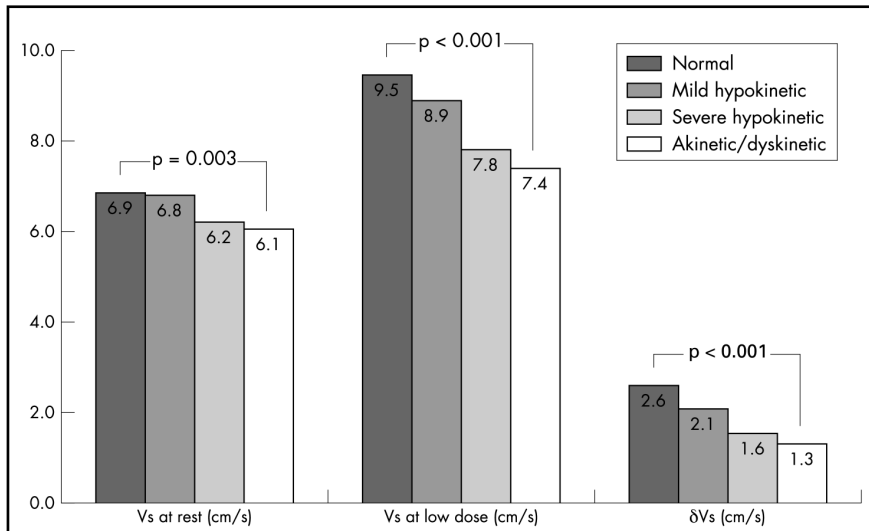


Figure 1. Systolic velocity (V_s) at rest, during low-dose dobutamine infusion, and the difference in V_s from rest to low-dose dobutamine infusion (ΔV_s) in normal, mildly hypokinetic, severely hypokinetic, and akinetic/dyskinetic regions.

dobutamine infusion, and ΔV_s in normal, mildly hypokinetic, severely hypokinetic, and akinetic/dyskinetic regions, according to the cross sectional echocardiographic assessment. Comparison between the four groups (by ANOVA) showed significant differences in V_s at rest ($P = 0.003$) and during low-dose dobutamine infusion ($P < 0.001$), as well as in ΔV_s ($P < 0.001$).

In dysfunctional regions with contractile reserve during low-dose dobutamine challenge, maximal V_s was 6.1 ± 1.6 cm/s at rest and 8.0 ± 2.2 cm/s during low-dose dobutamine, and ΔV_s was 1.9 ± 2.1 cm/s. In dysfunctional regions without contractile reserve, V_s was 6.2 ± 2.0 cm/s at rest ($P = 0.41$) and 7.3 ± 2.2 cm/s during low-dose dobutamine ($P = 0.04$), and ΔV_s was 1.1 ± 2.0 cm/s ($P = 0.008$).

SPECT imaging, tissue characterization

Dual isotope SPECT imaging showed that 132 of 253 dysfunctional regions (52%) had normal perfusion and glucose utilization; these segments were considered stunned. Reduced perfusion and relatively preserved glucose utilization (hibernating myocardium) was observed in 25 of the dysfunctional regions (10%). The remaining regions (96; 38%) had concordantly reduced perfusion and metabolism and were considered to be scar tissue.

Tissue Doppler imaging in stunned, hibernating, and scarred regions

V_s at rest

In the dysfunctional regions, V_s at rest in stunned, hibernating and scar tissue was, respectively, 6.3 ± 1.8 cm/s, 6.6 ± 2.2 cm/s, and 5.5 ± 1.5 cm/s ($P = 0.001$ by ANOVA).

V_s during low-dose dobutamine

During low-dose dobutamine infusion there was a gradual decline in V_s in stunned, hibernating, and scar tissue (8.3 ± 2.6 cm/s vs. 7.8 ± 1.5 cm/s vs. 6.8 ± 1.9 cm/s; $P < 0.001$ by ANOVA).

ΔV_s

The increase of tissue Doppler systolic velocity observed during low-

dose dobutamine stress (ΔV_s) is considered an indicator of contractile reserve. The comparison between the three groups showed that ΔV_s was significantly higher in stunned (2.1 ± 1.9 cm/s), than in hibernating (1.2 ± 1.4 cm/s, $P < 0.05$) or scarred regions (1.3 ± 1.2 cm/s, $P = 0.001$). Table 3 presents tissue Doppler systolic velocities in stunned, hibernating, and scarred myocardium.

DISCUSSION

Main findings

Quantitative analysis of myocardial wall motion showed that there is a gradual decline in wall motion velocities between stunned, hibernating, and scarred myocardium, which is more pronounced during low-dose dobutamine infusion. However, stunned myocardium had better-preserved dobutamine-induced contractile reserve, not only in comparison with scar tissue but also in comparison with hibernating myocardium.

Contractile reserve in stunning and hibernation

In this study, myocardial regions with severe dysfunction assessed by resting cross sectional echocardiography were classified as stunned, hibernating, or scarred, based on the combined scintigraphic assessment of glucose utilization and perfusion.⁹⁻¹¹ It has been hypothesized that resting perfusion is initially normal in myocardium affected by chronic coronary artery stenosis, and this state has been referred to as chronic stunning.²¹ When this condition is prolonged over time, animal studies have shown that resting perfusion may eventually become reduced, a state referred to as hibernation.^{11,21} Along these lines, it is thought that hibernating myocardium is more damaged on the myocyte level than chronically stunned myocardium. Indeed, biopsies taken from hibernating myocardium during surgical revascularization have shown a gradual loss of sarcomeres and a nearly absent

Table 3. Pulsed-wave tissue Doppler systolic velocities in stunned, hibernating, and scarred segments, at rest and during low-dose dobutamine infusion

	Stunning (n=132)	Hibernation (n=25)	Scarred tissue (n=96)	P Value (ANOVA)
Vs at rest (cm/s)	6.3 ± 1.8	6.6 ± 2.2	5.5 ± 1.5	0.001
Vs at low dose (cm/s)	8.3 ± 2.6	7.8 ± 1.5	6.8 ± 1.9	<0.001
ΔVs (cm/s)	2.1 ± 1.9	1.2 ± 1.3	1.3 ± 1.2	0.001

Values are mean ± SD.

sarcoplasmic reticulum, with accumulation of glycogen in the spaces previously occupied by the myofilaments.^{22,23} Thus, following chronic coronary stenosis, stunning may gradually progress to hibernation.¹¹ When this condition persists for a long time, irreversible damage may eventually occur, followed by scar formation.

Based on observations on a myocyte level, it is likely that resting contraction and contractile reserve may be more affected (reduced) in hibernating than in stunned myocardium. As cross sectional echocardiography is only based on visual assessment of wall motion, we have used tissue Doppler imaging to provide objective and quantitative information of resting contractile function and contractile reserve (assessed during infusion of low-dose dobutamine). Quantitative tissue Doppler imaging done in this way showed a gradual decline in wall motion velocities in stunned, hibernating, and scarred myocardium, reflecting different degrees of ultrastructural damage. In addition, stunned regions had better-preserved contractile reserve than either hibernating or scarred regions.

Previous studies

Our findings are in agreement with previous studies that showed a superior contractile reserve in stunned, than in hibernating tissue. Sambuceti and colleagues studied 21 patients one month after they had been given thrombolysis for acute anterior myocardial infarction.²² The

authors employed positron emission tomography (using combined assessment of perfusion and glucose utilization) to differentiate stunned from hibernating myocardium. In stunned myocardium, contractile reserve (assessed by infusion of low-dose dobutamine) was frequently intact, whereas hibernating myocardium less frequently exhibited contractile reserve. Schinkel et al studied 198 patients with ischemic cardiomyopathy and also demonstrated that contractile reserve was more frequently present in stunned than in hibernating myocardium.¹⁵ The present study confirms and extends these previous findings. This is the first quantitative data on contractile reserve in stunned, hibernating and scarred myocardium. Tissue Doppler velocities differed significantly in stunned, hibernating and scar tissue and may potentially be used to delineate these pathophysiological entities.

Clinical implications

An important question for clinicians treating patients with ischemic cardiomyopathy is the prediction of improvement of contractile function after coronary revascularization. Both hibernating and chronically stunned myocardium (based on the more severe ultrastructural damage) may need a longer time to recover after revascularization.¹² Accordingly, distinction of stunned from hibernating myocardium (and differentiation from scarred myocardium) may allow the clinicians to anticipate the time needed for recovery of function after revascularization. Quantification of contractile reserve by pulsed-wave tissue Doppler imaging may provide an easy, simple and relatively inexpensive method to acquire this information. To this end, studies in patients undergoing revascularization are needed.

Limitations

This study has several limitations. First, no outcome data after myocardial revascularization were available. Second, pulsed-wave

tissue Doppler imaging includes the effect of cardiac motion within the thorax, as well as the maintenance of the angle of incidence of the ultrasound beam in relation to the axis of myocardial longitudinal movement. This limitation was partially minimized by using only apical views, where the cardiac apex serves as a fixed reference point.²³ Finally, tissue Doppler imaging measurements are susceptible to the tethering effect of neighboring segments. We tried to avoid these effects by considering each one of the myocardial walls as a whole region, and by positioning the sample near the mitral annulus, where the vectorial sum of velocities along the longitudinal axis can be measured.

Conclusions

Quantitative tissue Doppler imaging showed a gradual reduction of wall motion velocities between stunned, hibernating and scarred myocardium. Dobutamine-induced contractile reserve assessed by tissue Doppler imaging was higher in stunned regions compared to hibernating and scarred myocardium. The gradual reduction in wall motion velocities probably reflects an increasing severity of ultrastructural damage in these different pathophysiological entities.

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CHAPTER 11

PULSED-WAVE TISSUE DOPPLER QUANTIFICATION OF SYSTOLIC AND DIASTOLIC FUNCTION OF VIABLE AND NONVIABLE MYOCARDIUM IN PATIENTS WITH ISCHEMIC CARDIOMYOPATHY



Source: M Bountiukos, AFL Schinkel, JJ Bax, E Biagini,
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ABSTRACT

Background: Detection of myocardial viability is crucial for clinical management of patients with ischemic cardiomyopathy. Currently, quantitative information for the evaluation of systolic and diastolic function of viable tissue is limited. Our aim was to compare quantitatively systolic and diastolic function in viable and nonviable dysfunctional myocardium in patients with ischemic cardiomyopathy.

Methods: A total of 93 patients (mean age: 62 ± 10 years) underwent dobutamine stress echocardiography to assess myocardial viability. Pulsed-wave tissue Doppler imaging (TDI) was used to assess systolic ejection velocity (V_s), as well as early (V_E) and late (V_A) diastolic velocities at rest and at low-dose dobutamine infusion ($10 \mu\text{g}/\text{kg}/\text{min}$) in viable and nonviable dysfunctional regions. Analysis was repeated after dividing study population in patients ≥ 65 years old ($n = 40$), and < 65 years old ($n = 53$).

Results: Pulsed-wave TDI demonstrated that V_s was comparable in dysfunctional viable and nonviable regions at rest (V_s , 6.3 ± 1.9 cm/s vs. 6.3 ± 2.0 cm/s, respectively, $P = 0.93$). However, at low-dose dobutamine challenge V_s was significantly higher in viable regions (8.5 ± 2.7 cm/s vs. 7.8 ± 2.4 cm/s, $P = 0.002$). Viable regions had higher V_E at rest compared with nonviable regions (8.4 ± 2.5 cm/s vs. 7.5 ± 2.8 cm/s, $P = 0.003$). Myocardial velocities were significantly higher in patients ≥ 65 years old, both in viable and nonviable regions.

Conclusions: Quantification of myocardial motion by pulsed-wave TDI demonstrates that at low-dose dobutamine stress, systolic velocity is markedly improved in viable myocardium, indicating the presence of contractile reserve in viable regions. A superior early diastolic filling at rest can also differentiate viable from nonviable myocardium.

INTRODUCTION

Noninvasive assessment of viable myocardium in patients with ischemic cardiomyopathy is important for clinical decision-making, since patients with a substantial amount of dysfunctional but viable myocardium may benefit from myocardial revascularization.¹ Several imaging techniques have been developed to assess myocardial viability. Among them, dobutamine stress echocardiography is widely used for this purpose. The hallmark of myocardial viability is improvement of systolic wall motion during low-dose dobutamine challenge.^{2,3}

Currently, quantitative information on the systolic function of viable and nonviable myocardium is limited, whereas there is no available information on quantification of diastolic function of viable and nonviable myocardium in patients with ischemic cardiomyopathy. Pulsed-wave tissue Doppler imaging (TDI) has the potential to provide quantitative information on dysfunctional myocardium by assessing longitudinal myocardial velocities. This technique allows the measurement of regional peak instantaneous myocardial velocities with high temporal resolution.^{4,5}

Accordingly, the aim of this study was to quantify regional myocardial velocities, and to compare systolic and diastolic function in viable and nonviable dysfunctional myocardium in a group of patients with impaired left ventricular function, due to chronic coronary artery disease.

METHODS

Patients

A total of 93 consecutive patients in clinically stable cardiac condition, with chronic coronary artery disease and depressed left ventricular ejection fraction (< 40%) were studied. Patients with primary cardiomyopathy, significant valvular heart disease, prosthetic valve implantation, pacemaker rhythm, recent (< 6 month) myocardial infarction or an inadequate acoustic window were not included in the

study. The study protocol was as follows: First, dysfunctional myocardium was identified by resting two-dimensional (2D) echocardiography; the dysfunctional myocardium was then evaluated for the presence of myocardial viability (contractile reserve) using dobutamine stress echocardiography; the viable and nonviable myocardial regions were subsequently interrogated by pulsed-wave TDI to quantify systolic and diastolic function. Analysis of myocardial velocities was also performed with respect to patient age, since there is evidence that myocardial velocities are age-dependent, especially during diastole. An age of 65 years was used as a cut-off point to divide patients into two subgroups: 40 patients with mean age 70 ± 4 years, and 53 patients with mean age of 54 ± 7 years. The Hospital Ethics Committee approved the protocol. All patients gave informed consent before the test.

Resting 2D echocardiography, Assessment of Regional Dysfunction

A commercially available imaging system (Hewlett Packard Sonos 5500, Andover, Mass.) and a 1.8 MHz transducer using second harmonic imaging to optimize endocardial border visualization were used. Two-dimensional imaging was performed with the patient in the left lateral position; standard views were recorded on optical disk (cine loops).⁶

Dobutamine stress echocardiography, assessment of contractile reserve

To assess the contractile reserve in dysfunctional myocardium, dobutamine stress echocardiography was performed, as described previously.⁷ Beta-blocker therapy was not routinely discontinued before dobutamine stress echocardiography. After the resting echocardiographic study, dobutamine was administered intravenously, starting at a dose of $5 \mu\text{g}/\text{kg}/\text{min}$ for 5 min, followed by a $10 \mu\text{g}/\text{kg}/\text{min}$ dose for 5 min (low-dose protocol). Dobutamine was then increased by $10 \mu\text{g}/\text{kg}/\text{min}$ every 3 min to a maximum dose of $40 \mu\text{g}/\text{kg}/\text{min}$. Atropine (up to 2 mg) was added at the end of the last stage if the target

heart rate had not been achieved. Other test end-points were horizontal or downsloping ST-segment depression > 2 mm at an interval of 80 ms after the J-point compared with baseline, severe angina, systolic blood pressure fall > 40 mmHg, blood pressure > 240/120 mmHg, or significant cardiac arrhythmia. An intravenous β -blocker was available to reverse the adverse effects of dobutamine/atropine.

