Predictive Echocardiography

Elena Biagini

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Promotor:	Prof.dr. D. Poldermans
	Prof.dr. M.L. Simoons
Overige Leden:	Prof.dr. J.R.T.C. Roelandt
	Prof.dr. ir. N. Bom
	Prof.dr. P.M.T. Pattynama
	Prof.dr. A. Branzi
Copromotor:	Dr. F.J. ten Cate

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Alla mia bella famiglia

Contents

	Preface	11
	Part 1: Prediction of clinical outcome	
Chapter 1	**The use of stress echocardiography for prognostication in coronary artery disease: an overview.** Biagini E, Elhendy A, Bax JJ, Schinkel AFL, Poldermans D. *Curr Opin Cardiol,* in press	15
Chapter 2	**7-year follow-up after dobutamine stress echocardiography. Impact of gender on prognosis.** Biagini E, Elhendy A, Bax JJ, Rizzello V, Schinkel AFL, van Domburg RT, Kertai MD, Krenning BJ, Bountioukos M, Rapezzi C, Branzi A, Simoons ML, Poldermans D. *J Am Coll Cardiol* 2005;45:93-7	35
Chapter 3	**Comparison of all-cause mortality in women with known or suspected coronary artery disease referred for dobutamine stress echocardiography with normal versus abnormal test results.** Biagini E, Elhendy A, Schinkel AFL, Rizzello V, van Domburg RT, Krenning BJ, Schouten O, Sozzi FB, Branzi A, Rocchi G, Simoons ML, Bax JJ, Poldermans D. *Am J Cardiol* 2005:95:1072-1075	43
Chapter 4	**Long-term prediction of mortality in the elderly by dobutamine stress echocardiography.** Biagini E, Elhendy A, Schinkel AFL, Rizzello V, Bax JJ, Sozzi FB, Kertai MD, van Domburg RT, Krenning BJ, Branzi A, Rapezzi C, Simoons ML, Poldermans D. *Journal of Gerontology Medical Science*, in press	49
Chapter 5	**Prognostic stratification using dobutamine stress 99mTc-tetrofosmin myocardial perfusion SPECT in elderly patients unable to perform exercise testing.** Schinkel AFL, Elhendy A, Biagini E, van Domburg RT, Valkema R, Rizzello V, Pedone C, Simoons ML, Bax JJ, Poldermans D. *J Nucl Med* 2005;46:12-8	61
Chapter 6	**Long-term outcome in patients with silent versus symptomatic ischemia during dobutamine stress echocardiography.** Biagini E, Schinkel AFL, Bax JJ, Rizzello V, van Domburg RT, Krenning BJ, Bountioukos M, Pedone C, Vourvouri EC, Rapezzi C, Branzi A, Roelandt JRTC, Poldermans D. *Heart,* in press	71

Chapter 7 **Clinical and prognostic implications of angina pectoris developing during dobutamine stress echocardiography in the absence of inducible wall motion abnormalities.** 85
Elhendy A, Biagini E, Schinkel AFL, van Domburg RT, Bax JJ; Rizzello V, Roelandt JRT, Poldermans D. *Am J Cardiol*, in press

Chapter 8 **Risk stratification of patients with classic angina pectoris and no history of coronary artery disease by dobutamine stress echocardiography.** 99
Biagini E, Elhendy A, Schinkel AFL, Bax JJ, Rizzello V, van Domburg RT, Rapezzi C, Simoons ML; Poldermans D. *J Am Coll Cardiol*, in press

Chapter 9 **Accuracy of non-invasive techniques for diagnosis of coronary artery disease and prediction of cardiac events in patients with left bundle branch block: a meta-analysis.** 107
Biagini E, Shaw L, Poldermans D, Schinkel AFL, Rizzello V, Elhendy A, Bax JJ.

Chapter 10 **Prognostic stratification of patients with right bundle branch block using dobutamine stress echocardiography.** 127
Biagini E, Schinkel AFL, Rizzello V, van Domburg RT, Pedone C, Elhendy A, Krenning BJ, Bountioukos M, Vourvouri EC, Branzi A, Rapezzi C, Simoons ML, Bax JJ, Poldermans D.
Am J Cardiol 2004;94:954-7

Chapter 11 **Pacemaker stress echocardiography predicts cardiac events in patients with permanent pacemaker and known or suspected coronary artery disease.** 133
Biagini E, Schinkel AFL, Elhendy A, Bax JJ, Rizzello V, van Domburg RT, Krenning BJ, Schouten O, Branzi A, Rocchi G, Simoons ML, Poldermans D. *Am J Med*, in press

Chapter 12 **Prognostic significance of left anterior hemiblock in patients with suspected coronary artery disease.** 145
Biagini E, Elhendy A, Schinkel AFL, Nelwan S, Rizzello V, van Domburg RT, Rapezzi C, Rocch G, Simoons ML, Bax JJ, Poldermans D. *J Am Coll Cardiol*, in press

Part 2: Prediction of cardiac function

Chapter 13 **Opposite patterns of left ventricular remodeling after coronary revascularization in patients with ischemic cardiomyopathy: role of myocardial viability.** 157
Rizzello V, Poldermans D, Boersma E, Biagini E, Schinkel AF, Krenning B, Elhendy A, Vourvouri EC, Sozzi FB, Maat A, Crea F, Roelandt JR, Bax JJ. *Circulation* 2004;110:2383-8

Chapter 14 **Stress and tissue Doppler echocardiographic evidence of effectiveness of myoblast transplantation in patients with ischemic heart failure.** 165
Biagini E, Valgimilgi M, Smits P, Poldermans D, Schinkel AFL, Onderwater EME, Bountioukos M, Serruys PW.

Chapter 15 **Myocardial wall thickness predicts recovery of regional contractile function after percutaneous coronary intervention for acute myocardial infarction.** 181
Biagini E, Galema TW, Schinkel AFL, Vletter WB, Roelandt JRTC, ten Cate FJ. *J Am Coll Cardiol* 2004;43:1489-93

Chapter 16 **Comparison between contrast echocardiography and magnetic resonance imaging to predict improvement of myocardial function after coronary intervention.** 189
Biagini E, van Geuns RJ, Baks T, Boersma E, Rizzello V, Galema TW, de Feyter PJ, ten Cate FJ.

Chapter 17 **Dilated-hypokinetic evolution of hypertrophic cardiomyopathy: prevalence, incidence, risk factors and prognostic implications in pediatric and adult patients.** 205
Biagini E, Coccolo F, Ferlito M, Perugini E, Rocchi G, Bacchi-Reggiani L, Lofiego C, Boriani G, Prandstraller D, Picchio F, Branzi A, Rapezzi C. *J Am Coll Cardiol,* in press

Chapter 18 **Intracardiac echocardiography to guide percutaneous transluminal septal ablation in patients with obstructive hypertrophic cardiomyopathy.** 221
Biagini E, Valgimigli M, Baks T, van der Lee C, Lighthart YML, Serruys PW, ten Cate FJ.

Summary and conclusions 233

Samenvatting en conclusies 241

Acknowledgements 247

Curriculum vitae 253

List of publications 255

Preface

Echocardiography is a widely spread, relatively inexpensive technique that is often used for non-invasive cardiac imaging. It is regularly the first cardiac test ordered when cardiac disease is suspected in a patient, because it provides an integrated non-invasive assessment of cardiac structure, function and hemodynamics. An evolution in different developments of ultrasound imaging such as stress echocardiography, myocardial contrast echocardiography, tissue Doppler imaging and intracardiac echocardiography, has further popularized echocardiography. Evaluation of regional or global myocardial function by one of these approaches can be useful to predict a change of function or prognosis by the time. This thesis evaluates the value of echocardiography in predicting clinical or functional outcome.

OUTLINE OF THE THESIS

Part 1. Prediction of outcome.

Dobutamine stress echocardiography has become an established imaging technique. The accuracy of dobutamine stress echocardiography for detection of significant coronary artery disease ranges from 80-90% (1). Dobutamine stress echocardiography offers also valuable information for risk stratification of patients (2, 3). The efficacy of prognostic stratification is related to the ability of this technique to provide information on resting left ventricular function, myocardial viability and stress-induced ischemia. The combination of rest and pharmacological stress echocardiography has been shown to give important information on the risk of late cardiac events and can be useful to guide therapeutic strategies as well as to provide risk stratification (2). However, different aspects need to be investigated and elucidated.

As medicine develops there is a trend towards more individual diagnostic evaluation and clical care. However, untill now the predictive value of stress echocardiography was often evaluted in unselected, mixed patient groups.The first part of this thesis deals with the assessment of prognostic value of dobutamine stress echocardiography in specific patient subsets. Prediction of future cardiac events may be a clinical challenge in these patient groups, because of anatomical differences, inability to exercise, and preexistent repolarization abnormalities. Therefore the central question of part I, of the thesis is:

Does dobutamine stress echocardiography provide incremental information for the prediction of cardiac events in women, elderly, patients with silent ischemia, and those with intraventricular conduction abnormalities?

Chapter 1 is a systematic review evaluating the additional value of stress echocardiography to common clinical cardiac risk factors and hemodinamic data for the assessment of prognosis in different subsets of patients with suspected or known coronary artery disease. The review includes stress echocardiography reports where exercise, inotropic agents (dobutamine) or vasodilatator stressors (dipyridamole or adenosine) are used.

In Chapter 2, the effects of gender on long-term prognosis of patients undergoing dobutamine stress echocardiography are investigated during a mean follow-up of 7 years. The aims of this study were: 1) to assess the predictors of cardiac death and nonfatal myocardial infarction during a long-term follow-up in men and women referred for dobutamine stress echocardiography; and 2) to find whether gender has an impact on outcome after controlling for clinical variables and stress echocardiographic data. A separate analysis in males and females with normal and abnormal stress test was also performed to obtained a better understanding of gender differences in low and high risk patients and allow to an aimed therapeutic treatment for each group.

Subsequently, Chapter 3 reports on the incremental value of dobutamine stress echocardiography in 1105 females who underwent dobutamine stress echocardiography. A prediction of the strongest end-point, all cause mortality, was specifically evaluated.