Two experienced observers, unaware of the clinical data, scored the digitized echocardiograms offline. In case of disagreement, a majority decision was achieved by a third observer. For each study, the left ventricle was divided into six regions (anterior, inferior, septal anterior, septal posterior, lateral, and posterior) as described previously.⁵ Regional wall motion and systolic wall thickening were scored using a five-point grading scale: (1) normal, (2) mildly hypokinetic, (3) severely hypokinetic, (4) akinetic, (5) dyskinetic. Regions with severe hypokinesia, akinesia or dyskinesia were considered abnormal; regions with mild hypokinesia were considered normal. Contractile reserve was defined as an improvement of regional wall motion score by ≥ 1 grade following infusion of low-dose dobutamine.

Tissue Doppler imaging

Pulsed-wave TDI was performed with the same system used for the assessment of wall motion abnormalities, with a pulse repetition frequency of 45 to 60 KHz. To relate both imaging modalities, an identical six-segment model was used for 2D echocardiography and tissue Doppler imaging. A sample volume of 4 mm³ was used. The measurement of myocardial velocity was sampled in apical views (four-chamber, two-chamber, and three-chamber) close to the mitral annulus and during a minimum of five consecutive beats, in order to minimize the variability induced by respiration. The depth of the sample volume of every wall was kept constant during dobutamine stress echocardiography to make sure that left ventricular myocardium was sampled close to the mitral annulus. The Doppler velocity profiles and electrocardiographic tracings were simultaneously stored on optical disk. All the measurements were performed offline using a

computer-assisted drawing system. The velocity values (cm/s) were obtained on calibrated still frames by manually measuring the distance between the zero baselines and the peak Doppler profile of the ejection phase, early and late diastole in reference to the electrocardiogram. Cardiac cycles with extrasystolic, post-extrasystolic beats or rhythm disturbance were excluded. Recordings and measurements were made at baseline and at low dose (10 μg /kg/min) dobutamine infusion rate.⁵

Statistical analysis

All continuous data are expressed as mean \pm standard deviation and percentages are rounded. Continuous variables were compared using the Student *t*-test for unpaired samples. Differences between proportions were compared using the chi-square test. A value of $P < 0.05$ was considered statistically significant.

RESULTS

Patient characteristics

Baseline characteristics of the 93 patients are shown in Table 1. Study patients (72 men and 21 women) had a mean age of 62 ± 10 years (range, 39 to 78). All patients had a history of previous myocardial infarction (at least 6 months before). The mean left ventricular ejection fraction was $32 \pm 9\%$ (range, 19 to 39%). Coronary revascularization had been previously performed in 39 patients (22 patients had coronary artery bypass grafting, and 17 patients had percutaneous transluminal coronary angioplasty).

Regional Dysfunction

2D echocardiography at rest was performed in a total of 558 regions. In 549 (98%) regions wall motion analysis was feasible. Of these, 133 (24%) regions were normal or mildly hypokinetic and were not

Table 1. Baseline clinical characteristics

Male gender (%)	77
Age (years)	62 ± 10
Left ventricular ejection fraction	32 ± 9 (%)
Diabetes mellitus ^a (%)	9
Hypercholesterolemia ^b (%)	41
Systemic hypertension ^c (%)	34
Current smoking (%)	28
History of angina (%)	59
Previous revascularization	
Percutaneous coronary intervention (%)	18
Coronary bypass graft surgery (%)	24
Medication	
Beta-blockers (%)	49
Angiotensin converting enzyme -inhibitors (%)	67

^aFasting glucose level of ≥ 140 mg/dl (7.8 mmol/L) or the need for insulin or oral hypoglycaemic agents.

^bTotal cholesterol of ≥ 200 mg/dl (5.2 mmol/L) or treatment with lipid-lowering drugs.

^cA blood pressure of $\geq 140/90$ mmHg or treatment with antihypertensive drugs.

considered for myocardial viability. There were 416 (76%) severely hypokinetic, akinetic, or dyskinetic regions.

Dobutamine stress echocardiography

The administration of dobutamine was well tolerated in all study patients; the protocol was completed in all patients and no serious side effects did occur. During low-dose dobutamine stimulation 238 (57%) of all 416 dysfunctional regions exhibited contractile reserve and were classified viable. The remaining 178 (43%) regions did not improve and were classified nonviable. Regions without viability at 10 μ g/kg/min did not show any improvement at higher rates of dobutamine infusion.

Pulsed-wave TDI, assessment of systolic function

Dysfunctional vs. nondysfunctional regions: Pulsed-wave TDI at rest demonstrated that dysfunctional viable and nonviable regions had lower systolic velocities compared with nondysfunctional regions (6.2 ± 1.9 cm/s, vs. 7.1 ± 1.8 cm/s, $P < 0.001$).

Viable vs. nonviable regions: There was no difference in V_s at rest between viable and nonviable regions (6.3 ± 1.9 cm/s vs. 6.3 ± 1.9 cm/s, respectively, $P = 0.93$), see Figure 1. However, during low-dose dobutamine infusion, V_s was significantly higher in viable regions (8.5 ± 2.7 cm/s vs. 7.8 ± 2.4 cm/s, respectively [$P = 0.002$]), see Figure 2.

Pulsed-wave TDI, assessment of diastolic function

Dysfunctional vs. nondysfunctional regions: Diastolic velocities were

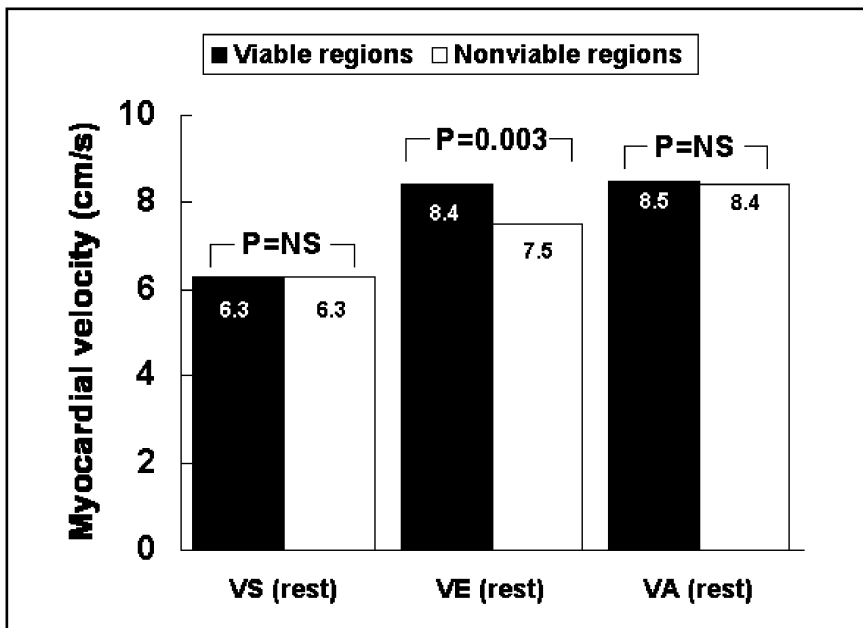


Figure 1. Systolic (V_s), early diastolic (V_E), and late diastolic (V_A) myocardial velocities at rest in viable and nonviable regions. Values are expressed in cm/s.

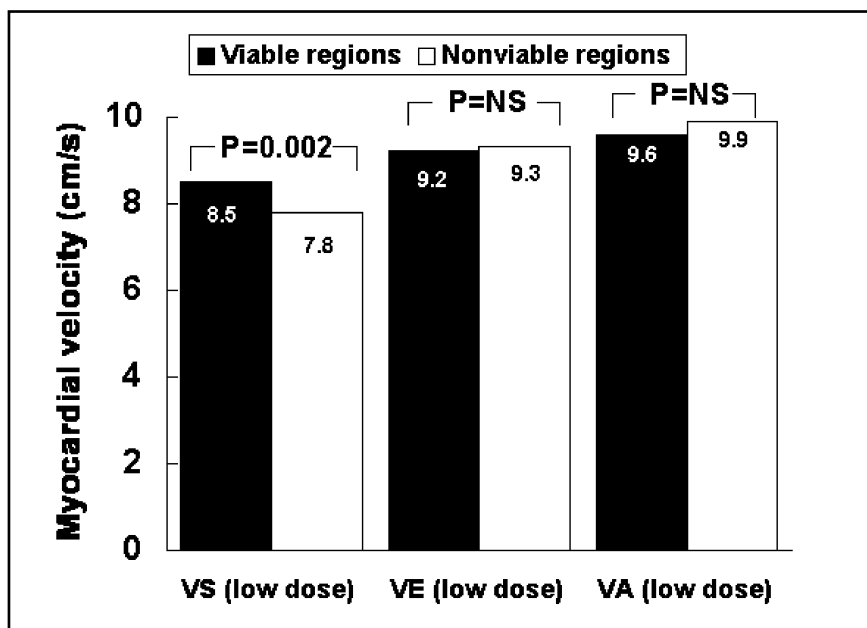


Figure 2. Systolic (V_S), early diastolic (V_E), and late diastolic (V_A) myocardial velocities at low-dose dobutamine challenge in viable and nonviable regions. Values are expressed in cm/s.

lower in dysfunctional, compared to nondysfunctional regions (V_E , 7.9 ± 2.7 cm/s vs. 8.5 ± 3.0 cm/s, $P = 0.03$, V_A , 8.4 ± 3.0 cm/s vs. 9.4 ± 2.9 cm/s, $P < 0.001$).

Viable vs. nonviable regions: Early diastolic velocity at rest was significantly higher in viable as compared to nonviable regions (8.4 ± 2.5 cm/s vs. 7.5 ± 2.9 cm/s, respectively, $P = 0.003$), see Figure 1. At low dose dobutamine infusion there was no difference in early diastolic velocity (9.2 ± 3.5 cm/s vs. 9.3 ± 3.4 cm/s, respectively, $P = 0.50$), see Figure 2. Also, no differences were observed between viable and nonviable regions with respect to late diastolic velocities at rest and at low dose dobutamine.

Effect of age on myocardial velocities

Systolic and diastolic myocardial velocities showed an age-dependency, being significantly higher in the younger patients (< 65

years), as compared to patients ≥ 65 years old. This difference was evident both in viable and nonviable regions (Table 2). The differences found between viable and nonviable regions in the total population remained significant in both patient groups: In patients ≥ 65 years old, V_s at low-dose dobutamine was 8.1 ± 2.8 cm/s in viable regions, and 7.3 ± 2.2 cm/s in nonviable regions ($P = 0.04$). In patients < 65 years old, V_s at low-dose dobutamine was 8.9 ± 2.6 cm/s in viable regions, and 8.1 ± 2.4 cm/s in nonviable regions ($P = 0.03$).

The same was true for V_E at rest: In patients ≥ 65 years old, V_E was 7.7 ± 2.6 cm/s in viable regions, and 6.6 ± 2.2 cm/s in nonviable regions ($P = 0.004$). In patients < 65 years old, V_s at low-dose dobutamine was 8.9 ± 2.4 cm/s in viable regions, and 8.2 ± 3.2 cm/s in nonviable regions ($P = 0.04$).

Table 2 presents systolic and diastolic myocardial velocities in viable and nonviable regions with respect to patient age.

DISCUSSION

Heart failure commonly results from chronic coronary artery disease causing left ventricular dysfunction.⁸ Dysfunctional myocardium does not always represent irreversibly damaged tissue. Patients with a substantial amount of dysfunctional but viable myocardium may benefit from coronary revascularization.⁹ Viable myocardium has the ability to respond to β_1 -adrenergic stimulation induced by dobutamine challenge, by increasing thickening and motion velocity.^{10,11} In the present study, 46 (49%) patients used beta blocker therapy. In our hospital, beta-blocker therapy is not routinely withheld before stress testing; we believe that this reflects daily clinical practice. Moreover previous data indicate that beta-blocker therapy may be continued during myocardial viability assessment in patients with ischemic cardiomyopathy.¹² Recently, it has become clear that not only systolic dysfunction but also abnormalities in diastolic function play an important role in producing signs and symptoms of heart failure.¹³ Pulsed-wave TDI allows quantification of systolic and diastolic wall motion, as well as quantification of

Table 2. Pulsed-wave systolic and diastolic velocities (cm/s) in viable and nonviable myocardium, according to patient age.

	≥65 years (n=40)	<65 years (n=53)	P Value
	Viable regions		
V _S (Rest)	5.7 ± 1.7	6.7 ± 1.8	<0.001
V _S (Ldd)	8.1 ± 2.8	8.9 ± 2.6	0.02
V _E (Rest)	7.7 ± 2.6	8.9 ± 2.4	0.004
V _E (Ldd)	8.4 ± 3.3	9.7 ± 3.4	0.003
V _A (Rest)	8.5 ± 3.4	8.5 ± 3.1	0.90
V _A (Ldd)	10.1 ± 4.0	9.3 ± 3.5	0.09
	Nonviable regions		
V _S (Rest)	5.9 ± 1.8	6.6 ± 1.8	0.003
V _S (Ldd)	7.3 ± 2.2	8.1 ± 2.4	0.01
V _E (Rest)	6.6 ± 2.2	8.4 ± 3.2	<0.001
V _E (Ldd)	8.8 ± 3.4	10.0 ± 3.5	0.03
V _A (Rest)	8.7 ± 3.1	8.2 ± 3.2	0.33
V _A (Ldd)	10.6 ± 4.0	9.3 ± 3.8	0.03

Data are presented as mean ± SD.

Ldd, low-dose dobutamine; V_A, late diastolic velocity; V_E, early diastolic velocity; V_S, systolic ejection velocity;

contractile reserve when this technique is combined with low-dose dobutamine challenge. Thus, pulsed-wave TDI can be used to identify dysfunctional but viable tissue in an objective manner. Currently, quantitative information on systolic function of viable and nonviable myocardium is limited, whereas data on quantification of diastolic function in viable and nonviable regions is not available.

Pulsed-wave TDI to quantify systolic myocardial function

Several studies in the past have shown that pulsed-wave TDI is an

effective method to assess quantitatively the existence of myocardial viability after myocardial infarction. Gorcsan et al.⁴ used tissue Doppler echocardiography to demonstrate that viable segments on myocardial perfusion imaging have a significantly higher systolic ejection velocity. Matsuoka et al.¹⁴ used pulsed-wave TDI of mitral annulus to study 45 patients with previous myocardial infarction and found that low-dose dobutamine infusion could reveal a significant increase of peak systolic myocardial velocities in viable, but not in nonviable myocardium. Our study is in accordance with these studies, since low-dose dobutamine infusion produced a higher increase of systolic velocity in dysfunctional but viable regions, as assessed by dobutamine stress echocardiography, indicating that these regions were either stunned or hibernating.

Pulsed-wave tissue Doppler to quantify diastolic myocardial function

Although cardiac catheterization is considered the reference technique to determine diastolic filling pressures and left ventricular relaxation, several noninvasive techniques were developed to determine diastolic function. Pulsed-wave TDI is one of them, since it has the potential to provide quantitative information on diastolic function by assessing longitudinal myocardial early and late (atrial-assisted) filling velocities. However, currently there is no data on the differences in myocardial diastolic velocities between viable and nonviable regions.

Age-dependency of myocardial velocities

Normal aging has been shown to affect diastolic ventricular relaxation in healthy subjects. Henein et al.¹⁵ studied 60 healthy hearts with pulsed-wave TDI and demonstrated an age-dependency in diastolic ventricular filling. Palka et al.¹⁶ reported a decrease with age in transmural gradients during early and late diastolic filling in healthy hearts. Both studies found no differences in systolic velocities with age.

In the present study, early diastolic velocities were significantly higher in patients < 65 years old, compared to older patients. In addition, systolic myocardial velocities in dysfunctional myocardium were also age-dependent. Further studies in dysfunctional hearts are needed to clarify this issue.

Study limitations

In the current study myocardial viability was assessed by dobutamine stress echocardiography. This is a safe and widely available imaging method, with a good sensitivity and specificity for the evaluation of myocardial viability.¹⁷ Still, functional improvement of contractile dysfunction after coronary revascularization is considered the final proof of myocardial viability. In this study functional improvement after coronary revascularization was not assessed.

Another limitation was the fact that there was no direct estimation of the velocities of the medial and apical segments, since measurements were performed from six myocardial regions adjacent to the mitral annulus. However, tissue Doppler velocities of mitral annulus are not influenced by tethering effects of adjacent segments, and correspond to the sum of longitudinal velocities from base to apex. Finally, further studies are needed to evaluate the application of the present findings.

Conclusions

Tissue Doppler imaging can become a useful and inexpensive tool to differentiate viable from nonviable myocardium in patients with ischemic cardiomyopathy. Regions containing dysfunctional but viable tissue (stunned or hibernating myocardium) show a contractile reserve, which can now be quantitatively and objectively assessed during low-dose dobutamine infusion. In addition, a superior early diastolic filling at rest can differentiate viable regions. The differences between viable and nonviable regions are present both in patients < 65 years old and in older patients, in spite of the fact that myocardial velocities are age dependent, decreasing significantly in the elderly.

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CHAPTER 12

QUANTIFICATION OF REGIONAL LEFT VENTRICULAR FUNCTION IN Q-WAVE AND NON-Q-WAVE DYSFUNCTIONAL REGIONS BY TISSUE DOPPLER IMAGING IN PATIENTS WITH ISCHEMIC CARDIOMYOPATHY



Source: M Bountiokos, AFL Schinkel, JJ Bax, V Rizzello,
R Rambaldi, EC Vourvouri, JRTC Roelandt, D Poldermans.
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ABSTRACT

Objective: To quantify regional left ventricular (LV) function and contractile reserve in Q-wave and non-Q-wave regions in patients with previous myocardial infarction.

Design: An observational study.

Setting: Tertiary care centre.

Patients: 81 patients with previous MI and depressed LV function.

Interventions: All patients underwent surface ECG at rest and pulsed-wave tissue Doppler imaging at rest and during low-dose dobutamine infusion. The left ventricle was divided into four major regions (anterior, inferoposterior, septal and lateral). Severely hypokinetic, akinetic, and dyskinetic regions on two-dimensional echocardiography at rest were considered dysfunctional.

Main outcome measures: Regional myocardial systolic velocity (V_s) at rest and the change in V_s during low dose dobutamine infusion (ΔV_s) in dysfunctional regions with and without Q waves on surface ECG.

Results: 220 (69%) regions were dysfunctional; 60 of these regions corresponded to Q waves and 160 were not related to Q waves. V_s and ΔV_s were lower in dysfunctional than in non-dysfunctional regions (V_s 6.2 ± 1.9 cm/s vs. 7.1 ± 1.7 cm/s; $P < 0.001$, and DVS 1.9 ± 1.9 cm/s vs. 2.6 ± 2.5 cm/s; $P = 0.009$, respectively). There were no significant differences in V_s and ΔV_s among dysfunctional regions with and without Q waves (Q-wave regions: V_s 6.2 ± 1.8 cm/s, ΔV_s 1.6 ± 2.2 cm/s; non-Q-wave regions: V_s 6.3 ± 1.9 cm/s, ΔV_s 2.0 ± 2.0 cm/s).

Conclusions: Quantitative pulsed-wave tissue Doppler demonstrated that, among dysfunctional regions, Q waves on the ECG do not indicate more severe dysfunction, and myocardial contractile reserve is comparable in Q-wave and non-Q wave dysfunctional myocardium.

INTRODUCTION

Traditionally, the classification of myocardial infarctions as transmural or subendocardial has been based on the presence or absence of Q waves on surface ECG. Even nowadays, chronic pathologic Q waves are often considered to represent myocardial regions with more extensive damage, than in dysfunctional non-Q-wave related regions. However, several studies have been shown a poor correlation between Q waves on the ECG and histopathological findings in patients with a healed myocardial infarction.^{1,2} Nuclear and echocardiographic techniques used for the detection of viable myocardium have shown that Q-wave related regions may contain hibernating myocardium - that is, dysfunctional but viable tissue.³⁻⁵ Moreover, disappearance of Q waves and improvement of regional left ventricular (LV) function have been observed after myocardial revascularization.⁶⁻⁸ Quantitative information on regional LV function and contractile reserve in Q-wave and non-Q-wave dysfunctional regions is lacking. Accordingly, the aim of this study was to quantify myocardial function at rest, and contractile reserve during low-dose dobutamine infusion by pulsed-wave tissue Doppler imaging (TDI) in Q-wave and non-Q-wave dysfunctional regions in patients with chronic coronary artery disease and reduced LV function.

METHODS

Study population

The patient population consisted of 81 consecutive patients with healed Q-wave myocardial infarction and ischaemic cardiomyopathy (left ventricular ejection fraction (LVEF) \leq 40% and symptoms of congestive heart failure). Patients with left bundle branch block, pacemaker rhythm, primary cardiomyopathy or significant valvar disease were not included. All patients underwent resting surface ECG to identify Q-wave and non-Q-wave regions. Two-dimensional echocardiography at rest and during low-dose dobutamine infusion (10

$\mu\text{g/kg/min}$) was performed to assess regional LV function and myocardial contractile reserve. Pulsed-wave TDI at rest and during low-dose dobutamine infusion was used to quantify regional wall motion velocity. The LVEF was assessed by radionuclide ventriculography. The hospital medical ethics committee approved the protocol and all patients gave informed consent.

Electrocardiographic analysis

Two experienced observers blinded to any other data and using the Selvester QRS screening criteria for Q-wave myocardial infarction evaluated the surface ECGs. Accordingly, Q waves were classified as pathological if the following criteria were met: (1) Q wave of ≥ 30 ms in aVF; (2) Q wave of ≥ 40 ms in I and aVL; (3) Q wave of ≥ 40 ms in two or more of V4-V6; (4) R wave ≥ 40 ms in V1; (5) any Q wave in V2; and (6) R wave ≤ 0.1 mV and ≤ 10 ms in V2.^{9,10} Pathological Q waves were assigned to four LV regions: anterior (preserved R wave in V1 and pathological Q wave in one or more of leads V2 to V5); septal (pathological Q waves in V1, V2, or V3); lateral (pathological Q wave in more than one of leads I, aVL, or V6); or inferoposterior (pathological Q wave in more than one of leads II, III, aVF).⁴

Two-dimensional echocardiography

A commercially available imaging system equipped with a 1.8 MHz transducer and second harmonic imaging to optimise endocardial border visualization was used to record two-dimensional echocardiograms (Hewlett Packard Sonos 5500, Andover, Massachusetts, USA). Four standard views were recorded and two experienced reviewers visually scored the digitised echocardiograms. Regional wall motion and systolic wall thickening were scored using a 16-segment model and a five-point grading scale: 1 is normal, 2 is mildly hypokinetic, 3 is severely hypokinetic, 4 is akinetic, 5 is dyskinetic. The 16-segment model was converted to correspond to the four major regions (anterior, inferoposterior, septal, and lateral). A region was considered

dysfunctional if one or more segments in the region were severely hypokinetic, akinetic, or dyskinetic on two-dimensional echocardiography.

Tissue Doppler imaging

Pulsed-wave TDI was performed with the same system used for the assessment of wall motion abnormalities, with a pulse repetition frequency of 45-60 KHz. A sample volume of 4mm³ was used. Myocardial velocity was sampled in apical views (posterior septum, anterior septum, and lateral, inferior, anterior, and posterior walls) close to the mitral annulus and during a minimum of five consecutive beats to minimise the variability induced by respiration. The depth of the sample volume of every wall was kept constant during dobutamine stress echocardiography to make sure that LV myocardium was sampled close to the mitral annulus.

The Doppler velocity profiles and ECG tracings were simultaneously stored on optical disk. All the measurements were performed off-line with a computer-assisted drawing system. The velocity values (cm/s) were obtained on calibrated still frames by manually measuring the distance between the zero baselines and the peak Doppler profile of the ejection phase in reference to the ECG. Cardiac cycles with extrasystolic or post-extrasystolic beats or rhythm disturbance were excluded. Recordings and measurements were made at baseline and at low dose (10 µg/kg/min) dobutamine infusion. The myocardial walls were related to the four major LV regions (anterior, septal, lateral, inferoposterior) by calculating the mean Doppler velocities of the anterior and posterior septum (septal region) and of the inferior and posterior wall (inferoposterior region). As described previously, a cut-off value of ≥ 1 cm/s in systolic ejection velocity at low-dose dobutamine infusion, was used to define viability of dysfunctional regions.¹¹

Radionuclide ventriculography

To assess the LVEF, radionuclide ventriculography at rest was

performed in all patients. A small field-of-view gamma camera system (Orbiter, Siemens, Erlangen, Germany) was used, oriented in a 45° left anterior oblique position with a 5-10° caudal tilt. After injection of ^{99m}Tc (740 MBq), radionuclide ventriculography was performed at rest with the patient in supine position. The LVEF was calculated by standard methods (Odyssey VP, Picker, Cleveland, Ohio, USA).

Statistical analysis

All continuous data are expressed as mean ± SD and percentages are rounded. Continuous variables were compared using Student's *t* test for unpaired samples. Differences between proportions were compared using the χ^2 test. A value of *P* < 0.05 was considered significant.

RESULTS

Study patients had a mean age of 61 ± 10 years (range 43-78 years). Mean LVEF was 32 ± 9 % (range 10-40 %). Table 1 shows the baseline patient characteristics.

ECG results

An abnormal Q-wave pattern was present in 89 regions; 27 (30%) of them were anterior, 27 (30%) inferoposterior, 19 (22%) septal, and 16 (18%) lateral regions. On average, the patients had 1.1 ± 0.5 regions associated with a Q-wave pattern on the ECG.

Wall motion analysis

A total of 320 of 324 (99%) regions were analysed both by two-dimensional echocardiography and by pulsed-wave TDI. Assessment of myocardial wall motion by two-dimensional echocardiography showed that 220 (69%) regions were dysfunctional (severely hypokinetic, akinetic, or dyskinetic). Among them, 60 (27%) regions were Q-wave

Table 1. Baseline clinical characteristics

Male sex	69 (85%)
Age (years)	61 ± 10
LVEF (%)	32 ± 10
Diabetes mellitus ^a	6 (7%)
Hypercholesterolemia ^b	36 (44%)
Systemic hypertension ^c	28 (35%)
Current smoking	30 (37%)
History of angina	50 (62%)
Previous revascularization	
PTCA	13 (16%)
CABG	20 (35%)
Medication	
Beta-blockers	40 (49%)
Angiotensin converting enzyme-inhibitors	51 (63%)

Data are presented as n (%) of patients or mean ± SD.

CABG, coronary artery bypass grafting; LVEF, left ventricular ejection fraction; PTCA, percutaneous transluminal coronary angioplasty.

^aPatients receiving oral antidiabetics or insulin.

^bDefined as a total cholesterol ≥6.4 mmol/L, or treatment with lipid-lowering medication.

^cDefined as blood pressure ≥140/90 mmHg, or treatment with antihypertensive medication.

related; 16 (27%) anterior, 17 (28%) inferoposterior, 13 (22%) septal, and 14 (23%) lateral regions. Figure 1 illustrates the distribution of myocardial regions.

Tissue Doppler imaging

The mean Vs of dysfunctional regions was 6.2 ± 1.9 cm/s and of non-dysfunctional regions was 7.1 ± 1.7 cm/s ($P < 0.001$). Figure 2 presents the mean systolic TDI velocities at baseline and at low-dose dobutamine infusion. Vs increased significantly at low-dose dobutamine infusion in both Q-wave and non-Q-wave dysfunctional

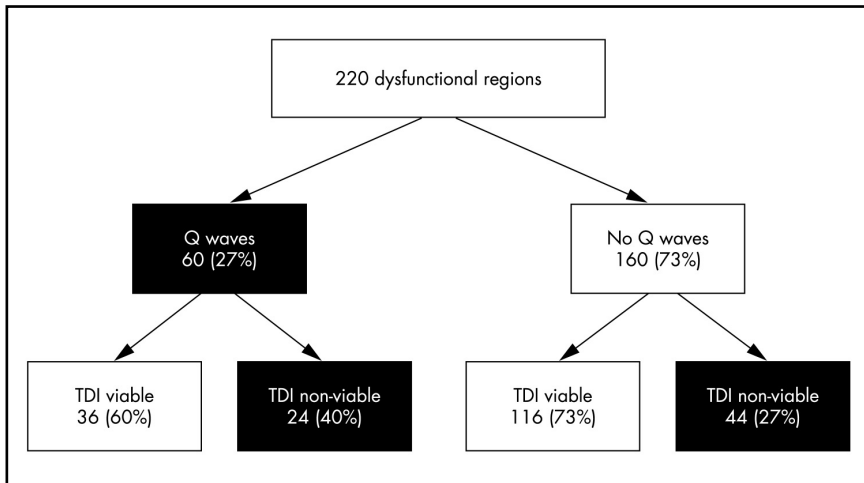


Figure 1. Distribution of myocardial regions in study patients.

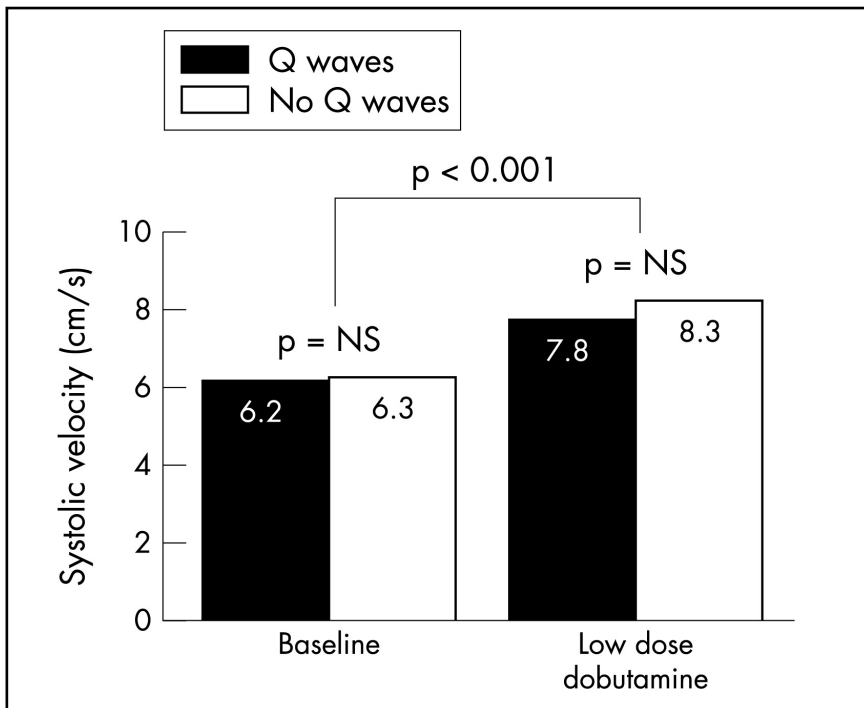


Figure 2. Myocardial systolic velocities in Q wave and non-Q wave dysfunctional regions.

regions (Q-wave regions: from 6.2 ± 1.8 cm/s at rest to 7.8 ± 2.9 cm/s at low dose, $P < 0.001$; non-Q-wave regions: from 6.3 ± 1.9 cm/s at rest to 8.3 ± 2.8 cm/s at low-dose, $P < 0.001$). There was no significant difference in Vs at rest and at low-dose dobutamine between Q-wave related and non-Q-wave related dysfunctional regions (baseline: 6.2 ± 1.8 cm/s vs. 6.3 ± 1.9 cm/s, $P = 0.948$; low-dose dobutamine infusion: 7.8 ± 2.9 cm/s vs. 8.3 ± 2.8 cm/s, $P = 0.268$), in Q-wave and non-Q-wave regions, respectively).