In Chapter 4 long-term prognostic value of dobutamine stress echocardiography is evaluated in patients over 65 years. The study population comprised 1140 patients with limited exercise capacities. These patients were followed-up during a 6.5-year period after stress test.

To investigate, similarly, the prognostic value of dobutamine stress 99mTc-tetrofosmin SPECT for the prediction of mortality and cardiac events in elderly patients unable to perform exercise testing, in Chapter 5 clinical information and SPECT results are analyzed in 272 consecutive patients ≥65 years old, during a mean follow-up of 3 years.

Chapter 6 assesses the prognostic significance of reversible wall motion abnormalities in patients without angina during dobutamine stress echocardiography compared with patients with symptomatic inducible ischemia. The study reports on cardiac events in 931 patients during a 5.5-year follow-up.

In Chapter 7 the incidence, clinical correlates and prognostic significance of angina during dobutamine stress echocardiography in patients without inducible wall motion abnormalities is evaluated in 2117 patients during 5.5-year follow-up.

In Chapter 8 prediction of cardiac death, hard cardiac events and all cause mortality by dobutamine stress echocardiography was evaluated in 299 patients with a high pre-test probability of coronary artery disease during a 6-year follow-up. According to the Bayes' theorem, a normal stress test in these patients does only modestly reduce the post-test probability of coronary artery disease. Therefore, it is not known whether patients with high pre-test probability of coronary artery disease would be considered a low risk population if they had a normal stress echocardiogram.

Chapter 9 is a meta-analysis evaluating the accuracy of non-invasive techniques for diagnosis of coronary artery disease and prediction of cardiac events in patients with permanent left bundle brunch block on resting electrocardiogram. Non-invasive evaluation of coronary artery disease in these patients has several limitations since pre-existent repolarization abnormalities due to the altered excitation activity with the consequent asynchronous ventricular contraction and myocardial perfusion abnormalities hamper and limit the diagnostic accuracy of all the available non-invasive techniques, as exercise electrocardiogram, echocardiography and myocardial perfusion imaging. A pooled analysis of the presently published data on the aforementioned non-invasive techniques was performed.

Subsequently, in Chapter 10 the role of dobutamine stress echocardiography for the prognostic stratification of patients with right bundle branch block is evaluated. A total of 176 patients were followed-up for 4 years.

Chapter 11 reports on prognostic value of pacing stress echocardiography in 136 patients with a permanent right ventricular pacemaker during 3.5 years of follow-up. Pacing stress echocardiography has been shown to have a good diagnostic accuracy for detection of coronary artery disease, however its prognostic value has never been evaluated since now.

In Chapter 12, the prognostic significance of left anterior hemiblock in 1187 patients with suspected coronary artery disease referred for dobutamine stress echocardiography is investigated.

Part 2. Prediction of left ventricular function.

Two-dimensional echocardiography (at rest or during low-dose dobutamine infusion) is an established technique to quantify regional and global myocardial dysfunction. The ability to assess even minor change in regional left ventricular function has been recently redefined by the introduction of tissue Doppler imaging in the clinical setting (4, 5). Differently, myocardial perfusion echocardiography, evaluating microvascular function, allows to predict recovery of function in patients with acute myocardial infarction undergoing medical or mechanical revascularization (6, 7).

In Chapter 13, the role of myocardial viability assessed by low dose dobutamine infusion in the left ventricular remodeling process after revascularization is assessed in a large cohort of patients (n=100) with ischemic cardiomyopathy. In addition, long-term clinical follow-up was performed.

Chapter 14 reports short- and long-term regional and global left ventricular functional effects of percutaneously transplanted skeletal myoblasts in patients with dilated ischemic cardiomyopathy. Left ventricular function is evaluated in 10 patients by two-dimensional echocardiography and tissue Doppler imaging at rest and during low dose dobutamine infusion to assess contractile reserve. New York Heart Association (NYHA) functional class and clinical follow-up at 29 months are also included.

In Chapter 15 an additional value of the wall thickness compared to myocardial perfusion echocardiography is evaluated to predict recovery of regional cardiac function. The study population comprises 40 patients with acute myocardial infarction undergoing percutaneous primary coronary intervention. Recovery of myocardial function is evaluated at two months follow-up.

In Chapter 16, myocardial contrast echocardiography is compared with the gold standard technique magnetic resonance imaging to predict recovery of regional and global left ventricular function in the setting of acute myocardial infarction. Both techniques are performed after primary percutaneous angioplasty in 35 patients.

In Chapter 17 the onset of dilated-hypokinetic evolution and cardiovascular events in patients with hypertrophic cardiomyopathy is evaluated by resting 2-D echocardiography.

Chapter 18 evaluates the role of intracardiac echocardiography during percutaneous septal myocardial ablation in patients with obstructive hypertophic cardiomyopathy.

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Chapter 1

The Use of Stress Echocardiography for Prognostication in Coronary Artery Disease: an Overview

Biagini E, Elhendy A, Bax JJ, Schinkel AFL, Poldermans D

Curr Opin Cardiol, in press

Introduction

Although myocardial perfusion imaging remains the most widely used non-invasive imaging tool for the diagnosis of coronary artery disease (CAD), stress echocardiography is increasingly used over the last few decades. Recent studies have proven the clinical usefulness in the evaluation of CAD in various populations of patients with known or suspected CAD. Therefore, stress echocardiography became an accepted technology for evaluation of CAD in common practice. The technique allows assessment of baseline cardiac function and direct evaluation of inducible myocardial ischemia by imaging reversible left ventricular dysfunction. The diagnosis of myocardial ischemia by stress echocardiography relies upon the detection of new or worsening wall motion abnormalities with stress (1). Wall motion abnormalities occur earlier than ECG changes and angina in the ischemic cascade and therefore, provide a particular advantage in patients with submaximal stress test in whom the duration and or the severity of ischemia may not be enough to induce ECG changes or angina. Stress testing can be achieved using dynamic exercise or pharmacologic alternatives. Exercise echocardiography is the preferred method in patients who are able to exercise, because exercise capacity and hemodynamic data provide useful prognostic information. In patients with limited exercise capacity, pharmacologic stress testing is a feasible alternative (1). Pharmacological stress testing is accomplished by using agents that increase myocardial oxygen demand (such as dobutamine) or induce coronary arterial vasodilation to increase myocardial blood flow (such as adenosine or dipyridamole). In patients who fail to achieve the target heart rate, the addition of atropine increases heart rate by its vagolytic effects. In patients who can not achieve the target heart rate with dobutamine-atropine or have a contraindication for dobutamine stress test, transesophageal atrial pacing represent a feasible alternative.

Furthermore, stress echocardiography has been proposed for risk stratification in different clinical setting, adding important prognostic information. Prognostic parameters of importance are resting left ventricular function, myocardial viability, stress-induced ischemia, vascular extent of wall motion abnormalities, and changes of end systolic volume and ejection fraction with stress. A large number of studies have shown stress echocardiography efficacy in predicting long-term cardiac events in a heterogeneous population (2-8). Additional information by this technique have been also reported in specific clinical settings. In patients with myocardial infarction the identification of residual viable tissue and myocardial ischemia can predict improvement of function after revascularization. The prognostic value has also been demonstrated in special patients subsets including patients undergoing major vascular or non vascular surgery, elderly, women, diabetes mellitus, systemic hypertension and patients with previous myocardial revascularization. The proper selection of management strategies in patients with suspected or known coronary artery disease should be based on an accurate estimation of the risk of adverse events. Recognition of patients at high risk of cardiac events is an essential step in guiding the use of invasive procedures and selecting patients who are most likely to benefit and thus avoiding the risk and cost of interventions in low risk patients. Patients with normal stress echocardiogram had a low cardiac event rate (1-2%) and can be exempted for invasive procedures.

This review attempts to define the role of stress echocardiography for prognostication in coronary artery disease, pointing out the ability of this technique in identifying low-risk and high-risk subsets among patients with known or suspected CAD and thus guide patient management decisions.

Outcome after a normal stress echocardiogram. Individuals with normal stress (exercise, dipyridamole or dobutamine) echocardiography, defined as absence of wall motion

abnormalities at rest and during stress have a very low event rate, which is equivalent to age matched population (7,9-11). Patients with resting left ventricular dysfunction but no inducible myocardial ischemia have an intermediate risk, whereas patients with new wall motion abnormalities are at increased risk for cardiac events and mortality (with an annual hard cardiac event rate reported up to 5.5%). In a meta-analysis of published data on the prognostic outcome after a normal stress echocardiogram, the overall annual hard cardiac event rate (cardiac death or nonfatal myocardial infarction) reported in 27 stress echocardiography studies (5 dipyridamole, 13 dobutamine, 9 exercise) involving 6,799 patients (mean age 58 years, 47% men, 37% with hypertension, 10% with diabetes) with a mean follow-up period of 27 months was 0.9%. Patients with normal exercise echocardiography had a significantly better prognosis ($p< 0.0001$) than patients with normal pharmacological stress echocardiography (12). This may be explained by the higher risk status of patients who are unable to perform exercise stress test or possibly, by a difference in the sensitivity of exercise versus pharmacologic stress test for the diagnosis of CAD.

Risk stratification after acute myocardial infarction. Risk stratification of patients who survived an acute myocardial infarction (MI) aims at identifying patients whose outcome can be improved through invasive procedures and coronary intervention, and patients who can be treated medically. Resting left ventricular function after acute MI is the major determinant of prognosis (13,14). Low-dose dobutamine echocardiography can identify the presence of stunned myocardium in the first week after reperfusion by observing contractile reserve in dysfunctional myocardial segments. This pattern that has been shown to predict both functional recovery and outcome (15,16). Pharmacological stress echocardiography can detect the presence, the severity and the extent of residual myocardial ischemia, which has important prognostic implications (17-30). The prognostic significance of myocardial viability in patients with previous MI detected by dobutamine stress echocardiography is controversial. In patients with an uncomplicated MI it has been shown to be associated with an increased risk of unstable angina but not hard events (21,24), whereas in patients with left ventricular dysfunction early after MI was shown to be associated with a higher probability of survival (18).