The increase of Vs from baseline to low-dose dobutamine infusion (Δ Vs) was higher in non-dysfunctional regions (2.6 ± 2.5 cm/s vs. 1.9 ± 1.9 cm/s in dysfunctional regions; $P = 0.009$). No difference in Δ Vs was found between Q-wave and non-Q-wave related regions (1.6 ± 2.2 cm/s vs. 2.0 ± 2.0 cm/s, respectively; $P = 0.129$). Table 2 shows the TDI velocities found in each of the four myocardial regions. Considering an increase in baseline Vs of ≥ 1 cm/s at low-dose dobutamine infusion as the cut-off value to define viability, 60% and 73% of Q-wave and non-Q-wave dysfunctional regions, respectively, were viable ($P = 0.104$) (Figure 1).

DISCUSSION

In the present study, pulsed-wave TDI, a relatively new echocardiographic technique with high temporal resolution for the quantification of myocardial wall motion velocity, was used. The results show that Q-wave regions on surface ECG do not necessarily represent more advanced myocardial dysfunction than do dysfunctional non-Q-wave regions. Although Vs was found to be significantly higher in non-dysfunctional regions, the comparison between dysfunctional Q-wave and dysfunctional non-Q-wave related regions showed no difference, both at rest and at low-dose dobutamine infusion. Furthermore, when a cut-off value of Δ Vs ≥ 1 cm/s from rest to low-dose dobutamine infusion was used to discriminate viable from non-viable dysfunctional regions, the prevalence of myocardial viability was similar in regions with and without Q waves.

Table 2. Pulsed-wave myocardial systolic velocities of Q-wave and non-Q-wave dysfunctional regions at rest and during low-dose dobutamine infusion.

Region	Systolic velocity at rest (cm/st)		
	Q-wave regions	Non-Q-wave regions	P value
Anterior	6.6 (1.9)	6.2 (2.0)	NS
Inferoposterior	6.2 (1.8)	6.6 (2.0)	NS
Septal	5.3 (1.2)	5.9 (1.8)	NS
Lateral	6.7 (2.0)	6.3 (1.8)	NS
Mean	6.2 (1.8)	6.3 (1.9)	NS
	Systolic velocity at low-dose dobutamine (cm/s)		
	Q-wave regions	Non-Q-wave regions	P value
Anterior	7.8 (3.5)	8.6 (2.9)	NS
Inferoposterior	8.5 (2.5)	8.6 (2.9)	NS
Septal	6.7 (2.0)	7.4 (2.4)	NS
Lateral	8.2 (3.1)	8.8 (2.9)	NS
Mean	7.8 (2.9)	8.3 (2.8)	NS
	Increase in systolic velocity from rest to low-dose (cm/s)		
	Q-wave regions	Non-Q-wave regions	P value
Anterior	1.1 (2.0)	2.4 (2.6)	NS
Inferoposterior	2.2 (1.7)	1.9 (1.6)	NS
Septal	1.4 (1.7)	1.5 (1.4)	NS
Lateral	1.5 (1.7)	2.4 (2.2)	NS
Mean	1.6 (2.2)	2.0 (2.0)	NS

Data are presented as mean \pm SD.

NS, not significant.

Comparison with previous studies

The detection of viable tissue in patients with ischaemic cardiomyopathy is considered a critical issue affecting patients' quality of life and survival. The decision for revascularization is influenced by the presence or absence of viability. Several studies have reported the beneficial effect of revascularization on LV function and on survival in patients with LV dysfunction and a substantial amount of viable myocardium.^{7,8,12-14} Various non-invasive techniques (mainly nuclear and echocardiographic) have been used to assess myocardial viability in patients with LV dysfunction caused by chronic coronary artery disease. For many years, Q waves in dysfunctional regions were believed to reflect irreversibly scarred myocardial tissue and Q waves were associated with more severely damaged myocardium. However, there is some evidence from histopathological studies that residual viable tissue may be present in dysfunctional regions with Q waves on the ECG. Moreover, non-invasive imaging techniques have shown signs of viable myocardium in Q-wave infarcted regions. The proportion of viable tissue found in patients with Q-wave myocardial infarction varies between studies that used positron emission tomography to assess viability, ranging from 36-68%.³⁻⁵

Q-waves represent the initial 40 ms of depolarisation. When a region is depolarised after this time period, as is the case for basal myocardial regions, Q waves are not produced on ECG. In addition, there are many Q-wave equivalent ECG signs that can be missed and be considered to be a lack of Q-waves. The present data show that Q-waves do not necessarily represent a transmural infarction; residual viable tissue was present in a high proportion of dysfunctional regions with Q waves on surface ECG.

Quantitative information on regional LV function and contractile reserve in Q-wave and non-Q-wave dysfunctional regions is lacking. Therefore this study quantified regional LV function at rest and contractile reserve during infusion of low-dose dobutamine in Q-wave and non-Q-wave dysfunctional regions. In accordance with the previous studies that assessed myocardial viability in Q-wave regions,

we found viable tissue in 60% of Q-wave related regions when an increase in Vs of ≥ 1 cm/s at low-dose dobutamine challenge was used to define viability. Dysfunctional non-Q-wave regions were more often viable (73%), although the difference did not reach significance.

Assessment of viability by tissue Doppler imaging

Dobutamine stress echocardiography can be used to assess the presence of viable myocardium by showing an improvement in myocardial wall motion during low-dose dobutamine challenge.⁶ The presence of increased wall thickening at low-dose dobutamine infusion with subsequent worsening during higher rates of infusion (biphasic response) has been found to increase the test's sensitivity for the detection of viability.¹⁵ However, the assessment of myocardial wall motion with dobutamine infusion is subjective, showing low sensitivity to detect minor alterations in myocardial wall motion.

Pulsed-wave TDI has the ability to quantify myocardial wall motion velocities.^{16,17} Several factors can influence TDI measurements, such as the translational and rotational motion of the heart within the thorax, as well as the angle of incidence of the ultrasound beam relatively to the axis of myocardial longitudinal movement. By assessing myocardial velocities from the apical views, the effect of translation and rotation of the heart on the measurement of myocardial velocities is minimised. In addition, the apex acts as a fixed reference point facilitating the assessment of contraction and relaxation in the axial plain without the need for angle correction.¹⁸ A possible limitation in the evaluation of TDI results may be tethering between adjacent regions that can influence its ability to localise differences in myocardial velocity. To avoid this effect, tissue Doppler tracings were obtained with the sample positioned near the mitral annulus to assess the vectorial sum of contraction velocities of the longitudinally oriented myocardial fibres between the base and the apex.¹⁹

Pulsed-wave TDI is a feasible and relatively inexpensive technique that can increase the sensitivity of the dobutamine stress test, having at the same time a specificity that is comparable to that of the dobutamine

stress test.^{11,20,21} Hence, pulsed-wave TDI can be used in clinical practice to provide additional information on viability, especially in regions where visual delineation of endocardium by two-dimensional echocardiography is suboptimal or interpretation of wall motion is difficult.

Study limitations

In the current study, TDI was used to assess regional LV function at rest and during low-dose dobutamine infusion. However, the results of functional outcome after revascularization were not examined. Secondly, although the LV was divided into four major regions to compare ECG with echocardiographic data, misalignment may have influenced the study results.^{22,23} Lastly, patients who underwent previous revascularization were included in the study. Myocardial revascularization might have influenced the presence and the number of Q waves as well as the presence of viable myocardium. Nevertheless, the time interval between revascularization and the current study was more than a year in all patients.

Conclusions

Quantitative TDI demonstrated comparable wall motion velocities at rest and during low-dose dobutamine infusion in dysfunctional regions with and without Q waves. Among dysfunctional regions, Q waves on the ECG do not indicate more severe dysfunction and myocardial contractile reserve was comparable in Q-wave and non-Q-wave dysfunctional myocardium. Hence, in patients with LV dysfunction caused by chronic coronary artery disease, viability should be assessed non-invasively irrespective of the presence of Q waves on the surface ECG.

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CHAPTER 13

POST-EXTRASYSTOLIC POTENTIATION
RECRUITS INCREMENTAL CONTRACTILE
RESERVE OF DYSSYNERGIC MYOCARDIUM
DURING DOBUTAMINE STRESS TESTING:
EVIDENCE BY PULSED-WAVE TISSUE
DOPPLER IMAGING.



Source: R Rambaldi, D Poldermans, JJ Bax,
M Bountiukos, JRTC Roelandt.
Eur J Echocardiogr 2003 Jun;4(2):148-51. **Adapted**

ABSTRACT

Dobutamine stress echocardiography is an established diagnostic method for the detection of myocardial viability in patients with severe left ventricular dysfunction.¹ The presence of viable myocardium identifies patients who will benefit from coronary revascularization, by improving both functional capacity and long-term survival. Occasionally, dobutamine infusion has been combined with other stressors, such as post-extrasystolic potentiation, in order to improve accuracy. The contractile reserve after combined dobutamine infusion and post-extrasystolic potentiation can be quantified by pulsed-wave tissue Doppler imaging. We describe a patient with severe left ventricular dysfunction, in which pulsed-wave tissue Doppler imaging allowed to demonstrate that post-extrasystolic potentiation superimposed on dobutamine infusion is able to further recruit contractile reserve, as compared to dobutamine infusion alone. A nuclear scan assessing glucose utilization was used as a reference.

INTRODUCTION

Dobutamine stress echocardiography is widely used to identify myocardial viability. Dobutamine activates adrenergic beta-receptors, which stimulate actin-myosin interaction, resulting in an increased myocardial thickening during systole. Detection of a substantial amount of viable myocardium identifies patients with left ventricular dysfunction who will benefit from coronary revascularization procedures. Occasionally, dobutamine infusion has been combined with post-extrasystolic potentiation. This technique exploits extrasystolic beats, whose post-extrasystolic pause prolongs ventricular filling period, thus activating the Frank-Starling mechanism. According to this mechanism, there is a relationship between ventricular end-diastolic volume and ventricular performance, resulting in contractile recruitment of viable myocardium.

We describe a patient with severe left ventricular dysfunction, studied by dobutamine stress echocardiography and post-extrasystolic potentiation. Pulsed wave tissue Doppler imaging allowed the quantification of the contractile response to both stressors. A single photon emission computed tomography scan assessing the ^{18}F fluorodeoxyglucose uptake was used as a reference.

CASE

A 67-year-old male with severe ischaemic left ventricular dysfunction (ejection fraction 33%, measured by radionuclide ventriculography) was referred for the evaluation of myocardial viability. Dobutamine stress echocardiography was performed as previously described and scored by visual wall motion assessment and pulsed-wave tissue Doppler imaging.² Severe dyssynergy (severe hypokinesia, akinesia or dyskinesia) was present in inferior and posterior walls. Extrasystolic beats, with a reproducible coupling time interval, were present at rest and during each stage of dobutamine stress echocardiography. The six-segment model (posterior, anterior septum, lateral, inferior, anterior,

posterior walls) of longitudinal shortening was selected as the optimal approach of pulsed-wave tissue Doppler imaging during the technically demanding setting of stress echocardiography. The mitral annulus served as anatomical reference point in order to reproduce consistent sampling sites. A Toshiba Powervision echocardiographic imaging system was used, with a 3.7 MHz probe, with a pulse repetition frequency of 4.5 - 6.0 KHz. A temporal resolution of 6 - 8 ms was achieved at rest and during stress echocardiography. Systolic velocities by pulsed-wave tissue Doppler imaging of normal and post-extrasystolic beats were recorded on tape at rest, low dose (10 μ g/kg/min) and peak-dose dobutamine infusion and measured off-line. At 18 F fluorodeoxyglucose-single photon emission computed tomography the left ventricle was divided into six segments (posterior, anterior septum, lateral, inferior, anterior, posterior walls), corresponding to the echocardiographic segments. 18 F fluorodeoxyglucose-single photon emission computed tomography detected viability in the inferior wall. Systolic velocities (cm/s) of normal and post-extrasystolic beats during dobutamine stress echocardiography are shown in Table 1. The average exceeding of systolic velocity of post-extrasystolic vs. normal beats was > 60% at rest, > 30% at low dose and > 15% at peak stress (Figures 1 and 2). This finding predicted myocardial viability in the inferior wall as detected by 18 F fluorodeoxyglucose-single photon emission computed tomography, and segmental contractile improvement after revascularization of the stenotic left circumflex coronary artery.

Table 1. Systolic velocities (cm/s) of normal and post-extrasystolic beats during the main steps of dobutamine stress echocardiography.

cm/2	PS		L		I		A		P		AS	
	NB	PESP	NB	PESP	NB	PESP	NB	PESP	NB	PESP	NB	PESP
(1) Rest DSE	6	9	5	8	5	8	5	8	6	7	5	8
(2) Low DSE	8	11	7	9	8	10	7	9	8	9	7	9
(3) Peak DSE	9	12	8	9	10	12	9	10	9	10	9	11

A = anterior wall, AS = anterior septum, DSE = dobutamine stress echocardiography three main steps (rest, low: 10 g/kg1/min1, peak), I = inferior wall, L = lateral wall, NB = normal beat, P = posterior wall, PESP = post-extrasystolic potentiation, PS = posterior septum.

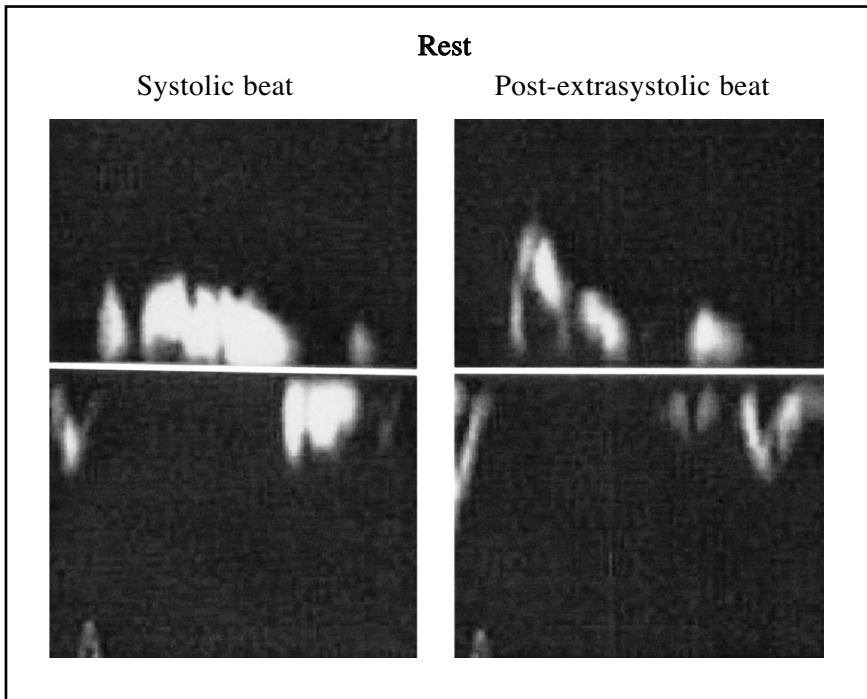


Figure 1. *‘Post-extrasystolic potentiation recruits incremental contractile reserve of dyssynergic myocardium at rest: evidence by pulsed-wave tissue Doppler imaging’.* Riccardo Rambaldi, MD, Ph.D.

DISCUSSION

The identification of myocardial viability is important to select patients with severe left ventricular dysfunction who may benefit from coronary revascularization. Dobutamine infusion is used to activate adrenergic beta-receptors, which in turn activate myocardial contractility. Less used is post-extrasystolic potentiation, a technique based on the contractile recruitment of myocardium occurring after a premature extrasystolic beat. The Frank-Starling mechanism is involved in this case; a longer ventricular filling period following post-extrasystolic pause occurs and the subsequent ventricular contraction is

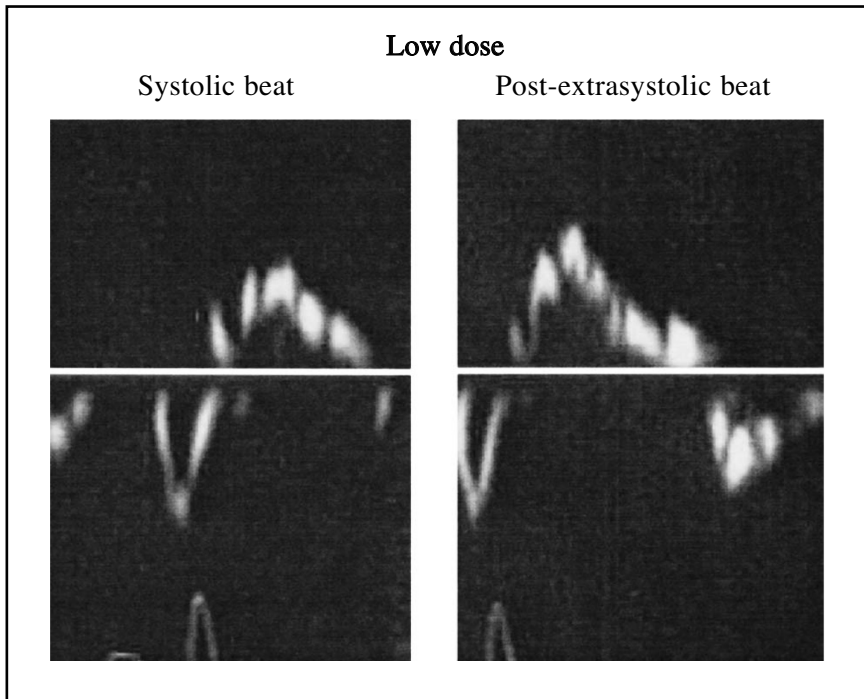


Figure 2. *‘Post-extrasystolic potentiation recruits incremental contractile reserve of dyssynergic myocardium during low-dose dobutamine infusion: evidence by pulsed-wave tissue Doppler imaging’.* Riccardo Rambaldi, MD, Ph.D.

potentiated. The study of Scognamiglio et al.³ assessed the value of the combination of dobutamine and post-extrasystolic potentiation for the evaluation of myocardial viability in 45 patients. The authors found no incremental value of the combined use of dobutamine and post-extrasystolic potentiation for the prediction of myocardial viability. However, the authors used the subjective standard wall motion scores, while we used quantitative pulsed-wave tissue Doppler imaging. In our case we were able to measure an incremental contractile response of dyssynergic segments during simultaneous stimulation by dobutamine and post-extrasystolic potentiation. Our findings suggest that the contractile response to dobutamine infusion does not exhaust all the

available contractile reserve. This finding might be tested in a wider patient population.

Contractile reserve potentiation after post-extrasystolic potentiation was most pronounced at rest and became less obvious during increasing dobutamine doses. This finding might be related to the shortened diastolic filling period during dobutamine-induced tachycardia, which resulted in reduced end-diastolic fibre stretch, thus opposing the Frank-Starling mechanism.

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CHAPTER 14

CATHETER-BASED INTRAMYOCARDIAL INJECTION OF AUTOLOGOUS SKELETAL MYOBLASTS AS A PRIMARY TREATMENT OF ISCHEMIC HEART FAILURE



Source: PC Smits, R-JM van Geuns, D Poldermans, M Bountiukos,
EEM Onderwater, CH Lee, APWM Maat, PW Serruys
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ABSTRACT

Objectives: We report on the procedural and six-month results of the first percutaneous and stand-alone study on myocardial repair with autologous skeletal myoblasts.

Background: Preclinical studies have shown that skeletal myoblast transplantation to injured myocardium can partially restore left ventricular (LV) function.

Methods: In a pilot safety and feasibility study of five patients with symptomatic heart failure (HF) after an anterior wall infarction, autologous skeletal myoblasts were obtained from the quadriceps muscle and cultured in vitro for cell expansion. After a culturing process, 296 ± 199 million cells were harvested (positive desmin staining $55 \pm 30\%$). With a NOGA-guided catheter system (Biosense-Webster, Waterloo, Belgium), 196 ± 105 million cells were transendocardially injected into the infarcted area. Electrocardiographic and LV function assessment was done by Holter monitoring, LV angiography, nuclear radiography, dobutamine stress echocardiography, and magnetic resonance imaging (MRI).

Results: All cell transplantation procedures were uneventful, and no serious adverse events occurred during follow-up. One patient received an implantable cardioverter-defibrillator after transplantation because of asymptomatic runs of nonsustained ventricular tachycardia. Compared with baseline, the LV ejection fraction increased from $36 \pm 11\%$ to $41 \pm 9\%$ (three months, $P = 0.009$) and $45 \pm 8\%$ (six months, $P = 0.23$). Regional wall analysis by MRI showed significantly increased wall thickening at the target areas and less wall thickening in remote areas (wall thickening at target areas vs. three months follow-up: 0.9 ± 2.3 mm vs. 1.8 ± 2.4 mm, $P = 0.008$).

Conclusions: This pilot study is the first to demonstrate the potential and feasibility of percutaneous skeletal myoblast delivery as a stand-alone procedure for myocardial repair in patients with post-infarction HF. More data are needed to confirm its safety.

DISCUSSION

Cell transplantation is emerging as a potential novel therapeutic approach for the treatment of heart failure (HF). Initial studies with different cell types have shown promising results of cell transplantation in ischemic animal models. Most preclinical experience has been reported on transplantation of skeletal myoplasts in infarcted myocardium. These studies demonstrated that transplanted skeletal myoplasts in damaged myocardium are capable of cellular engraftment, myotube formation, expression of the slow fiber marker beta-myosin heavy chain, long-term graft survival, and augmentation of ventricular function.¹⁻⁶ As a result of the outcomes of these animal studies, a pilot safety and feasibility study on percutaneous transplantation of autologous skeletal myoblasts by transendocardial injection as a stand-alone procedure in five patients with ischemic HF was completed. We report on the procedural and six-month follow-up results.

PROCEDURE

Objectives

The primary objectives of this pilot study are feasibility and safety at six months. The secondary objective was to assess improvement of the left ventricular (LV) function by iterative investigations at baseline and one, three, and six months. The protocol was approved by the local medical ethics committee, and written, informed consent was obtained from all patients.

Patient selection

Only symptomatic patients with New York Heart Association functional class > II under optimal medical therapy were selected. All patients were known to have a previous anterior wall myocardial infarction and depressed LV function (left ventricular ejection fraction

[LVEF] between 20% and 45% by radionuclide radiography). Myocardial infarction had to be > 4 weeks old at the time of implantation. The presence and location of a myocardial scar were defined by: akinesia or dyskinesia at rest during echocardiography, LV angiography, and magnetic resonance imaging (MRI); no contractile reserve during dobutamine stress echocardiography (DSE); and hyperenhancement by gadolinium on the MRI scan. Exclusion criteria for myoblast injections were: target region wall thickness < 5 mm by echocardiography or MRI; a history of syncope or sustained ventricular tachycardia or fibrillation or (potential candidate for) implantable cardioverter defibrillator (ICD) placement; and positive serologic test results for human immunodeficiency virus, hepatitis B or C, or syphilis.

Muscle biopsy

Biopsy of the quadriceps muscle was done under local anesthesia. On average, 8.4 g (range 5 to 13g) of muscle biopsy was excised through a 10-cm-long surgical incision. All five biopsy procedures were uneventful and done on an outpatient basis. Biopsies were placed in a bottle containing a proprietary solution designed to preserve the biopsy during controlled shipment. The bottle was put in an insulated thermobox with frozen and refrigerated gel packs to maintain temperatures between 2° C and 8° C during transit. The transport conditions were monitored by the use of a programmable temperature monitor (Sensitech, Beverly, Massachusetts). The container was sent to clinical Good Manufacture Practice (Bio Whittaker, Cambrex Corp., Walkersville, Maryland) for myoblast cell isolation and expansion. The average transit duration was 41 h (range 35 to 50 h); no temperature excursions were noted.

Cell-culturing process

On receipt at the culturing facility, the biopsies were processed according to the Myocell protocols by Bioheart Inc. The biopsy was

minced finely and then dissociated using digestive enzymes. The dissociated tissue was washed several times and filtered until a single cell suspension was achieved. The expansion culture was initiated when the cells were plated into sterile tissue culture flasks in growth media for skeletal muscle myoblasts. The media were changed at regular intervals; the cells were harvested and replated according to cell confluence parameters. Final harvest was done after three to five passages. Myoblasts were identified using an immunohistochemical market specific for desmin (DAKO) to identify cells committed to a myogenic differentiation. Specific cell lot release specifications (cell viability, cell identity, and sterility tests) were established before the start of the trial, which, if not met, would result in a re-biopsy of the patient and re-initiation of the culture process. In three patients a re-biopsy was required due to the desmin staining results falling below the lot release criteria. In these patients, a prestimulation procedure was performed using multiple needle punctures of the muscle three days before the biopsy procedure to increase the percentage of myoblast cells in the muscle biopsy.⁷

After a culturing period of 17 days (range 14 to 19 days), the harvested cells were formulated in a specially designed transport/injectate media and transferred into a sterile 30-ml bag and sent to our hospital. Shipment was done under the same controlled conditions as after biopsy. The transit time averaged 62 h (range 24 to 96 h), and no temperature excursions were noted. The cells have been validated for having a 96-h shelf life under controlled conditions.

Transplantation procedure

The transplantation procedure was scheduled the day after arrival of the cells. Cell transplantation was done in the cardiac catheterization laboratory. Access was obtained through the femoral artery, and 100 IU/kg heparin was given. The target activated clotting time was between 250 s and 300 s and was regularly checked every half hour. After a coronary and biplane LV angiogram (left anterior oblique [LAO] 60° and right anterior oblique [RAO] 30°) was obtained, an

outline of the LV chamber was drawn on transparent tabloids that were taped to the fluoroscopy monitors. Then an electromechanical NOGA map⁸ of the LV was obtained using a 7F NOGASTAR catheter (F-curve) connected to the NOGA console (Biosense-Webster, Waterloo, Belgium). Areas exhibiting low voltages and linear local shortening (unipolar voltage < 4 mV and linear local shortening < 4%) on the NOGA map were considered as the target areas of treatment if these areas were geographically concordant with the scar areas assessed by the preprocedural DSE, MRI, and LV angiogram. We refrained from transendocardial injections into areas with a known wall thickness < 5 mm by MRI. With an 8F MYOSTAR (Biosense-Webster) injection catheter, 16 ± 4 (mean \pm SD; range 9 to 19) transendocardial injections were made. The catheter has nitinol tubing that ends in a 27-gauge retractable needle. Depending on the average wall thickness of the target region, the needle length was set at 4.5 to 6.0 mm when the catheter tip had a 90° curve. By connecting a 1-ml Luer-Lok syringe to the injection port, the catheter was preloaded with the skeletal myoblast solution. After establishing stable endomyocardial contact on the NOGA map and fluoroscopy, the needle was advanced manually, which often caused ventricular extra beats. Whenever a regular electrocardiographic (ECG) rhythm resumed with persisting, stable endomyocardial contact, injections of 0.3 ml (16.6 million cells) were made. Only the first patient received 0.1-ml injections (2.5 million cells) because of the limited volume of myoblast solution. Injection sites were marked on the NOGA map (Figure 1) and the transparent tabloids. Spacing between injection sites was approximately 1.0 cm apart. After the injection procedure, a control biplane LV angiogram was obtained. Afterward, patients were ECG monitored for 18 h, and cardiac enzymes were checked twice at six to eight h intervals. In all five cases, the in-hospital stay was uneventful, and the patients were discharged within 24 h after the procedure.