Risk stratification in patients with old myocardial infarction. In patients with chronic ischemic left ventricular dysfunction stress echocardiography has a major role in detecting viable myocardium and myocardial ischemia. Patients with a substantial amount of dysfunctional but viable myocardium (extending to ≥25% of the left ventricle) have been shown to have a high likelihood to improve function and a better prognosis after myocardial revascularization compared to patients with an extensive myocardial scar and no contractile reserve (31-43). It has also been shown that the presence of viable or ischemic myocardium is associated with an adverse prognosis (44). Accordingly, assessment of viability can guide a tailored therapeutic strategy, where patients with viable myocardium should be considered for early revascularization (38). A substantial amount of viable myocardium detected by low does dobutamine echocardiography has been shown to prevent ongoing remodeling after revascularization and to be associated with persistent improvement of heart failure symptoms and a lower incidence of cardiac events (35). Combination of the LV size and presence/absence of viability provide a better risk stratification in these patients. In particular, despite the presence of viable myocardium, patients with left ventricular remodeling (mainly a large end-systolic volume) may not improve in left ventricular ejection fraction and have a worse long-term prognosis as compared with patients with a smaller left ventricular end-systolic volume (45).

Evaluation of myocardial ischemia is important in the decision to revascularize patients with chronic left ventricular dysfunction, since improvement in left ventricular ejection fraction is likely to occur when a substantial amount of viable and/or ischemic myocardium is present (31,33). Studies of the association between myocardial ischemia and long-term outcome yielded discordant findings. Smart et al. (46), reported that inducible ischemia during dobutamine stress echocardiography was the major determinant of outcome in patients with chronic left ventricular dysfunction and independent of clinical data and left ventricular function. Conversely, Sawada et al. (47), demonstrated that the presence of viability was independently associated with a higher risk of cardiac death, whereas ischemia did not add significant prognostic value.

Elderly. Demographic studies have shown that the elderly constitutes a rapidly expanding segment of our population, expected to constitute 20% in the next few decades. CAD is the leading cause of death and disability in the elderly and its clinical manifestations are more severe in patients older than 65 years (48,49). Thus, the identification of patients at high risk for coronary events who could benefit of tailored medical therapy and aggressive risk factors management or eventually early myocardial revascularization appears particularly important (50). Exercise echocardiography has been demonstrated as a useful non-invasive tool for evaluation of CAD in the elderly (51). The addition of exercise echocardiographic variables to clinical and exercise ECG data improved prediction of cardiac events. The most powerful exercise echocardiographic parameters were especially the change in left ventricular end-systolic volume with exercise and the exercise ejection fraction. However, exercise stress testing is not feasible in many elderly patients (52), manly because of deconditioning or neurologic, respiratory, peripheral vascular, or orthopaedic limitations, so that pharmacological stress echocardiography can be a feasible alternative in these patients (2,4,53). Published reports with dipyridamole, dobutamine or adenosine stress have documented the independent and additional value of pharmacological stress to predict cardiac events in the elderly during short term follow up (54-58). The long-term prognostic value of dobutamine stress echocardiography for prediction of all cause mortality and hard cardiac events has been recently studied in 1434 patients ≥ 65 years (Biagini E et al. Long-term Prediction of Mortality in the Elderly by Dobutamine Stress Echocardiography. The Journal of Gerontology: Medical Sciences, in press 2005). Patients with both resting and dobutamine induced wall motion abnormalities were at highest risk of cardiac events with an annual rate of 8%. The presence and the extent of ischemia during DSE provided incremental information over clinical and resting echocardiographic data for the prediction of both hard cardiac events and all cause mortality.

Women. Despite significant advances in the diagnosis and treatment of coronary artery disease (CAD) in the last decades, it remains the leading cause of death in women in industrialized country. With the aging of the population, the overall number of cardiac deaths has recently increased, and the trend is expected to continue, especially in women due to a longer life expectancy than men (59,60). Diagnosis of CAD in women is challenging due to the differences in clinical presentation as well as to the diminished accuracy of some non-invasive diagnostic techniques and the lower prevalence of the disease (61,62). Pharmacologic stress echocardiography, with dipyridamole or dobutamine, has been reported as a valuable diagnostic and prognostic tool in women, with a reported higher specificity and sensitivity in detecting CAD compared to exercise electrocardiography and myocardial perfusion imaging (63-72). Moreover, the prognostic value of stress echocardiography has been shown to be maintained in women as well as in men (5,73-75), with a positive predictive value higher compared to exercise electrocardiography (76), consistent with myocardial

perfusion imaging studies (77-80). A recent study (Biagini E et al. Comparison of All-Cause Mortality in Women with Known or Suspected Coronary Artery Disease Referred for Dobutamine Stress Echocardiography with Normal vs. Abnormal Test Results. Am J Cardiol, in press 2005), has shown that DSE provides independent prognostic information for prediction of all cause mortality during long-term follow-up in 1105 women with known or suspected CAD. Both resting and dobutamine induced wall motion abnormalities were associated with increased risk of death in women with and without history of CAD.

Additionally, the effects of gender on long-term prognosis of patients undergoing dobutamine stress echocardiography was investigated in 2276 men and 1105 women with known or suspected coronary artery disease, during a mean follow-up of 7 years (6). Dobutamine stress echocardiography provided independent prognostic information for prediction of cardiac events in both genders. The prognosis after a normal dobutamine stress echocardiography was more favorable in women than in men, after correction for clinical variables. In patients with a normal DSE the annual hard cardiac event rate during 7 years of follow-up was 2.5% in men and 1.2% in women ($p<0.0001$). There was no difference in annual hard cardiac event rate between men and women with rest wall motion abnormalities (2.9% vs 2.1%, $p=0.1$) or men and women with both rest and new wall motion abnormalities (5.9% vs 4.6%, $p=0.3$). The outcome of patients with abnormal dobutamine stress echocardiography was related to severity of left ventricular dysfunction and ischemia on dobutamine stress echocardiography, but not related to gender after adjusting for other variables.

Patients with diabetes mellitus. Diabetes mellitus is a major risk factor for CAD and its complications. Diabetic patients have higher cardiac event rates, more silent ischemia, and a higher morbidity after acute myocardial infarction than nondiabetic patients (81). Therefore, it is clinically important to determine the risk of cardiac events in patients with diabetes in order to select the appropriate management strategy. The use of stress echocardiographic results to plan further management may be confounded by the propensity to develop resting wall motion abnormalities in the absence of previous infarction, the occurrence of microvascular ischemia and the accelerated rate of progression of CAD that may limit the long term negative predictive value of a normal stress echocardiographic study in diabetic patients. Several techniques have been proposed for the prognostic stratification of diabetic patients, such as exercise stress testing, in conjunction with radionuclide scintigraphy (82-84) or echocardiography (85-88). However, many diabetic patients are unable to undergo an exercise stress test due to the higher prevalence of stroke, peripheral vascular disease, and neuropathy. Such patients generally represent a higher risk population than patients who are able to undergo exercise stress testing, and therefore, pharmacologic stress testing may predict a greater number of cardiac events in these patients (89, 90).

Patients with systemic hypertension. Detection of CAD and identification of patients who are at high risk of mortality and cardiac events in patients with hypertension is particularly relevant since systemic hypertension is strongly associated with CAD (91). Non-invasive evaluation of CAD in patients with hypertension by exercise electrocardiography is limited by the low specificity due to the presence of resting electrocardiographic abnormalities (92-95). Stress echocardiography and myocardial perfusion scintigraphy have been shown to be accurate techniques for the diagnosis of CAD, with some studies reporting a higher diagnostic specificity for stress echocardiography (96, 97). Both techniques have also been shown to provide prognostic information for cardiac death (98-100) and cardiac events (76-78) in patients with hypertension (96, 98, 99), as well as specifically in patients with left ventricular hypertrophy (97). In the report of Marwick et al. (96), stress echocardiography

was shown to provide incremental information for the prediction of cardiac mortality rate. In patients who underwent exercise echocardiography, cardiac death was predicted by ischemia, whereas in patients who underwent DSE it was predicted by any stress echocardiographic abnormality. Elhendy et al. (101), reported that left ventricular ejection fraction response to exercise was an independent predictor of mortality, incremental to clinical data, left ventricular mass index and resting left ventricular function among patients with left ventricular hypertrophy. The study by Sozzi et al (102-107), showed an incremental value of DSE for risk stratification of patients who have hypertension after adjustment for the left ventricular mass index, that was also predictive of mortality rate and cardiac events. Therefore, another advantage of stress echocardiography is the ability to assess both left ventricular function and the left ventricular mass index in addition to myocardial ischemia. Patients with multivessel distribution of wall motion abnormalities have the highest risk and therefore should represent a target group of patients in whom invasive strategies should be implemented.

Patients with normal left ventricular function. In patients with CAD a normal left ventricular systolic function is a powerful determinant of a good prognosis (108). However, inducible myocardial ischemia in these patients has been shown to be independently associated with increased risk of cardiac events and all cause mortality (10, 11, 109). Prognostic studies focused on patients with normal left ventricular ejection fraction by stress echocardiography are scarce (9-11), however various studies have demonstrated the prognostic value of myocardial ischemia during stress echocardiography in a heterogeneous population with and without left ventricular dysfunction (2,3, 5-8, 110).

Resting ECG abnormalities. Patients with conduction defects on resting electrocardiogram, such as left or right bundle branch block (LBBB or RBBB) and patients with a permanent right ventricular pacemaker, represent a challenging subgroup for non-invasive detection of CAD. In fact, not only exercise ECG have a reduced diagnostic accuracy due to the pre-existent repolarization abnormalities (111-113), but also myocardial perfusion imaging (114-116) have a limited diagnostic value due to the wall motion and perfusion abnormalities related to the altered excitation, in particular in patients with LBBB or a permanent pacemaker. However, detection of CAD and risk stratification for future cardiac events in these patients is particularly important since the presence LBBB or RBBB are associated with cardiovascular disease and adverse outcome, particularly in patients with known CAD or after myocardial infarction. Similarly, CAD may concomitantly exist in patients with pacemaker or may be the underlying cause of conduction. Stress echocardiography has been shown to have a good diagnostic accuracy in these patients groups (117, 118), showing a higher specificity compared to perfusion imaging in patients with LBBB (119-122), and an excellent diagnostic accuracy in patients with RBBB. Moreover, multiple studies have recently shown an efficient prognostic stratification by stress echocardiography in patients with LBBB or RBBB (123), addictive to clinical and resting echocardiographic variables. A recent report from our group (Biagini E et al. Long-term Prognositc Value of Pacing Stress Echocardiography. Eur J Echocardiogr. 2004;5 (Suppl.1):S246) showed that pacing stress echocardiography in patients with a permanent right ventricular pacemaker can provide independent information for prediction of cardiac death and all cause mortality.

Risk stratification in patients who undergo major vascular surgery. Patients undergoing major vascular surgery are at increased risk for perioperative and long-term cardiac complications. Despite recent advances in perioperative and long-term care, the 30-

day cardiac death of major vascular surgery varies between 3-6%, and the cardiac event rate during long-term follow-up between 30-40% (79-81). The incidence of perioperative and late cardiac complications in these patients is associated with the prevalence of CAD (127-133). Thirty-six percent of patients undergoing abdominal aortic aneurysm repair and in about 28% of patients undergoing infrainguinal revascularization have severe CAD, and only 6% of all vascular patients have normal coronary artery. Cardiac risk factors and noninvasive diagnostic tests for CAD may help to identify high-risk patients before major vascular surgery. Subsequent pharmacological therapy may be utilized in these high-risk individuals in order to lower their risk during and after vascular surgery. Thus, preoperative identification of high-risk patients, including perioperative cardiac risk assessment and strategies to reduce this risk in particular, has become crucial. Pharmacological stress echocardiography with either dipirydamole or dobutamine, have been shown to play an important role for the assessment of perioperative (4, 124, 134-139) and late cardiac risk (140) in patients scheduled for major vascular surgery, particularly in those with an intermediate to high risk according to clinical variables. The documentation of marked induced myocardial ischemia has a strong independent prognostic value to identify patients at high risk of coronary complications who could benefit of early revascularization before peripheral vascular surgery. Conversely, the absence of ischemia has been shown to be powerfully associated with a very low incidence of cardiac events allowing a safe surgical procedure (negative predictive value between 90 and 100%). In a recent meta-analysis , the comparative performance of six non-invasive techniques used for preoperative risk stratification in patients selected for vascular surgery was evaluated. Pharmacological stress tests showed a higher overall sensitivity and specificity than the other tests. In particular, dobutamine stress echocardiography showed a similar sensitivity to myocardial perfusion scintigraphy but a higher specificity and a better overall predictive performance. Dipyridamole stress echocardiography had a lower sensitivity and a higher specificity than myocardial perfusion scintigraphy. However, further conclusions about dipyridamole stress echocardiography are limited by the reported differences between studies and the limited number of studies reported to date. A positive trend for dobutamine stress echocardiography towards better diagnostic performances than the other tests was evident, but this only reached significant difference in comparison with myocardial perfusion scintigraphy. Dobutamine stress echocardiography could be the favoured test in situations where there is a suspicion of valvular heart disease or left ventricular systolic dysfunction.

Stress echocardiography after coronary revascularization. The role of exercise and pharmacologic stress testing in the diagnosis of restenosis after angioplasty and graft occlusion after CABG has been extensively studied (53). The main advantages of this technique are the ability to localize restenosis or graft occlusion and to detect myocardial viability in resting dysfunctional regions. Scarce data are available regarding the prognostic value of the technique after revascularization (141-144). Some reports have shown as a positive stress echocardiography test after coronary angioplasty identifies patients at with a high risk for recurrence of angina symptoms (143-144). More recently, Bountioukos et al. (141), studied the prognostic value of DSE in 331 patients with previous percutaneous or surgical coronary revascularisation. During a mean follow up of 24 months, 37 (13%) patients died and 89 (30%) had at least one cardiac event (21 cardiac deaths, 11 non-fatal myocardial infarctions, and 68 late revascularizations). In multivariate analysis of clinical data, independent predictors of late cardiac events were hypertension and congestive heart failure. Ischemia on DSE was incrementally predictive of cardiac events. Arruda et al. (82), studied the value of exercise echocardiography in predicting outcome of 718 patients who were studied at a mean of 5.7 years after CABG. During a median follow-up of 2.9 years, cardiac events included cardiac death in 36 patients and nonfatal myocardial infarction in 40 patients.

The addition of the exercise echocardiographic variables, abnormal left ventricular end-systolic volume response and exercise ejection fraction to the clinical, resting echocardiographic and exercise electrocardiographic model provided incremental information in predicting cardiac events.

Summary and Conclusions

Stress echocardiography is a useful technique for the risk stratification of patients with known or suspected coronary artery disease. In particular, patients with resting ECG abnormalities or reduced exercise capacity are candidates for stress echocardiography due to the low feasibility of exercise ECG under these circumstances. Patients with normal stress echocardiography have a very low cardiac event rate and in most instances do not require further diagnostic evaluation. Patients with extensive abnormalities in multi-vascular distribution are at a high risk of death and myocardial infarction. In these patients, coronary angiography and subsequent myocardial revascularization may be justified, with additional consideration of symptomatic status, functional capacity and resting left ventricular function. Evaluation of myocardial viability has a potential impact on the outcome after revascularization by selecting patients with significant left ventricular dysfunction in whom revascularization will improve myocardial function, exercise tolerance and survival. The development of new techniques for improved imaging quality during stress testing is expected to have a favorable impact on the utility of stress echocardiography in guiding management of patients with known or suspected coronary artery disease.

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Chapter 2

Seven-Year Follow-Up after Dobutamine Stress Echocardiography. Impact of Gender on Prognosis

Biagini E, Elhendy A, Bax JJ, Rizzello V, Schinkel AFL, van Domburg RT, Kertai MD, Krenning BJ, Bountioukos M, Rapezzi C, Branzi A, Simoons ML, Poldermans D

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Seven-Year Follow-Up After Dobutamine Stress Echocardiography

Impact of Gender on Prognosis

Elena Biagini, MD,*† Abdou Elhendy, MD, FACC,‡ Jeroen J. Bax, MD,§ Vittoria Rizzello, MD,* Arend F. L. Schinkel, MD,* Ron T. van Domburg, PHD,* Miklos D. Kertai, MD,* Boudewijn J. Krenning, MD,* Manolis Bountioukos, MD,* Claudio Rapezzi, MD,† Angelo Branzi, MD,† Maarten L. Simoons, MD, FACC,* Don Poldermans, MD*

Rotterdam and Leiden, the Netherlands; Bologna, Italy; and Omaha, Nebraska

OBJECTIVES The aim of this study was to investigate the effects of gender on long-term prognosis of patients undergoing dobutamine stress echocardiography (DSE).

BACKGROUND Gender differences in the predictors of outcome among patients with known or suspected coronary artery disease undergoing DSE have not been adequately studied.

METHODS We studied 2,276 men and 1,105 women with known or suspected coronary artery disease who underwent DSE. Follow-up events were cardiac death and nonfatal myocardial infarction (MI).

RESULTS Dobutamine stress echocardiography was normal in 687 men (30%) and 483 women (44%) ($p < 0.0001$). Ischemia on DSE was present in 1,194 men (52%) and 416 women (38%) ($p < 0.001$). During a mean follow-up of 7 ± 3.4 years, there were 894 (26%) deaths (442 attributed to cardiac causes) and 145 (4%) nonfatal MIs. The annual cardiac event rate was 2.5% in men and 1.2% in women with normal DSE. Independent predictors of cardiac events in patients with normal DSE using a Cox proportional hazards regression analysis were male gender (hazard ratio [HR]: 1.7 [range 1.1 to 2.8]), age (HR: 1.02 [range 1.01 to 1.04]), history of heart failure (HR: 3.4 [range 1.5 to 7.9]), previous MI (HR: 1.7 [range 1.1 to 2.8]), and diabetes (HR: 2.4 [range 1.3 to 4.5]). Independent predictors of cardiac events in patients with an abnormal DSE were age (HR: 1.03 [range 1.02 to 1.04]), history of heart failure (HR: 1.7 [range 1.3 to 2.1]), diabetes (HR: 1.4 [range 1.1 to 1.8]), heart rate at rest (HR: 2.8 [range 1.4 to 5.8]), wall motion abnormalities at rest (HR: 1.06 [range 1.04 to 1.09]), and ischemia on DSE (HR: 1.04 [range 1.02 to 1.07]). Myocardial ischemia was an independent predictor of cardiac events in both men and women.

CONCLUSIONS Dobutamine stress echocardiography provides independent prognostic information in both men and women. In patients with normal DSE, gender is independently associated with cardiac events. The outcome of patients with abnormal DSE is not related to gender, after adjusting for stress echocardiographic abnormalities. (J Am Coll Cardiol 2005;45:93–7)

Coronary artery disease (CAD) is a leading cause of mortality and morbidity in industrialized countries, in men as well as in women (1). Previous studies of the effect of gender on long-term survival of patients with known or suspected CAD have yielded conflicting results (2,3). Clinical evaluation of CAD has traditionally been more challenging in women compared with men because of the lower prevalence of the disease, the higher incidence of referral bias, and the intrinsic performance of various modalities of stress testing. Dobutamine stress echocardiography (DSE) has been reported as an effective noninvasive tool in detecting CAD and assessing prognosis in women (4,5). There is a controversy regarding the presence of a gender-based difference in the accuracy of DSE in detecting CAD (5–7). However, gender differences in the predictors of outcome among patients with known or suspected CAD undergoing DSE have not been adequately studied. The aims of this study were: 1) to assess the predictors of cardiac death and nonfatal myocardial infarction (MI) during a long-term follow-up in men and women referred for DSE for evaluation of MI on DSE; and 2) to find whether gender has an impact on outcome after controlling for clinical variables and stress echocardiographic data.