Methods of assessment

At baseline and one, three, and six months of follow-up, 24-h

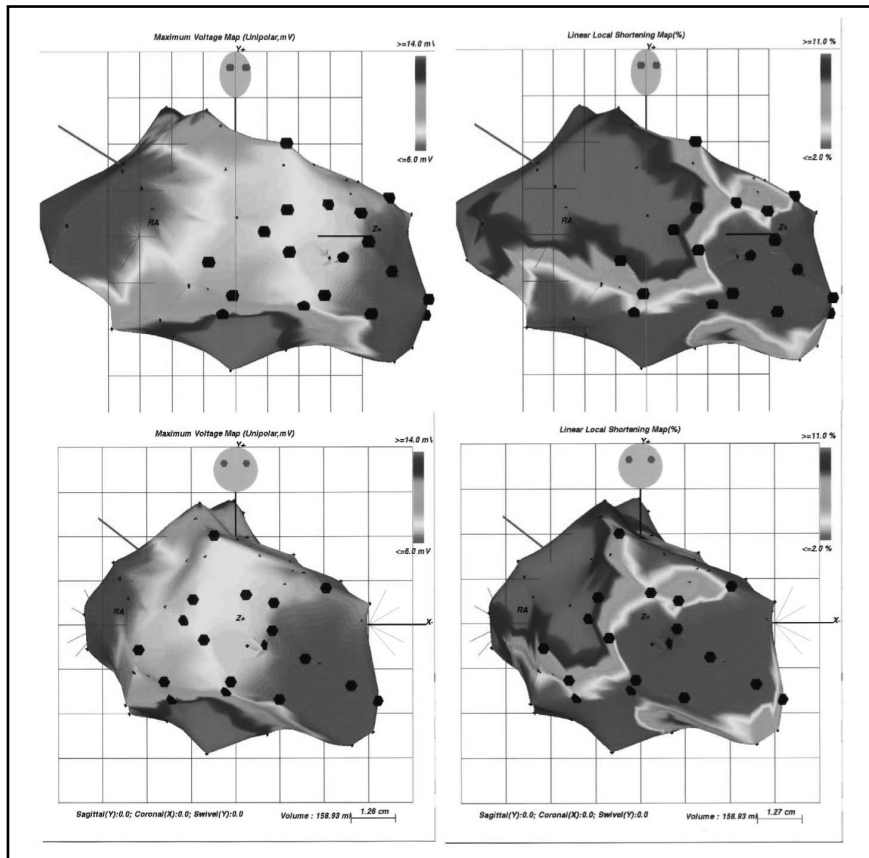


Figure 1. NOGA maps (*left* unipolar voltage maps; *right* linear local shortening maps) in the right anterior oblique (*top*) and anteroposterior (*bottom*) views of Patient no. 2 after 19 injections with autologous skeletal myoblasts in the anteroseptal and anterior myocardial scar and border zone. The myocardial scar is indicated in **red** on the unipolar voltage map (6 mV) and on the local linear shortening map (2%). The **black dots** indicate the transendocardial injection sites.

ambulant ECG monitoring and DSE with pulsed-wave tissue Doppler imaging (TDI) were done. The DSE and TDI procedures were performed with a Hewlett-Packard Sonos 5500 (Andover, Massachusetts) imaging system equipped with second harmonic

imaging to optimize endocardial border detection and performed as previously described.^{9,10} In short, after baseline echocardiography, dobutamine was infused at a starting dose of 5 $\mu\text{g}/\text{kg}/\text{min}$ for 5 min, followed by 10 $\mu\text{g}/\text{kg}/\text{min}$ for 5 min (low-dose stage). Dobutamine was then increased by 10 $\mu\text{g}/\text{kg}/\text{min}$ every 3 min up to a maximum dose of 40 $\mu\text{g}/\text{kg}/\text{min}$. Atropine (1 to 2 mg) was added at the end of the last stage if the target heart rate had not been achieved. Images were acquired continuously and recorded on tape at the end of every dose step. In addition, the baseline, low-dose, peak stress, and recovery images (standard apical and short-axis views) were displayed in a cine loop format. Wall motion was scored according to the criteria of the American Society of Echocardiography by two experienced reviewers blinded to the MRI data for systolic wall thickening. Pulsed-wave TDI was performed with a Hewlett-Packard Sonos 5500, and a transducer operating at frequencies of 1.8 or 2.1 MHz with a pulse repetition frequency of 45 to 60 KHz was used. Using a six-segment model, pulsed-wave TDI was performed close to the mitral annulus in the apical four-chamber, apical two-chamber, and apical three-chamber views with high temporal resolution (4 ± 3 ms; range 1 to 7). The depth of the sample volume was kept constant in each patient during DSE. A sample volume with a fixed length of 4 mm was used. The ECG and phonocardiogram were simultaneously recorded with the pulsed-wave TDI velocity profile and stored on videotape. The peak pulsed-wave TDI velocity amplitude of the ejection phase and early and late diastole were measured off-line using a computer-assisted drawing system, and the values were expressed in cm/s.¹⁰ Five consecutive beats were analyzed, and the mean velocity values were calculated to minimize the measurement variability determined by respiration. The E/A ratio was also calculated. Cardiac cycles with extrasystolic or postextrasystolic beats or any disturbance of the rhythm were excluded. Recordings and measurements were repeated at baseline and at a low-dose (10 $\mu\text{g}/\text{kg}/\text{min}$) dobutamine infusion rate.

Furthermore, at baseline and three and six months of follow-up, the LV volume and LVEF were assessed by biplane LV angiography and technetium-99m-labeled erythrocyte radionuclide scintigraphy. Biplane

LV angiography was done in the LAO 60° and RAO 30° projections with 100-ml sphere calibration in the isocenter. Quantitative analysis was performed using CAAS II software (Pie Medical, Maastricht, The Netherlands). Also, at baseline and three-month follow-up, a MRI scan of the heart was obtained. The studies were performed on a 1.5-T wholebody MRI system (Sonata, Siemens, Erlangen, Germany). Patients were placed in a supine position with a fourchannel quadrature body phased-array coil placed over the thorax. For quantitative analysis, multiple parallel short-axis slices covering the heart from base to apex were obtained using a ECG-triggered breath-hold cine gradient-echo sequence. Imaging parameters were: repetition time of 3.2 ms, echo time of 1.6 ms, and flip angle 65°, which resulted in a temporal resolution of 47 ms. Quantitative analysis was performed using standardized software (Argus Siemens, Erlangen, Germany). Endocardial and epicardial contours were traced using semi-automatic software to calculate the LV volumes and LVEF. Each short-axis image was divided into eight segments of 45°, which resulted in 64 to 80 segments per patient, depending on the number of short axis slices covering the heart from base to apex. Regional wall thickening was calculated for each segment by subtracting the end-diastolic wall thickness from the end-systolic wall thickness. Delayed contrast-elucidated MRI images were used to identify transmural and nontransmural infarcts using a three-dimensional inversion-recovered gradient echo sequence 15 min after injection of 0.1 mmol gadolinium-based contrast agent.

RESULTS

Baseline patient characteristics and cell-culturing results are summarized in Table 1. No procedural complications occurred. Only in one patient (Patient no. 5) was minor elevation of creatine kinase and its MB fraction (< 2 times upper lever) and troponin T (0.16 µg/l) noted after the procedure.

During follow-up, Patient no. 3 needed to be hospitalized at six

Table 1. Patient and Cell Culture Characteristics

Pt. No.	Gender, Age (yrs)	Previous Anterior AMI (years ago)	NYHA Class	Patent LAD	Known Arrhythmias	Cells at Harvest × 10 ⁶	Cells Injected × 10 ⁶	Desmin Staining (%)	Cell Viability (%)	Potency (%)
1	F, 78	6	III	Yes	PAT runs	25	25	85	98	90
2	M, 53	3	II/III	Yes	PAT runs	544	293	12	97	20-40
3	M, 55	11	III/IV	No*	PAF, NSVT runs†	183	183	54	95	70
4	M, 59	7	III	Yes	No	211	211	80	95	100
5	M, 49	2	III	Yes	No	382	270	44	98	40

*LAD filled by collateral channels. †Asymptomatic, 8 complexes.

AMI acute myocardial infarction; LAD left anterior descending coronary artery; NSVT non-sustained ventricular tachycardia runs; NYHA New York Heart

Table 2. Global Left Ventricular Function Results

Pt. No.	Baseline			3-Month Follow-Up			6-Month Follow-Up		
	LVEF (%) by Angiography (EDV/ESV)	LVEF (%) by Nuclear Radiography	LVEF (%) by MRI (EDV/ESV)	LVEF (%) by Angiography (EDV/ESV)	LVEF (%) by Nuclear Radiography	LVEF (%) by MRI (EDV/ESV)	LVEF (%) by Angiography (EDV/ESV)	LVEF (%) by Nuclear Radiography	LVEF (%) by MRI (EDV/ESV)
1	43 (187/107)	39	36 (189/120)	47 (203/108)	42	41 (190/113)	54 (200/93)	56	56
2	40 (135/82)	45	43 (167/96)	42 (150/87)	40	37 (166/104)	49 (156/80)	39	39
3	18 (153/126)	32	22 (169/132)	26 (148/109)	26	25 (166/125)	46 (150/82)	42	42
4	40 (201/120)	36	26 (206/152)	44 (195/110)	31	24 (202/154)	33 (211/141)	32	32
5	42 (141/83)	37	35 (125/82)	47 (119/64)	40	37 (132/82)	43 (129/43)	57	57
Average	36 ± 11 (163 ± 29/103 ± 21)	38 ± 5	32 ± 8 (171 ± 30/116 ± 28)	41 ± 9* (163 ± 35/95 ± 20)	36 ± 7	33 ± 8 (171 ± 27/116 ± 26)	45 ± 8 (169 ± 35/94 ± 27)	45 ± 11	45 ± 11

*LAD filled by collateral channels. †Asymptomatic, 8 complexes.

AMI acute myocardial infarction; LAD left anterior descending coronary artery; NSVT non-sustained ventricular tachycardia runs; NYHA New York Heart

weeks after the procedure due to progressive HF and long asymptomatic runs of non-sustained ventricular tachycardia (NSVT) on Holter monitoring. After recompensation, telemetry still showed NSVT, and an ICD was implanted prophylactically. In the other four patients, no adverse events or ventricular arrhythmias were observed.

Global LV function results at three- and six-month follow-up are summarized in Table 2. Compared with baseline, angiographic LVEF at three months increased from $36 \pm 11\%$ to $41 \pm 9\%$ ($P = 0.009$). This increase in LVEF, however, was not observed by nuclear or MRI assessment at three-month follow-up. At six-month follow-up, both angiographic and nuclear LVEF assessments showed a trend toward increased LVEF ($36 \pm 11\%$ to $45 \pm 8\%$ [$P = 0.23$] and $38 \pm 8\%$ to $45 \pm 11\%$ [$P = 0.07$], respectively).

The MRI analysis of regional wall thickening showed a descriptive

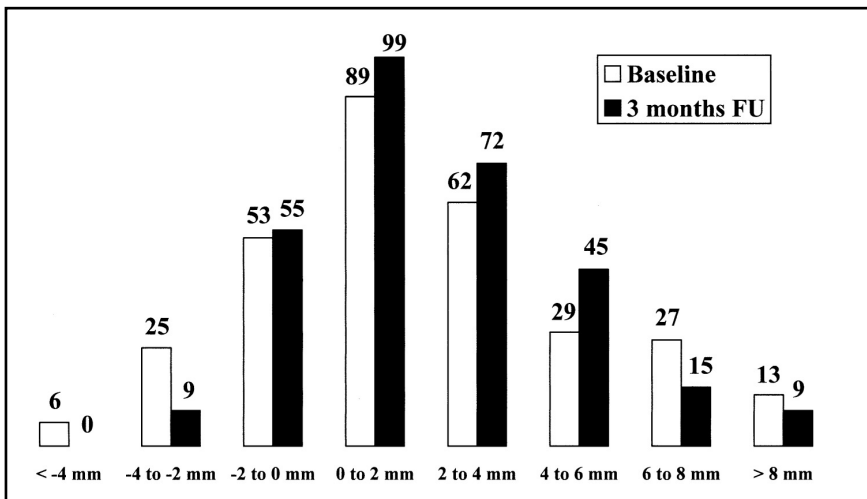


Figure 2. Changes in regional wall thickening for all 304 magnetic resonance imaging segments. The open and solid bars indicate the number of segments with wall thickening at baseline and three-month follow-up (FU), respectively. Compared with baseline, less segments showed thinning and more segments showed moderate thickening at three-month follow-up, and less segments with greater wall thickening were observed at that point.

shift toward more regional wall thickening in the target segments and less regional wall thickening in the remote hyperkinetic segments (Figures 2 and 3). By comparing the marked injection sites on the NOGA map and the fluoroscopy sheets with the MRI segments, 87 of the 304 MRI segments (all five patients) were identified as injected segments. Paired analysis of these injected segments showed significantly increased wall thickening at follow-up (0.9 ± 2.3 mm at baseline vs. 1.8 ± 2.4 mm at three-month follow-up, $P = 0.008$).

In all five patients at baseline, DSE showed no signs of ischemia or ventricular tachycardias. Compared with baseline, the TDI results of the target anteroseptal and anterior wall showed a trend toward increased

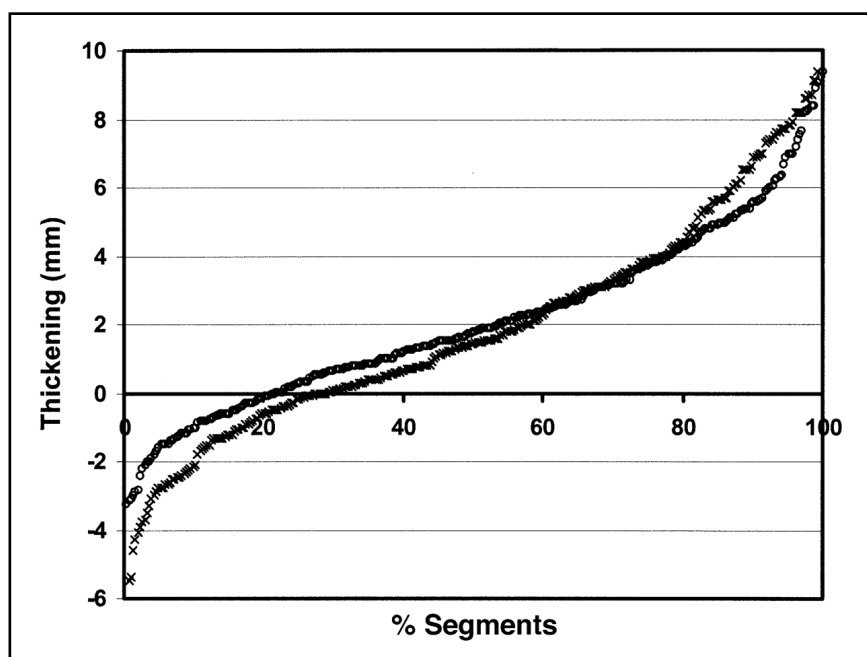


Figure 3. Cumulative distribution of regional wall thickening segments by magnetic resonance imaging at baseline (open circles) and three-month follow-up (x). At follow-up, there was a descriptive shift toward less thinning and moderate thickening in the target regions and less thickening in the normokinetic and hyperkinetic remote areas, indicating a kind of left ventricular remodeling.

contraction velocity at six-month follow-up (anteroseptal wall: 5.4 ± 1.9 cm/s vs. 6.1 ± 0.8 cm/s at rest and 8.8 ± 3.4 cm/s vs. 9.1 ± 2.5 cm/s at low-dose dobutamine; anterior wall: 5.2 ± 1.9 cm/s vs. 5.9 ± 0.7 cm/s at rest and 6.7 ± 1.7 vs. 7.5 ± 1.6 cm/s at low-dose dobutamine).

DISCUSSION

Treatment of ischemic HF remains a problem. A significant proportion of patients with congestive HF remain symptomatic despite maximal medication. Alternative therapies, including surgical cardiomyoplasty, resynchronization therapy, LV assist device, and cardiac transplantation, have their own indications and limitations. Cell transplantation has emerged as a potential new treatment strategy. Different cell types have been used for transplantation in initial preclinical experiments, but to date, most experience has been accumulated with skeletal myoblasts. There are several features that make skeletal myoblasts an attractive cell type for cardiac cell transplantation. Skeletal myoblasts can easily be obtained in sufficient quantity directly from the patient (autologous), negating the problems of organ shortage, ethical concerns, and immunosuppressive therapy. Skeletal myoblasts are relatively more resistant to ischemia than cardiomyocytes, thus favoring cellular engraftment within the ischemic or infarcted myocardium. Furthermore, the capillary density of infarcted myocardium resembles the environment in which normal skeletal muscle is obtained. The biopsy procedure is mildly invasive, and patients can be discharged within 1 h after the procedure. Although skeletal myoblasts are not cardiomyocytes, *in vitro* studies and *in vivo* observations have shown that these cells can transform into contractile cells with expression of beta-myosin heavy chain, like cardiomyocytes.^{6,11} The major limitation, however, is the lack of evidence of electromechanical coupling between the grafted myoblasts and the native cardiomyocytes *in vivo*,¹¹ as well as the potential danger of inducing a reentry circuit for ventricular arrhythmias by the formed grafted myotubes in the scarred myocardium. It is known that skeletal

myoblasts lose their capability to express major adhesion and gap junction proteins like N-cadherin and connexin-43, which are essential for electromechanical coupling, when the cells differentiate into myotubes.¹¹

We report on the first five percutaneous and stand-alone cellular cardiomyoplasty procedures as a potential new treatment modality for ischemic HF. In post-myocardial infarction patients with LVEF < 45% and symptoms of HF, autologous skeletal myoblasts were injected into the scarred myocardium by an injection catheter. No periprocedural complications occurred, and during a 3- to 12-month follow-up period, in one case, an ICD was implanted at 2 months based on a prophylactic indication because of asymptomatic NSVT runs. At three-month follow-up, in all five patients, a significant moderate increase in global LV function by LV angiography was noted. This angiographic LVEF improvement, however, was not consistently observed in all patients by nuclear or MRI assessment. Because MRI and, to a lesser extent, radionuclide angiography have been recently recognized as the most reliable and accurate methods for assessment of LV dimensions and function,^{12,13} cellular cardiomyoplasty efficacy studies focusing on change in LVEF should incorporate one or both of these techniques.