From the *Department of Cardiology, Thoraxcenter, Erasmus MC, Rotterdam, the Netherlands; †Institute of Cardiology, S. Orsola Hospital, Bologna, Italy; ‡University of Nebraska Medical Center, Omaha, Nebraska; and the §Department of Cardiology, Leiden University Medical Center, Leiden, the Netherlands.

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MATERIALS AND METHODS

Patients. The study population consisted of 3,875 consecutive patients with limited exercise capacity and known or suspected CAD, referred for DSE between January 1990 and January 2003 at the Thoraxcenter, Rotterdam, the Netherlands. Follow-up was successful in 3,836 patients (99%). A total of 455 patients (12%) underwent early coronary revascularization in the first 60 days after DSE and were excluded from the analysis. The final population consisted of 3,381 patients. The protocol was approved by the Hospital Ethics Committee. All patients gave informed

Abbreviations and Acronyms

CAD = coronary artery disease
DSE = dobutamine stress echocardiography
HR = hazard ratio
MI = myocardial infarction

consent before the test. Clinical characteristics and indications for testing were entered into a computerized database before DSE. Known CAD was defined as documentation of previous MI or myocardial revascularization or angiographic documentation of significant coronary artery stenosis. Suspected CAD was defined as the presence of symptoms related to CAD or the evidence of an abnormal baseline electrocardiogram associated with the presence of cardiac risk factors for CAD.

Dobutamine stress protocol. Low- to high-dose DSE (up to 40 μg/kg/min plus 2 mg atropine, if necessary) was performed according to a standard protocol as previously reported (6). Test end points were achievement of target heart rate (85% of maximal age- and gender-predicted heart rate), maximal dose of dobutamine and atropine, extensive new wall motion abnormalities, >2 mV downsloping ST-segment depression measured 80 ms after the J point compared with baseline, hypertension (blood pressure >240/120 mm Hg), a decrease in systolic blood pressure of >40 mm Hg compared with at rest, significant arrhythmias, or any intolerable adverse effect considered to be the result of dobutamine or atropine.

Echocardiographic imaging and interpretation. Two-dimensional echocardiographic images were acquired at rest, during dobutamine stress, and during recovery using standard views. Regional wall motion and systolic wall thickening were scored on a five-point scale using a standard 16-segment left ventricular model. 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. A biphasic response in an akinetic or severely hypokinetic segment was considered as an ischemic response. Ischemia was not considered present when akinetic segments at rest became dyskinetic during stress. For each patient, a wall motion score index was calculated by dividing the sum of segment scores by the total number of interpreted segments.

Follow-up. Follow-up data collection was performed by contacting the patient's general practitioner and by review of hospital records. The date of the last review or consultation was used to calculate follow-up time. Follow-up events noted were overall mortality and hard cardiac events (nonfatal MI and cardiac death). Myocardial revascularization procedures were also noted.

Statistical analysis. Continuous data were expressed as mean values ± SD. The Student *t* test was used to analyze continuous data and the chi-square test was used for differences between proportions. Univariate and multivariate Cox proportional hazard regression models (BMDP Statistical Software Inc., Los Angeles, California) were used to identify independent predictors of follow-up events (8). Variables were selected in a stepwise forward selection manner with entry and retention set at a significance level of

Table 1. Clinical Characteristics

	Men (n = 2,276)	Women (n = 1,105)	p Value
Age, yrs (SD)	61.6 ± 13	60.6 ± 11	0.03
Hypertension (%)	604 (27)	401 (36)	< 0.001
Hypercholesterolemia (%)	1,222 (54)	733 (66)	< 0.001
Smoking (%)	747 (33)	241 (22)	< 0.001
History of typical angina (%)	675 (30)	286 (26)	0.02
History of atypical angina (%)	301 (13)	289 (26)	< 0.001
Diabetes mellitus (%)	334 (15)	133 (12)	0.3
History of heart failure (%)	107 (5)	110 (10)	< 0.001
Previous myocardial infarction (%)	992 (44)	264 (24)	< 0.001
Beta-blockers (%)	754 (33)	362 (33)	0.8
Calcium-channel blockers (%)	543 (24)	273 (25)	0.6
ACE inhibitors (%)	588 (26)	257 (23)	0.1
Diuretics (%)	313 (14)	164 (15)	0.4
Nitrates (%)	726 (32)	305 (28)	0.01
Indication for DSE			
Diagnosis of CAD (%)	1,230 (54)	770 (70)	< 0.0001
Preoperative evaluation before non-cardiac surgery (%)	764 (34)	253 (23)	< 0.0001
Risk stratification after myocardial infarction (%)	280 (12)	84 (8)	< 0.0001

ACE = angiotensin-converting enzyme; CAD = coronary artery disease; DSE = dobutamine stress echocardiography.

Table 2. Dobutamine Stress Echocardiographic Data

	Men (n = 2,276)	Women (n = 1,105)	p Value
Heart rate at rest (beats/min)	72 ± 14	74 ± 14	< 0.0001
Heart rate at peak (beats/min)	131 ± 15	126 ± 13	< 0.0001
Rest systolic blood pressure (mm Hg)	121 ± 24	125 ± 25	< 0.0001
Peak systolic blood pressure (mm Hg)	146 ± 31	148 ± 27	0.09
Rest rate-pressure product	9,451 ± 2,497	10,035 ± 2,641	< 0.0001
Peak rate-pressure product	19,330 ± 4,544	18,718 ± 3,867	0.0002
Maximal dobutamine dose (μg/kg/min)	36 ± 7	33 ± 9	< 0.0001
Atropine use, patients (%)	739 (32)	270 (24)	< 0.0001
Angina during dobutamine stress (%)	420 (18)	148 (13)	< 0.0001
ST-segment depression (%)	652 (29)	206 (19)	< 0.0001
Resting wall motion score index	1.5 ± 0.6	1.3 ± 0.5	< 0.0001
Number of ischemic segments	3.6 ± 4.9	2.3 ± 4.1	< 0.0001
Normal DSE, patients (%)	687 (30)	483 (44)	< 0.0001
Resting abnormalities, patients (%)	395 (17)	206 (19)	0.4
New or worsening wall motion abnormalities, patients (%)	117 (5)	52 (5)	0.6
Resting plus new or worsening wall motion abnormalities, patients (%)	1,077 (47)	364 (33)	< 0.0001

Abbreviations as in Table 1.

0.05. The probability of survival was calculated using the Kaplan-Meier method, and survival curves were compared using the log-rank test. A p value <0.05 was considered statistically significant.

RESULTS

Patient characteristics and hemodynamic response. Mean age was 61 ± 10 years. There were 2,276 men (67%) and 1,105 women (33%). Clinical and hemodynamic data are presented in Tables 1 and 2, respectively. Arrhythmias were non-sustained ventricular tachycardia in 124 patients (4%), atrial fibrillation in 43 patients (1%), severe hypotension (decrease in systolic blood pressure >40 mm Hg compared with baseline) in 33 patients (1%), and ventricular fibrillation in four patients (0.1%). Defibrillation was successful and no electrocardiographic or cardiac enzymatic changes suggestive of MI were observed in these four patients. The test was terminated for achievement of the target heart rate in 3,009 patients (89%), maximal dobutamine/atropine dose in 101 patients (3%), ST-segment changes in 99 patients (3%), arrhythmias in 30 patients (1%), angina in 40 patients (1%), abnormal blood pressure in 38 patients (1%), and other symptoms in 64 patients (2%).

Echocardiographic data and outcome. Dobutamine stress echocardiography was normal in 687 men (30%) and 483 women (44%) ($p < 0.0001$). Ischemia on DSE was detected in 1,194 men (52%) and 416 women (38%) ($p < 0.0001$); of these patients 1,077 men (47%) and 364 women (33%) had resting wall motion abnormalities as well ($p < 0.0001$).

During a mean follow-up of 7 ± 3.4 years, there were 894 deaths (26%), of which 442 (13%) were attributed to cardiac causes (Table 3). Men had a higher annual total mortality rate (5.7% vs. 3.9%) and cardiac event rate (4.2% vs. 2.6%) compared with women (both $p < 0.0001$). Of the 372 patients (11%) who did not reach the target heart rate during DSE, 93 (25%) had normal DSE, 19 (5%) had ischemia, 74 (20%) had fixed wall motion abnormalities, and 186 (50%) had both ischemia and fixed wall motion abnormalities.

Predictive value of clinical data and test results. There were 1,170 patients (35%) with normal DSE. Independent clinical predictors of hard cardiac events in these patients were male gender (hazard ratio [HR]: 1.7 [range 1.1 to 2.8]), age (HR: 1.02 [range 1.01 to 1.04]), history of heart failure (HR: 3.4 [range 1.5 to 7.9]), previous MI (HR: 1.7 [range 1.1 to 2.8]), and diabetes (HR: 2.4 [range 1.3 to 4.5]). Independent predictors of cardiac events in patients with abnormal DSE were age (HR: 1.03 [range 1.02 to 1.04]), history of heart failure (HR: 1.7 [range 1.3 to 2.1]), diabetes (HR: 1.4 [range 1.1 to 1.8]), heart rate at rest (HR: 2.8 [range 1.4 to 5.8]), wall motion abnormalities at rest (HR: 1.06 [range 1.04 to 1.09]), and ischemia on DSE (HR: 1.04 [range 1.02 to 1.07]).

Univariate and multivariate predictors of hard cardiac events evaluated separately in men and women are shown in Tables 4 and 5, respectively. Resting wall motion score index and ischemia on DSE were predictive of cardiac events in both genders. Kaplan-Meier survival curves for the end point of cardiac death/nonfatal infarction are presented

Table 3. Follow-Up Events in Both Genders

	Men (n = 2,276)	Women (n = 1,105)	p Value
All death (%)	678 (30)	216 (20)	< 0.0001
Cardiac death (%)	335 (15)	107 (10)	< 0.0001
Nonfatal myocardial infarction (%)	113 (5)	32 (3)	0.007
Hard cardiac events (%)	448 (20)	139 (13)	< 0.0001
Late revascularization (%)	576 (25)	178 (16)	< 0.0001
Coronary angioplasty (%)	271 (12)	106 (9)	< 0.0001

Table 4. Univariate Predictors of Hard Cardiac Events

Model	Men			Women		
	HR	95% CI	p Value	HR	95% CI	p Value
Smoking	1.4	1.1–1.7	0.0008			
History of heart failure	3.6	2.7–4.8	< 0.0001	3.5	2.1–5.8	< 0.0001
Diabetes mellitus	1.4	1.0–1.9	0.01	1.8	1.1–3.0	0.005
Previous myocardial infarction	2.1	1.7–2.5	< 0.0001	3.7	2.6–5.4	< 0.0001
ST-segment depression	1.6	1.3–2.0	< 0.0001			
Target heart rate				1.6	1.1–2.3	0.01
Wall motion score index at rest	2.36	2.24–2.93	< 0.0001	3.70	2.85–4.70	< 0.0001
Abnormal segments at rest	1.7	1.4–2.2	< 0.0001	2.2	1.5–3.2	< 0.0001
New or worsening wall motion abnormalities	1.6	1.3–2.0	< 0.0001	2.4	1.7–3.6	< 0.0001

CI = confidence interval; HR = hazard ratio.

in Figure 1. In patients with normal DSE, the annual hard cardiac event rate during seven years of follow-up was 2.5% in men and 1.2% in women ($p < 0.0001$). There was no difference in annual hard cardiac event rate between men and women with wall motion abnormalities at rest (2.9% vs. 2.1%, $p = 0.1$) or men and women with both rest and new wall motion abnormalities (5.9% vs. 4.6%, $p = 0.3$). Survival curves according to the results of DSE are shown in Figure 2 (men) and Figure 3 (women).

DISCUSSION

This study demonstrated an independent prognostic value of DSE for the prediction of cardiac events in both men and women during a long-term mean follow-up of seven years.

In patients with normal DSE, male gender remained an independent predictor of cardiac death and nonfatal MI after adjustment for other clinical variables. In patients with abnormal DSE the outcome was related to the severity of left ventricular dysfunction and inducible ischemia on DSE, but not to the gender. These data indicate that women with abnormal DSE should be treated as aggressively as men considering the clinical and echocardiographic risk profiles, as the risk imposed by these parameters was not gender related.

The underlying cause for the association of male gender with a higher cardiac event rate among patients with normal DSE is not clear. One explanation could be a gender-related difference in the prevalence and/or progression of non-obstructive coronary arterial lesions that were not severe enough to induce ischemia on DSE in the group with normal DSE. Another explanation could be a gender difference in the diagnostic accuracy of DSE, with some studies showing a better accuracy of DSE in women than in men (6). However, there is controversy among published reports regarding this issue, with some studies reporting better accuracy in men (7) and others reporting similar accuracy in both genders (5).

The association of higher heart rate at rest with adverse outcome may be related to onset of autonomic dysfunction as an early compensatory mechanism with incipient heart failure (9). Some investigators suggested that sympathetic overactivity could be the common factor acting on cholesterol, heart rate, pulse pressure, and arterial stiffness with subsequent increase in cardiac workload (10,11).

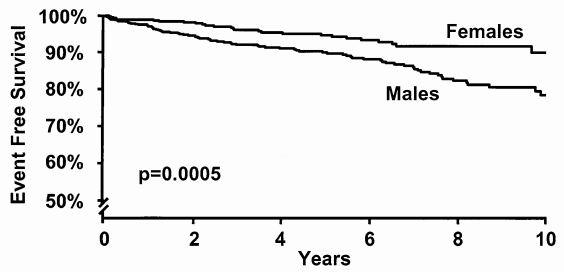
Comparison with previous studies. Data in published reports regarding the impact of gender on long-term prognosis of patients with CAD are inconsistent. Few studies have specifically focused on gender differences in the predictors of outcome after noninvasive stress testing. Although some of these studies showed incremental prognostic value of stress imaging techniques in both genders, most of these studies did not specifically address the impact of gender on survival after adjusting for other clinical and stress imaging parameters (12–14).

Study limitations. Patients with chronic non-cardiac diseases such as end-stage renal disease or chronic obstructive pulmonary disease were not excluded from the study. These patients may be at a higher risk for cardiac death despite a

Table 5. Multivariate Predictors of Hard Cardiac Events

Model	Men			Women		
	HR	95% CI	p Value	HR	95% CI	p Value
Age*	1.03	1.02–1.04	< 0.0001	1.09	1.04–1.2	< 0.0001
Smoking	1.2	1.0–1.5	0.05			
History of heart failure	1.7	1.4–2.3	0.005			
Diabetes mellitus	1.4	1.1–1.9	0.04			
Heart rate at rest	2.4	1.1–5.1	0.02			
Wall motion score index at rest	1.7	1.4–2.0	< 0.0001	4.3	2.8–6.7	0.001
New or worsening wall motion abnormalities	2.2	1.7–2.9	< 0.0001	3.2	1.7–6.3	0.0003

*Hazard ratios referred per year of age.
Abbreviations as in Table 4.



Patients at risk:

Females	483	314	234	151	67	21
Males	687	410	240	315	214	35

Figure 1. Kaplan-Meier survival curves (end point of hard cardiac events) in men and women with normal dobutamine stress echocardiography.

negative stress test for ischemia. Patients enrolled in January 2003 had a short follow-up period. Finally, the study enrolled patients over 13 years with implementation of new changes in imaging such as second harmonic imaging and myocardial contrast overtime. Differences in accuracy related to the use of these methods may have had an impact on the results.

Clinical implications and conclusions. Dobutamine stress echocardiography provides independent prognostic information for the prediction of cardiac events during long-term follow-up in both genders. The prognosis after a normal DSE is more favorable in women than in men, after correction for clinical variables. The outcome of patients with abnormal DSE is related to severity of left ventricular dysfunction and ischemia on DSE, but not related to gender after adjusting for other variables. Therefore, women with abnormal DSE should be treated as aggressively as men, because the risk imposed by echocardiographic abnormalities is not gender related.

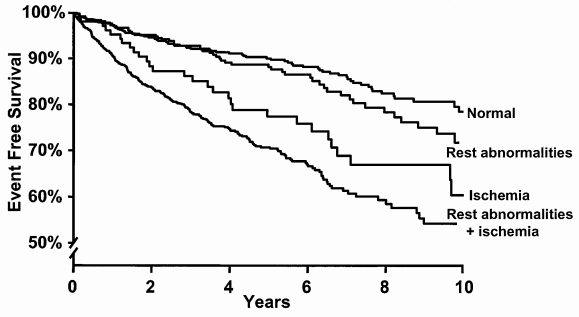


Figure 2. Kaplan-Meier survival curves (end point of hard cardiac events) in men according to results of dobutamine stress echocardiography.

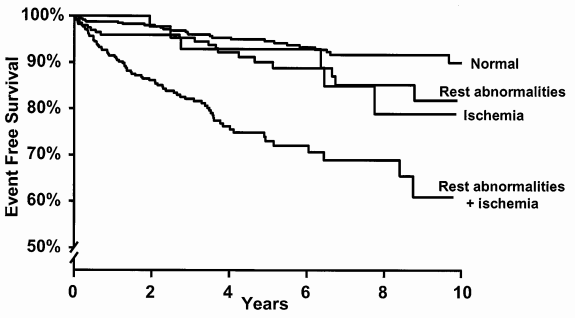


Figure 3. Kaplan-Meier survival curves (end point of hard cardiac events) in women according to results of dobutamine stress echocardiography.

Reprint requests and correspondence: Dr. Don Poldermans, Department of Cardiology, Thoraxcenter Room Ba 300, Erasmus MC, Dr. Molewaterplein 40, 3015 GD Rotterdam, the Netherlands. E-mail: d.poldermans@erasmusmc.nl.

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Chapter 3

Comparison of All-Cause Mortality in Women with Known or Suspected Coronary Artery Disease Referred for Dobutamine Stress Echocardiography with Normal versus Abnormal Test Results

Biagini E, Elhendy A, Schinkel AFL, Rizzello V,
van Domburg RT, Krenning BJ, Schouten O, Sozzi FB,
Branzi A, Rocchi G, Simoons ML, Bax JJ, Poldermans D

Am J Cardiol 2005;95:1072-1075

Comparison of All-Cause Mortality in Women With Known or Suspected Coronary Artery Disease Referred for *Dobutamine* Stress Echocardiography With Normal Versus Abnormal Test Results

Elena Biagini, MD, Abdou Elhendy, MD, Arend F.L. Schinkel, MD, Vittoria Rizzello, MD, Ron T. van Domburg, PhD, Boudewijn J. Krenning, MD, Olaf Schouten, MD, Fabiola B. Sozzi, MD, Angelo Branzi, MD, Guido Rocchi, MD, Maarten L. Simoons, MD, Jeroen J. Bax, MD, and Don Poldermans, MD

The presence of myocardial ischemia during dobutamine stress echocardiography is independently associated with an increased risk of all-cause mortality in women after adjustment for clinical data. This association is observed in patients who have proved coronary artery disease and in patients who have no history of coronary artery disease. ©2005 by Excerpta Medica Inc.

(Am J Cardiol 2005;95:1072–1075)

This study evaluated predictors of all-cause mortality in women who had known or suspected coronary artery disease (CAD) and were referred for dobutamine stress echocardiography (DSE).

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The study population consisted of 1,172 consecutive women who had limited exercise capacity and were referred for DSE between January 1990 and January 2003 at the Thoraxcenter (Rotterdam, The Netherlands). Follow-up was successful in 1,168 patients (99%). Sixty-three patients (5%) underwent early coronary revascularization ≤60 days after DSE. These patients were excluded from analysis because referral to myocardial revascularization ≤60 days after stress testing tends to be based on results of the test, whereas referral to revascularization at >60 days after testing tends to be based on worsening of the patient's clinical status.[1] The final population consisted of 1,105 patients. The protocol was approved by the hospital ethics committee. All patients gave informed consent before the test.