Regional analysis by MRI showed a significant increase in wall thickening at the target areas at three-month follow-up in all five patients. This paradox between equal global and improved regional LV function is probably explained by the remodelling of the LV, in which regional improvement of injected dyskinetic and akinetic segments is counterbalanced by less thickening of the hypercontractile remote segments, as seen by MRI. Potentially, less neurohormonal stimulation after treatment may also have occurred, resulting in less vigorous contraction of normal segments and less dyskinesia of infarcted segments. One of the limitations in our functional assessment is the missing information on the pulsepressure double product at the different assessment time points. Pressure-volume loop and neurohormonal marker measurements in future may overcome this limitation.

Feasibility and safety

We cannot draw firm conclusions from this initial experience, but we believe that catheterbased cell transplantation in HF patients is feasible and that the transendocardial catheter-based cell delivery technique is safe from a procedural point of view. An important question about potential arrhythmogenic properties of skeletal myoblast transplantation is still unanswered. Although no syncope or malignant arrhythmias were observed in our pilot study, we have observed in two consecutive follow-up studies on catheter-based autologous skeletal myoblast transplantation in eight patients, two sudden deaths and three ventricular arrhythmias (one symptomatic and two asymptomatic) within three months after the procedure (unpublished data, P. C. Smits, 2003). These serious adverse events necessitated elementary changes in the protocols of the consecutive studies. Currently, both phase 1 follow-up studies have restarted with enrollment of patients with ICDs and rigorous rhythm monitoring before and after the procedure.

Also, Menasche et al.¹⁴ have reported four ICD implantations within one month after the procedure in a phase 1 trial involving transepical autologous skeletal myoblast injections during bypass surgery in 10 post myocardial infarction patients with an average baseline LVEF of 23%. However, the arrhythmogenic incidents observed in this study and in other skeletal myoblast cell transplantation studies may also reflect the natural course of this high-risk population for arrhythmias. Furthermore, the likelihood of finding a non-sustained ventricular arrhythmia recording on serial Holter monitoring is 40% in patients with HF.¹⁵ Therefore, the question remains unanswered whether skeletal myoblast transplantation is arrhythmogenic and safe.

From this initial experience, we conclude that catheter-based cell transplantation with autologous skeletal myoblasts for the treatment of ischemic HF is feasible and promising. However, extensive pre- and post-procedural monitoring studies for arrhythmias and well-defined function parameters are needed to evaluate the safety and efficacy of cellular cardiomyoplasty procedures in the near future.

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SUMMARY
AND
CONCLUSIONS



SUMMARY

The present thesis deals with the use of dobutamine stress echocardiography in various settings, as well as with quantification of dobutamine stress echocardiography using tissue Doppler imaging.

Part 1:

New applications of dobutamine stress echocardiography

In chapter 2, echocardiographic assessment of wall motion and mitral inflow pattern was used in a repetitive manner, i.e. before chemotherapy, during, at the end, and 6 months after chemotherapy for the early prediction of cardiotoxicity in patients receiving anthracyclines for the treatment of hematological diseases. Thirty-one patients were studied at rest and during low-dose dobutamine infusion. Radionuclide ventriculography was used as an independent reference of ejection fraction. A baseline abnormal mitral inflow pattern was found to be the only independent echocardiographic predictor of cardiotoxicity. Additionally, wall motion score index measured by two-dimensional echocardiography showed a good relation to radionuclide ejection fraction.

In chapter 3, 108 consecutive patients with moderate (mean gradient, 25 to 49 mmHg) or severe (mean gradient, \geq 50 mmHg) aortic stenosis were studied. Patients underwent noncardiac surgery, and the outcome was compared to that of 216 controls. There was a significant increase in the incidence of the composite endpoint (perioperative mortality and nonfatal myocardial infarction) in patients with aortic stenosis, even after adjusting for cardiac risk factors. Moreover, the risk for complications was substantially higher in patients with severe aortic stenosis, compared to patients with moderate aortic stenosis.

Dobutamine stress echocardiography is frequently applied in patients with mild or moderate aortic stenosis to detect ischaemia, or before

noncardiac surgery for risk assessment. In addition, dobutamine stress echocardiography at low rates of dobutamine infusion can be used in patients with low gradient aortic stenosis and poor left ventricular function, in order to assess whether the aortic stenosis is fixed or dynamic. This is important for decision making, since patients with fixed aortic stenosis may benefit from valve replacement, whereas patients with dynamic stenosis will not. In chapter 4, side effects were assessed in 55 patients with mild or moderate aortic stenosis (group A) who underwent high-dose dobutamine stress echocardiography, and 20 patients with low-gradient aortic stenosis and poor left ventricular function (group B) who underwent low-dose dobutamine stress echocardiography. Serious cardiac arrhythmias occurred frequently in both groups. Notably, no relation was found between side effects and stress-induced ischemia.

Patients with previous coronary interventions comprise a growing subgroup of patients referred for non-invasive testing to evaluate symptoms or to rule out coronary restenosis, graft occlusion, or progression of coronary artery disease. In chapter 5, we studied the prognostic value of dobutamine stress echocardiography in 332 consecutive patients with previous coronary revascularization (percutaneous or surgical). During a mean follow-up of 24 ± 20 months, 13% of patients died, and 30% had at least one cardiac event (7% cardiac death, 4% nonfatal myocardial infarction, and 23% late revascularization). In multivariate analysis, myocardial ischaemia on dobutamine stress echocardiography was an independent predictor of cardiac events, after controlling for clinical data.

QT dispersion on surface electrocardiogram (the difference between the maximum and minimum QT interval) is prolonged in patients with various cardiac diseases. This is consistent with the concept that QT dispersion represents a general repolarization abnormality. In chapter 6, we evaluated the influence of myocardial viability on QT dispersion. One hundred three consecutive patients with ischemic cardiomyopathy were studied. QT dispersion and left ventricular

ejection fraction were measured in patients with substantial viability (≥ 4 viable segments according to low-dose dobutamine stress echocardiography) and in patients without substantial viability (<4 viable segments according to low-dose dobutamine stress echocardiography). Patients with substantial viability had lower QT dispersion compared to those without substantial viability. The number of viable segments negatively correlated to QT dispersion, whereas there was no correlation between left ventricular ejection fraction and QT dispersion.

A similar study was performed in 97 consecutive patients with ischemic cardiomyopathy (chapter 7). This time, myocardial viability was evaluated by single-photon emission computed tomography. The results were in accordance with the previous study, since QT dispersion was significantly related to the number of viable segments. Additionally, a cutoff value of QT dispersion ≤ 62 ms had the highest sensitivity and specificity to predict the presence of substantial viability.

Patients with permanent atrial fibrillation have shown to improve their symptoms and quality of life after transcatheter ablation of the atrioventricular (AV) node. In chapter 8, low-dose dobutamine stress echocardiography was used as a means to determine whether the absence of contractile reserve before AV node ablation could identify those patients whose left ventricular function deteriorates after AV node ablation. The presence of contractile reserve was defined as an improvement in regional function of ≥ 1 grade at low-dose dobutamine infusion in at least four segments. Radionuclide ventriculography at a paced rate of 80 beats/min was used to assess left ventricular ejection fraction six days and three months after AV node ablation. Quality of life measurements were taken using Minnesota, NHBP and MPWB questionnaires. The absence of contractile reserve did not predict deterioration of cardiac function after AV node ablation, whereas higher baseline ejection fraction predicts deterioration of cardiac function.

Part 2:

Quantitative dobutamine stress echocardiography

In several studies, statins have shown a beneficial effect that extends beyond their lipid-lowering action. This effect is probably attributed to their so-called pleiotropic actions. A number of different mechanisms have been proposed to explain these actions, among which is flow-dependent vasodilatation. In chapter 9, we examined the effect of statins in a cohort of 26 consecutive patients without heart disease, but with moderate hypercholesterolemia and peripheral arterial disease. Patients received either 10 mg of atorvastatin (13 patients), or 80 mg of atorvastatin (13 patients). Six patients with similar characteristics but without statin use made-up the control group. Contractile reserve was assessed at three and six months by pulsed-wave tissue Doppler at rest and at low-dose dobutamine infusion. At six-month follow-up there was a significant increase in systolic myocardial velocities at low-dose dobutamine infusion in those patients receiving atorvastatin. This increase occurred irrespective of the dose of atorvastatin. Control patients did not show any significant change in systolic velocity.

It is likely that stunned and hibernating myocardium do not represent different entities but rather consist of a continuum of myocardial dysfunction in ascending order of severity. Clinically, it is often important to differentiate between stunned, hibernating and scarred tissue in patients with coronary artery disease, since patients with a substantial amount of viable myocardium are likely to benefit from coronary revascularisation. Previous studies have shown that hibernating myocardium may need a longer time to recover contractility than stunned myocardium. In chapter 10, we used a quantitative approach to differentiate between stunning and hibernation. Dysfunctional myocardium was defined by resting cross sectional echocardiography in 70 patients with chronic coronary artery disease. Assessment of perfusion and glucose utilization was done by Tc-99m-tetrofosmin SPECT and 18F-fluorodeoxyglucose SPECT, respectively. Calculation of myocardial systolic velocities by pulsed-

wave tissue Doppler demonstrated that there was a gradual decline in systolic velocities during low-dose dobutamine infusion in stunned, hibernating, and scar tissue. Moreover, contractile reserve, defined as the difference in systolic velocities between low dose dobutamine and the resting value, was significantly higher in stunned, than in hibernating and scar tissue.

The next step was to compare quantitatively systolic and diastolic function in viable and nonviable myocardium in 93 patients with ischaemic cardiomyopathy (chapter 11). Viability was assessed by low-dose dobutamine stress echocardiography. Pulsed-wave Doppler tissue imaging was the means for the measurement of systolic and early and late diastolic velocities in viable and nonviable regions. A separate analysis was done after dividing study population in patients ≥ 65 and <65 years old. Mean systolic velocity was comparable in viable and nonviable regions at rest. However, at low-dose dobutamine infusion, mean systolic velocity was significantly higher in viable, than in nonviable regions. In addition, viable regions demonstrated a better-preserved diastolic function at rest, compared with nonviable regions. Myocardial velocities demonstrated an age dependency, since they were significantly higher in younger patients (less than 65 years old).

Traditionally, it is believed that myocardial regions corresponding to Q waves on surface electrocardiogram represent scarred myocardium, or more severely damaged myocardium compared to dysfunctional regions not corresponding to Q waves. In chapter 12, eighty-one patients with previous myocardial dysfunction and depressed left ventricular function were studied. Severely hypokinetic, akinetic, or dyskinetic regions on two-dimensional echocardiogram were considered dysfunctional. All patients underwent surface electrocardiogram at rest, and pulsed-wave tissue Doppler imaging at rest and during low-dose dobutamine infusion. Assessment of myocardial systolic velocities at rest and the increase in systolic velocities from rest to low-dose infusion demonstrated that there was no significant difference among dysfunctional regions with or without Q waves.

Dobutamine infusion enhances myocardial systolic function. In chapter 13, we measured myocardial systolic velocities using pulsed-wave tissue Doppler in a patient with ischemic cardiomyopathy and we assessed the additional potentiation of myocardial recruitment after an extrasystolic beat. A nuclear scan assessing glucose utilization was used as a reference.

Skeletal myoblast transplantation to injured myocardium has been shown to partially restore left ventricular function in preclinical studies. Chapter 14 describes a pilot study concerning safety and feasibility of percutaneous injection of autologous skeletal myoblasts in five patients with ischaemic heart failure. Electrocardiographic and left ventricular function assessment was done by Holter monitoring, left ventricular radiography, dobutamine stress echocardiography, tissue Doppler at rest and during low-dose dobutamine infusion, and magnetic resonance imaging. At six-month follow-up, both angiographic and nuclear assessment of ejection fraction showed a trend toward increased ejection fraction. In all five patients at baseline, dobutamine stress echocardiography showed no signs of ischemia or ventricular tachycardia. Compared to baseline, the tissue Doppler imaging velocities of the target anteroseptal and anterior wall showed a trend toward increased contraction velocity at six-month follow-up.

CONCLUSIONS

A low early/late mitral inflow pattern before chemotherapy with anthracyclines can independently predict deterioration of cardiac function. Echocardiographic assessment of wall motion score index can be an inexpensive and safe alternative to nuclear ventriculography for the serial evaluation of left ventricular function.

Aortic stenosis is a risk factor for perioperative complications. The more severe the stenosis, the higher the risk for perioperative mortality and myocardial infarction.

Patients with aortic stenosis are prone to develop arrhythmias and hypotension during dobutamine stress echocardiography. Hence, dobutamine stress echocardiography should be used in these patients only when it is really important, and always under close monitoring.

Reversible wall motion abnormalities on dobutamine stress echocardiography can predict the composite of cardiac events in patients with previous (more than six months before) coronary intervention.

QT dispersion on surface ECG in patients without substantial amount of viable myocardium is more prolonged, compared to patients with substantial viability.

AV node ablation should be avoided in patients with permanent atrial fibrillation and normal left ventricular function, since left ventricular ejection fraction deteriorates more in these patients.

Atorvastatin can increase contractile reserve in patients with moderate hypercholesterolemia and peripheral vascular disease. A pleiotropic effect of atorvastatin on flow-dependent coronary dilatation may be responsible for this beneficial action.

In patients with depressed left ventricular dysfunction due to coronary artery disease viability studies should be performed irrespective of the presence and extend of Q waves on surface electrocardiogram.

Tissue Doppler imaging can differentiate between stunned, hibernating and scar myocardium in patients with ischemic cardiomyopathy.

Quantification of myocardial systolic velocities using tissue Doppler imaging may provide a simple and inexpensive method of acquiring prognostic information in patients with coronary artery disease and

depressed left ventricular function.

Tissue Doppler imaging can become a useful and inexpensive tool to differentiate viable from nonviable myocardium in patients with ischemic cardiomyopathy.

The myocardial contractile reserve after combined dobutamine infusion and post-extrasystolic potentiation can be quantified by pulsed-wave tissue Doppler imaging.

Catheter-based cell transplantation with autologous skeletal myoblasts is a feasible and promising technique for the treatment of patients with coronary artery disease and severely damaged myocardium.

SAMENVATTING
EN
CONCLUSIES



SAMENVATTING

Dit proefschrift beschrijft het gebruik van dobutamine stress echocardiografie in verschillende klinische situaties en de kwantificatie van dobutamine stress echocardiografie met Tissue Doppler Imaging.

Deel 1:

Nieuwe toepassingen van dobutamine stress echocardiografie

Hoofdstuk 2 beschrijft het herhaaldelijk gebruik van echocardiografie om de wandbeweging en het mitraalklep instroom patroon te bepalen, voor, tijdens, en 6 maanden na chemotherapie om de cardiotoxiciteit van chemotherapie vroeg vast te stellen bij patiënten die vanwege een hematologische aandoening behandeling met anthracycline ondergaan. Eenendertig patiënten werden onderzocht in rust en tijdens lage dosis dobutamine toediening. Radionuclide ventriculografie werd gebruikt als een onafhankelijke methode om de ejectie fractie vast te stellen. Een abnormaal mitraalklep instroom patroon bleek de enige onafhankelijke echocardiografische voorspeller van cardiotoxiciteit te zijn. Daarnaast toonde de wandbewegings score index een goede correlatie met de radionuclide ejectie fractie.

In hoofdstuk 3 werden 108 opeenvolgende patiënten met een matig ernstige (gemiddelde gradiënt 25 tot 49 mmHg) of ernstige (gemiddelde gradiënt, ≥ 50 mmHg) aorta stenose onderzocht. De patiënten ondergingen niet-cardiale chirurgie en werden vergeleken met 216 controle patiënten. Er was een significant verhoogde incidentie van het eindpunt perioperatieve mortaliteit en niet-fataal myocardinfarct, bij patiënten met aorta stenose, zelfs na correctie voor cardiale risicofactoren. Bovendien was bij patiënten met ernstige aorta stenose het risico op complicaties aanzienlijk hoger dan bij patiënten met een matig ernstige stenose.

Dobutamine stress echocardiografie wordt vaak toegepast bij patiënten met een lichte of matig ernstige aorta stenose om ischemie

vast te stellen of in het kader van risico stratificatie voor niet-cardiale chirurgie. Daarnaast kan lage-dosis dobutamine stress echocardiografie gebruikt worden bij patiënten met een aortastenose met een lage drukgradiënt en verminderde linker ventrikelfunctie om te bepalen of de stenose vast danwel dynamisch is. Dit is van klinisch belang, omdat patiënten met een gefixeerde aorta stenose baat kunnen hebben bij klepvervanging, terwijl dit bij patiënten met een dynamische stenose geen voordeel heeft. In hoofdstuk 4 werd de veiligheid van hoge-dosis dobutamine stress echocardiografie onderzocht bij 55 patiënten met een lichte tot matig ernstige aorta stenose (groep A), en van lage-dosis dobutamine stress echocardiografie bij 20 patiënten met aorta stenose met een lage drukgradiënt en een verminderde linker ventrikel functie. In beide groepen kwamen frequent ernstige hartritmestoornissen voor. Er werd geen relatie gevonden tussen bijwerkingen en stress geïnduceerde ischemie.

Patiënten die coronaire interventies hebben ondergaan, worden steeds vaker verwezen voor noninvasief onderzoek om symptomen te evalueren, en om coronaire reocclusie of progressie van de coronaire hartziekte uit te sluiten. In hoofdstuk 5 onderzochten we de prognostische waarde van dobutamine stress echocardiografie bij 332 opeenvolgende patiënten met een eerdere coronaire interventie (percutaan of chirurgisch). Tijdens de follow-up van 24 ± 20 maanden, overleed 13% van de patiënten, en 30% had een of meer cardiale problemen (7% cardiale dood, 4% niet-fataal myocardinfarct en 23% late revascularisatie). Multivariate analyse liet zien dat myocardischemie tijdens dobutamine stress echocardiografie, na correctie voor klinische gegevens, een onafhankelijke voorspeller van cardiale problemen is.

De QT dispersie op het oppervlakte electrocardiogram (het verschil tussen het maximale en minimale QT interval) kan verlengd zijn bij verschillende hartaandoeningen. Dit komt overeen met het concept dat de QT dispersie een algemene repolarisatie stoornis is. In hoofdstuk 6 onderzochten we de invloed van myocardvitaliteit op de QT dispersie.

Honderddrie opeenvolgende patiënten met een ischemische cardiomyopathie werden onderzocht. De QT dispersie en linker ventrikel ejectie fractie werden gemeten bij patiënten met een substantiële hoeveelheid myocardvitaliteit (≥ 4 vitale segmenten volgens lage-dosis dobutamine stress echocardiografie) en bij patiënten zonder substantiële vitaliteit (< 4 vitale segmenten volgens lage-dosis dobutamine stress echocardiografie). Patiënten met substantiële myocardvitaliteit hadden een lagere QT dispersie dan patiënten zonder substantiële myocardvitaliteit. Er was een negatieve correlatie tussen het aantal vitale segmenten en QT dispersie, terwijl er geen correlatie was tussen de linker ventrikel ejectie fractie en QT dispersie.

Een soortgelijke studie met single-photon emission computed tomography (SPECT scan) werd verricht bij 97 opeenvolgende patiënten met een ischemische cardiomyopathie (hoofdstuk 7). De resultaten waren in overeenstemming met de eerdere studie, de QT dispersie was significant gerelateerd aan het aantal vitale segmenten. Bovendien bleek dat een QT dispersie van ≤ 62 ms de hoogste sensitiviteit en specificiteit had om de aanwezigheid van myocardvitaliteit te voorspellen.

Bij patiënten met permanent atriumfibrilleren kunnen de symptomen en kwaliteit van leven aanzienlijk verbeteren met transcatheter ablatie van de atriaventriculaire (AV) knoop. In hoofdstuk 8 werd lage-dosis dobutamine stress echocardiografie gebruikt om te bepalen of de afwezigheid van contractiele reserve voor AV knoop ablatie, patiënten kan identificeren bij wie de linker ventrikelfunctie verslechtert na AV knoop ablatie. De aanwezigheid van contractiele reserve was gedefinieerd als een verbetering van contractiele functie van ≥ 1 graad bij lage-dosis dobutamine infusie in tenminste 4 segmenten. Radionuclide ventriculografie bij een gepaced ritme van 80 slagen/min werd gebruikt om de linker ventrikel ejectie fractie vast te stellen, 6 dagen en 3 maanden na AV knoop ablatie. Kwaliteit van leven werd vastgesteld met Minnesota, NHBP en MPWB vragenlijsten. De afwezigheid van contractiele reserve was niet voorspellend voor de

cardiale functie na AV knoop ablatie; een hogere ejectie fractie in rust was een voorspellend voor verslechtering van de cardiale functie.

Deel 2:

Kwantitatieve dobutamine stress echocardiografie.

Verschillende onderzoeken hebben aangetoond dat statines een gunstig effect hebben naast hun cholesterolverlagende werking. Dit effect wordt waarschijnlijk veroorzaakt door de zogenoemde pleiotrope werking. Een aantal mechanismen is voorgesteld om deze werking te verklaren, waaronder flow-afhankelijke vasodilatatie. In hoofdstuk 9 hebben we het effect van statines onderzocht in een groep van 26 opeenvolgende patiënten zonder hartaandoening, maar met een matig verhoogd cholesterolgehalte en perifeer vaatlijden. Patiënten kregen 10 mg (13 patiënten) of 80 mg atorvastatine (13 patiënten). Zes patiënten met gelijke klinische gegevens maar zonder gebruik van statine vormden de controlegroep. Na 3 en 6 maanden werd de contractiele reserve bepaald met pulsed-wave tissue Doppler in rust en tijdens lage-dosis dobutamine infusie. Na 6 maanden was er een significante stijging van de systolische contractie snelheid tijdens lage-dosis dobutamine infusie bij de patiënten die atorvastatine kregen. Deze stijging trad op onafhankelijk van de atorvastatine dosis. De controle patiënten hadden geen significante verandering van de systolische contractie snelheid.

Waarschijnlijk zijn “stunned” en “hibernating” hartspierweefsel geen verschillende entiteiten, maar vormen ze een continuüm van myocard dysfunctie. Het is van klinisch belang een onderscheid te maken tussen stunned, hibernating en littekenweefsel bij patiënten met coronarialijden, omdat patiënten met een substantiele hoeveelheid vitaal weefsel waarschijnlijk baat hebben bij coronaire revascularisatie. Eerdere onderzoeken hebben aangetoond dat het herstel van de contractiliteit bij hibernating myocardweefsel langere duurt dan bij stunned myocard. In hoofdstuk 10 hebben we een kwantitatieve benadering toegepast om te differentiëren tussen stunning en hibernation. Dysfunctioneel myocard werd vastgesteld met een rust

echocardiogram bij 70 patiënten met coronarialijden. Vaststellen van perfusie en glucose verbruik werd gedaan met Tc-99m tetrofosmin SPECT en 18F fluorodeoxyglucose SPECT. Berekening van de systolische contractiesnelheid toonde dat deze minder hoog was in litteken weefsel dan in hibernating en stunned weefsel. Bovendien was de contractiele reserve (verschil in systolische snelheid tussen lage-dosis dobutamine en de waarde in rust) significant hoger in stunned dan in hibernating en littekenweefsel.

De volgende stap was om de systolische en diastolische functie in vitaal en nonvitaal myocard kwantitatief te vergelijken bij 93 patiënten met ischemische cardiomyopathie (hoofdstuk 11). Vitaliteit werd vastgesteld met lage-dosis dobutamine stress echocardiografie. Pulsed-wave Doppler tissue onderzoek werd gebruikt om de systolische en vroege en late diastolische snelheden in vitaal en nonvitaal weefsel te meten. Een afzonderlijke analyse werd gedaan om patiënten ≥ 65 jaar en <65 jaar te vergelijken. De gemiddelde systolische snelheid in rust was significant hoger in vitaal dan in nonvitaal weefsel. Echter, tijdens lage-dosis dobutamine infusie was de gemiddelde systolische snelheid significant hoger in vitale dan in nonvitale gebieden. Bovendien hadden vitale gebieden een betere diastolische functie in rust vergeleken met nonvitale gebieden. De myocardsnelheden waren leeftijdsafhankelijk, en waren hoger in jongere patiënten (minder dan 65 jaar oud).

Van oudsher wordt er verondersteld dat myocardgebieden met Q golven op het oppervlakte ECG, uit littekenweefsel bestaan, en dat deze gebieden ernstig beschadigd zijn in vergelijking met dysfunctionele gebieden zonder Q golven op het electrocardiogram. In hoofdstuk 12 werden 81 patiënten met myocarddysfunctie en een verminderde linker ventrikel functie onderzocht. Ernstig hypokinetische, akinetische of dyskinetische gebieden op het tweedimensionale echocardiogram werden als dysfunctioneel beschouwd. Alle patiënten ondergingen een oppervlakte electrocardiogram in rust en pulsed-wave tissue Doppler onderzoek in rust en tijdens lage-dosis dobutamine infusie. Bepaling van de systolische myocard snelheid in rust en de stijging in systolische

snelheid van rust naar lage-dosis dobutamine infusie toonde dat er geen significant verschil was tussen gebieden met of zonder Q golven.

Dobutamine infusie verbetert de systolische myocardfunctie. In hoofdstuk 13, maten we de systolische myocard snelheid met pulsed-wave tissue Doppler bij een patiënt met ischemische cardiomyopathie en we stelden de toegevoegde potentiatie vast na een extrasystole. Een nucleaire scan die het glucose verbruik vaststelt, werd gebruikt als referentie techniek.

Transplantatie van skelet myoblastcellen naar beschadigd myocard kan de linker ventrikel functie herstellen volgens preklinische onderzoeken. Hoofdstuk 14 beschrijft een pilot studie naar de veiligheid en geschiktheid van percutane injectie van autologe skeletmyoblasten bij 5 patiënten met ischemisch hartfalen. Electrocardiografisch onderzoek en vaststellen van de linker ventrikel functie werd gedaan met Holter, linker ventrikel ventriculografie, dobutamine stress echocardiografie, Tissue Doppler in rust en tijdens lage-dosis dobutamine infusie, en magnetic resonance imaging. Na 6 maanden follow-up toonden zowel angiografie als het nucleair onderzoek een trend naar een verbetering van de ejectionfraction. Bij alle 5 patiënten liet het eerste dobutamine stress echocardiogram geen aanwijzingen voor ischemie of ventriculaire tachycardie zien. Na 6 maanden was er een trend naar een verbeterde contractie snelheid volgens tissue Doppler imaging van de anteroseptale wand.

CONCLUSIES

Een laag vroeg/laat mitraalklep instroompatroon voor chemotherapie met anthracyclines kan onafhankelijk een verslechtering van de hartfunctie voorspellen. Vaststellen van de wandbewegings score index met echocardiografie vormt een goedkoop en veilig alternatief voor nucleaire ventriculografie voor het herhaald onderzoeken van de linker ventrikel functie.

Aorta stenose vormt een risico factor voor perioperatieve complicaties. Hoe ernstiger de stenose, hoe hoger het risico op perioperatieve mortaliteit en myocardinfarct.

Patiënten met aorta stenose ontwikkelen gemakkelijker aritmieën en hypotensie tijdens dobutamine stress echocardiografie. Daarom zou dobutamine stress echocardiografie bij deze patiënten alleen gebruikt worden wanneer het echt klinisch belang heeft, en altijd onder strenge bewaking.

Reversibele wandbewegingsstoornissen op dobutamine stress echocardiografie zijn voorspellend voor cardiale problemen bij patiënten met een eerdere (>6 maanden eerder) coronaire interventie.

De QT dispersie op het oppervlakte ECG bij patiënten zonder substantiële hoeveelheid vitaal myocardweefsel is langer dan bij patiënten met een substantiële hoeveelheid myocardvitaliteit.

AV knoop ablatie moet vermeden worden bij patiënten met permanent atriumfibrilleren en een normale linker ventrikel functie, omdat de linker ventrikelfunctie verslechtert bij deze patiënten.

Atorvastatine kan de contractiele reserve verhogen bij patiënten met een matig ernstige hypercholesterolemie en perifere vaatlijden. Een pleiotrope werking van atorvastatine op de perfusie afhankelijke coronaire dilatatie kan dit gunstige effect veroorzaken.

Bij patiënten met een verminderde linker ventrikelfunctie als gevolg van coronarialijden dient vitaliteitsonderzoek uitgevoerd te worden onafhankelijk van de aanwezigheid en uitgebreidheid van Q golven op het oppervlakte electrocardiogram.

Tissue Doppler imaging kan differentiëren tussen stunned, hibernating en littekenweefsel bij patiënten met een ischemische cardiomyopathie.

Kwantificatie van de systolische myocardsnelheid met tissue Doppler imaging kan een eenvoudige en goedkope methode zijn om prognostische informatie te verkrijgen bij patiënten met coronarialijden en een verminderde linker ventrikelfunctie.

Tissue Doppler imaging kan een nuttig en goedkoop instrument worden om te differentiëren tussen vitaal en niet vitaal myocard bij patiënten met een ischemische cardiomyopathie.

De contractiele reserve van het myocard na gecombineerde dobutamine infusie en post-extrasystolische potentiatie kan gekwantificeerd worden middels pulsed-wave tissue Doppler imaging.

Autologe celtransplantatie met skelet myoblasten, via een catheter, is een geschikte en veelbelovende techniek voor de behandeling van patiënten met coronarialijden en ernstig beschadigd myocard.

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