A structured interview and clinical history were taken and cardiac risk factors were assessed before DSE. Cardiac risk factors included a history of current or stable angina pectoris, previous myocardial infarction, congestive heart failure, hypertension, diabetes mellitus, and hypercholesterolemia. Congestive heart failure was defined according to Framingham criteria.[2] Hypertension was defined as a blood pressure ≥140/90 mm Hg or use of antihypertensive medication. Diabetes mellitus was defined as a fasting glucose level ≥7.8 mmol/L or the need for insulin or oral hypoglycemic agents. Hypercholesterolemia was defined as a total cholesterol level ≥6.4 mmol/L or use of a lipid-lowering medication. History of CAD was defined as previous myocardial infarction, angiographically documented coronary artery stenosis, and/or myocardial revascularization.

Dobutamine/atropine stress testing was performed according to a standard protocol as previously reported.[3] After obtaining a baseline echocardiogram, dobutamine was administered intravenously, starting at a dose of 10 μg/kg/min for 3 minutes (5 μg/kg/min in patients who had left ventricular dysfunction at rest). Incremental dobutamine doses of 10 μg/kg/min were given at 3-minute intervals to a maximum dose of 40 μg/kg/min. If the test end point was not reached at a dobutamine dose of 40 μg/kg/min, atropine (≤2 mg) was given intravenously. Blood pressure, heart rate, and electrocardiography were constantly monitored. Test end points were achievement of a target heart rate (85% of maximum age- and gender-predicted heart rates), maximal doses of dobutamine and atropine, extensive new wall motion abnormalities, >2 mV downsloping ST-segment depression measured 80 ms after the J point compared with baseline, hypertension (blood pressure >240/120 mm Hg), a decrease in systolic blood pressure of >40 mm Hg compared with at rest, significant arrhythmias, or any intolerable adverse effect considered to be the result of dobutamine or atropine. An intravenous β blocker (metoprolol 1 to 5 mg) was available to reverse the adverse effects of dobutamine/atropine.

Two-dimensional echocardiographic images were acquired at rest, during dobutamine stress, and during recovery using the standard views. Echocardiograms were recorded in a quad-screen format. Two experienced observers who were unaware of the clinical data scored the echocardiograms using a standard 16-segment model. In case of disagreement, a consensus decision was achieved by a third observer. Regional wall motion and systolic wall thickening were scored on a 5-point scale. Ischemia was defined as new or worsened wall motion abnormalities during stress that was indicated by a wall motion score increase of ≥1

From the Department of Cardiology, Thoraxcenter, Erasmus MC, Rotterdam, The Netherlands; the Department of Cardiology, Leiden University Medical Center, Leiden, The Netherlands; and the Institute of Cardiology, S. Orsola Hospital, Bologna, Italy. Dr. Poldermans's address is: Department of Cardiology, Thoraxcenter Room Ba 300, Erasmus MC, Dr. Molewaterplein 40, 3015 GD Rotterdam, The Netherlands. E-mail: d.poldermans@erasmusmc.nl. Manuscript received October 25, 2004; revised manuscript received and accepted December 16, 2004.

TABLE 1 Clinical Characteristics

Age (yrs)	61 ± 12
Systemic hypertension*	401 (36%)
Hypercholesterolemia†	251 (23%)
Smoker	241 (22%)
Diabetes mellitus	133 (12%)
Previous heart failure	110 (10%)
Previous myocardial infarction	264 (76%)
β Blockers	362 (33%)
Calcium channel blockers	273 (25%)
Angiotensin-converting enzyme inhibitors	257 (23%)
Diuretics	164 (15%)
Nitrates	305 (28%)

Values are mean ± SD or numbers of patients (percentages).
*Hypertension was defined as a blood pressure ≥140/90 mm Hg or use of antihypertensive medication.
†Hypercholesterolemia was defined as a total cholesterol level ≥6.4 mmol/L or use of a lipid-lowering medication.

TABLE 2 Dobutamine Stress Echocardiographic Data

	Normal (n = 483)	Abnormal (n = 622)	p Value
Heart rate at rest (beats/min)	75 ± 14	74 ± 14	0.4
Heart rate at peak (beats/min)	126 ± 12	126 ± 14	0.7
Systolic blood pressure at rest (mm Hg)	127 ± 25	123 ± 22	0.01
Peak systolic blood pressure (mm Hg)	150 ± 25	147 ± 27	0.1
Rate–pressure product at rest	10,236 ± 2,633	9,886 ± 2,640	0.03
Peak rate–pressure product	18,972 ± 3,686	18,529 ± 3,989	0.06
Maximal dobutamine dose (μg/kg/min)	33 ± 9	33 ± 9	0.8
Atropine use	104 (21%)	166 (27%)	0.06
Angina during dobutamine stress	54 (11%)	94 (15%)	0.06
ST-segment depression	77 (16%)	129 (21%)	0.05
Wall motion score index at rest	1.00 ± 0.5	1.64 ± 0.6	<0.0001
Wall motion abnormalities at rest	0	52 (8%)	<0.0001
Ischemia	0	206 (33%)	<0.0001
Abnormalities plus ischemia at rest	0	364 (58%)	<0.0001
No. of ischemic segments	0	2.4 ± 3.6	<0.0001

TABLE 3 Univariate and Multivatiate Predictors of Mortality in the Entire Population

	Univariate		Multivariate	
	HR	95% CI	HR	95% CI
Age (yrs)	1.03	1.01–1.04	1.1	1.06–1.14
History of CAD	1.6	1.2–2.1		
Previous heart failure	2.9	1.8–4.5	2.7	1.5–4.7
Smoking	2.1	1.1–3.2	2.3	1.4–3.1
Systemic hypertension	1.5	1.1–2.5	1.7	1.1–2.6
Previous myocardial infarction	1.9	1.4–2.6		
Wall motion score index at rest	1.92	1.21–3.12	1.7	1.1–2.8
Myocardial ischemia	1.4	1.01–1.9	1.5	1.1–2.7

CI = confidence interval; HR = hazard ratio.

grade in ≥1 segment. Ischemia was not considered present when akinetic segments at rest became dyskinetic during stress. For each patient, a wall motion score index was calculated by dividing the sum of segment scores by the total number of interpreted segments.

Follow-up was obtained by review of the hospital records and by contacting general practitioners. In addition, vital status was verified through civil registries. If no further information from the general practitioner could be obtained, patients were approached after retrieval of vital status. The primary follow-up event was death from any cause. Myocardial revascularization and nonfatal myocardial infarction were also noted.

Continuous data were expressed as mean ± SD. Student's *t* test was used to analyze continuous data. Differences between proportions were compared with chi-square test. Univariate and multivariate Cox's proportional hazard regression models (BMDP Statistical Software Inc., Los Angeles, California) were used to identify independent predictors of death.[4] Variables were selected in a stepwise forward selection manner, with entry and retention set at a significance level of 0.05. The risk of a variable was expressed as a hazard ratio with a corresponding 95% confidence interval. The probability of survival was calculated with the Kaplan-Meier method, and survival curves were compared with the log-rank test. A p value <0.05 was considered statistically significant.

Mean age was 61 ± 12 years. Clinical and hemodynamic data are presented in Tables 1 and 2, respectively. There were 346 patients (31%) who had known CAD and 759 patients (69%) who had no history of CAD. Heart rate and systolic blood pressure increased significantly from rest to peak stress ($p<0.001$). Arrhythmias during the test were nonsustained ventricular tachycardia in 25 patients (2%) and atrial fibrillation in 11 patients (1%). Hypotension occurred in 9 patients (1%). The test was terminated for achievement of the target heart rate in 1,004 patients (91%), maximal dobutamine/atropine dose in 29 (3%), chills or nausea in 31 (3%), arrhythmias in 18 (1%), abnormal blood pressure in 12 (1%), and ST-segment changes in 11 patients (1%).

Dobutamine stress echocardiograms were normal in 483 patients (44%). Fixed wall motion abnormalities were detected in 206 patients (19%) and ischemia (new or worsening wall motion abnormalities) was detected in 416 patients (38%). Among patients who had ischemia, 364 (33%) also had wall motion abnormalities at rest.

During a mean follow-up of 5.1 ± 3.1 years (range 2 months to 9.5 years), there were 216 deaths (19%). Thirty-two patients (3%) developed nonfatal myocardial infarction. Late myocardial revascularization was performed in 178 patients (16%).

Univariable and multivariable predictors of death in the entire population are presented in Table 3.

TABLE 4 Univariate and Multivariate Predictors of Mortality in Women With and Without a History of Coronary Artery Disease (CAD)

	Univariate		Multivariate	
	HR	95% CI	HR	95% CI
History of CAD				
Age (yrs)	1.01	0.99–1.03	1.1	1.03–1.17
Previous myocardial infarction	1.9	1.1–3.3		
Previous heart failure	2.1	1.3–3.2	3.2	1.4–7.5
Smoking	1.8	1.1–3.5	2.3	1.1–5.5
Systemic hypertension	1.6	1.0–3.1	2.3	1.1–5.1
Wall motion score index at rest	1.7	1.1–2.8		
Myocardial ischemia	2.2	1.1–3.9	2.1	1.1–4.5
No history of CAD				
Age (yrs)	1.04	1.02–1.07	1.1	1.05–1.16
Previous heart failure	2.2	1.3–3.6	2.2	1.1–5.2
Smoking	1.9	1.2–4.1	2.4	1.2–5.0
Diabetes mellitus	2.1	1.1–4.9	2.4	1.2–5.0
Myocardial ischemia	2.0	1.1–4.0	2.2	1.2–4.3

Abbreviations as in Table 3.

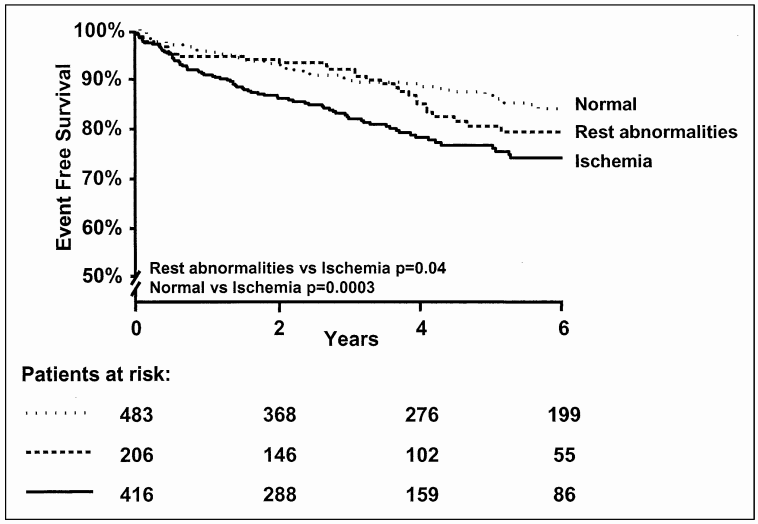

FIGURE 1. Kaplan-Meier survival curves (all-cause mortality) in women according to dobutamine stress echocardiographic results.

Independent clinical predictors were age, history of heart failure, smoking, and hypertension. Multivariate analysis demonstrated that DSE provided incremental prognostic information for the prediction of events over clinical and stress test data. Independent echocardiographic predictors were wall motion score index at rest and the presence of ischemia during DSE. Among the 346 patients who had previous CAD, independent predictors of death were age, history of heart failure, smoking, hypertension, and the presence of ischemia (Table 4). In patients who had no history of CAD, independent predictors of death were age, history of heart failure, smoking, diabetes mellitus, and the presence of ischemia (Table 4). Kaplan-Meier survival curves based on the results of DSE are presented in Figure 1. The annual death rates were 2.7% in women who had a normal dobutamine stress echocardiogram, 3.4% in patients who had fixed wall motion abnormalities, and 4.4% in patients who had ischemia. The annual event rate (cardiac death or nonfatal myocardial infarction) for women who had a normal dobutamine stress echocardiogram was 1.3% (Figure 2).

• • •

This study assessed the predictors of all-cause mortality in 1,105 women who had known or suspected CAD and underwent DSE. During follow-up, 216 women (19%) died. Annual mortality rates were 2.7% in women who had a normal dobutamine stress echocardiogram and 4.4% in women who had new wall motion abnormalities ($p < 0.001$). The annual event rate (cardiac death or nonfatal myocardial infarction) for women who had a normal dobutamine stress echocardiogram was 1.3%. Predictors of mortality were age, history of heart failure, smoking, hypertension, wall motion score index at rest, and presence of ischemia during DSE. Multivariate analysis demonstrated that DSE provided incremental prognostic information for the prediction of events over clinical and stress test data.

Information on the utility of DSE to predict all-cause mortality in women is scarce. Cortigiani et al[5] evaluated 456 women (mean age 63 ± 10 years) who underwent pharmacologic stress echocardiography with dipyridamole (305 patients) or dobutamine (151 patients) for evaluation of chest pain. During a mean follow-up of 32 ± 19 months, 3 deaths (0.6%) and 10 myocardial infarctions (2%) occurred. The presence of ischemia during the stress test was the only independent predictor of cardiac death and myocardial infarction. The death rate was low in that study and analysis was based on a composite end point. Previous studies have demonstrated an incremental prognostic value of DSE for prediction of cardiac death and other composite end points of cardiac events.[6–8] However, a few studies used all-cause mortality as the primary end point. Marwick et al[6] studied 3,156 patients (mean age 63 ± 12 years; 1,355 women) who underwent DSE. After a mean follow-up of 3.8 ± 1.9 years, death occurred in 716 patients (23%). Ischemia was an independent predictor of total mortality rate. However, the study did not analyze the incremental prognostic value of DSE in women separately. Studies of prognostic utility of stress myocardial perfusion imaging in women have focused mainly on composite end points or cardiac death.[9–11] A recent study[12] demonstrated an

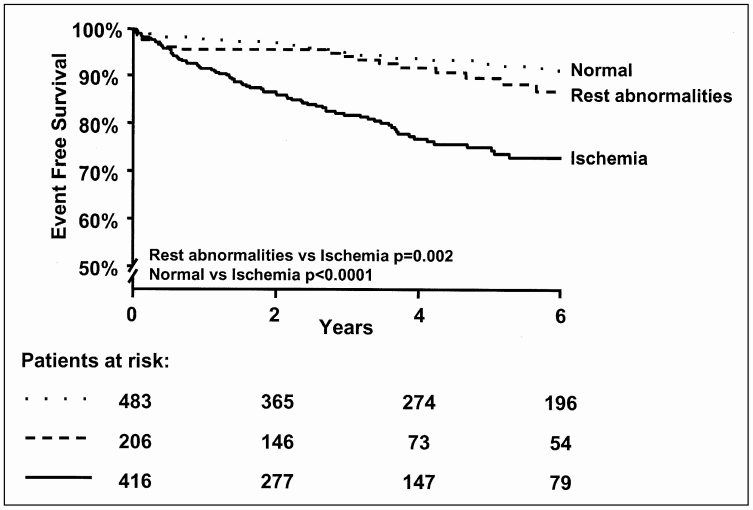

FIGURE 2. Kaplan-Meier survival curves (cardiac death or nonfatal myocardial infarction) in women according to dobutamine stress echocardiographic results.

incremental value of stress technetium-99m tetrofosmin imaging in predicting all-cause mortality in 503 women (mean age 58 ± 19 years) who had known or suspected CAD and were followed for 3.5 years.

In the present study, a history of heart failure, smoking, hypertension, and diabetes were independent clinical predictors of mortality. Previous epidemiologic studies have shown that risk factors, such as hypertension, current smoking, and diabetes considered individually or in association are positively associated with all-cause mortality in women.[13–15] Moreover, a history of diabetes, particularly if associated with known CAD and heart failure, has been shown to identify a particularly high-risk group for cardiac death and all-cause mortality in women.[15] The effect of left ventricular function and ischemia was not evaluated in these studies.

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Chapter 4

Long-term Prediction of Mortality in the Elderly by Dobutamine Stress Echocardiography

Biagini E, Elhendy A, Schinkel AFL, Rizzello V, Bax JJ, Sozzi FB, Kertai MD, van Domburg RT, Krenning BJ, Branzi A, Rapezzi C, Simoons ML, Poldermans D

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Abstract

Background. Dobutamine stress echocardiography (DSE) was shown to provide incremental prognostic information. However, its role in the prediction of mortality in the elderly is not well defined. We assessed the value of DSE in the prediction of mortality and hard cardiac events during long-term follow-up in patients older than 65 years.

Methods. We studied 1434 patients >65 years (mean age 72 ± 3 years) who underwent DSE for evaluation of coronary artery disease. Ischemia was defined as new or worsening wall motion abnormalities. Follow-up events were total mortality and hard cardiac events (cardiac mortality and nonfatal myocardial infarction). Multivariable Cox regression analysis was used to identify the independent predictors of follow-up events.

Results. Ischemia was detected in 675 (47%) patients. Five hundred-six patients (35%) had a normal study and 253 (18%) fixed wall motion abnormalities. During a mean follow-up of 6.5 years, 532 (37%) deaths occurred, of which 249 (17%) were due to cardiac causes. A nonfatal myocardial infarction occurred in 45 (3%) patients. Independent predictors of all cause mortality in a multivariate analysis model were age (HR:1.06 [1.05-1.08]), male gender (HR:1.5 [1.2-1.8]), hypertension (HR:1.2 [1.1-1.4]), smoking (HR:1.3 [1.1-1.6]), diabetes (HR:1.4 [1.1-1.8]), rest wall motion abnormalities (HR:1.07 [1.06-1.09]), and ischemia (HR:1.3 [1.1-1.6]). Independent predictors of hard cardiac events were age (HR:1.07 [1.05-1.09]), male gender (HR:1.3 [1.1-1.7]), smoking (HR:1.3 [1.1-1.6]), diabetes (HR:1.6 [1.2-2.2]), rest wall motion abnormalities (HR:1.13 [1.12-1.16]), and ischemia (HR:2.1 [1.5-2.8]).

Conclusions. DSE provides independent prognostic information to predict all cause mortality and hard cardiac events in elderly patients.

Introduction

Demographic studies have shown that the elderly constitutes a rapidly expanding segment of our population. Coronary artery disease (CAD) is a major cause of morbidity and mortality in the elderly and becomes more prevalent with increasing age (1, 2). Technical advances in myocardial revascularization procedures have recently contributed to a high success rate of coronary artery bypass grafting and percutaneous coronary intervention in the elderly (3-6) with an improved clinical outcome (7). Exercise echocardiography has been demonstrated as a useful non-invasive tool for evaluation of CAD in the elderly (8). However, exercise stress testing is not feasible in many elderly patients (9), mostly because of non cardiac factors, such as arthritis, obstructive lung disease, claudication and poor physical conditioning. Dobutamine stress echocardiography (DSE) is a feasible alternative to exercise in these patients (10-12). Published studies of the prognostic value of DSE in the elderly are limited by inclusion of small number of patients, short-term follow-up and the use of composite end-points. Additionally, there are currently no data to suggest a role of DSE in the prediction of all cause mortality in the elderly. Accordingly, the aim of this study was to assess the long-term value of DSE for prediction of all cause mortality and hard cardiac events in a large number of patients with known or suspected CAD who are >65 years old.

Methods

Patients. The study population was composed of 1606 consecutive patients >65 years old referred for DSE for the evaluation of suspected or known CAD at the Thoraxcenter, Rotterdam between January 1988 and January 2003, who were unable to perform an adequate exercise test. Follow-up was successful in 1590 patients (99%). A total of 156 (10%) patients underwent early coronary revascularization in the first 60 days after the DSE. These patients were excluded from the analysis, because referral to myocardial revascularization in the first 60 days after stress testing tends to be based on the results of the test (13). Therefore, 1434 patients represented the final population. The protocol was approved by the Hospital Ethics Committee. All patients gave informed consent before the test. A structured interview and review of records were conducted prior to the stress test to obtain clinical history and to determine cardiac risk factors.

Dobutamine Stress Protocol. Low-high dose DSE (up to 40 μg/kg/min plus 2 mg atropine, if necessary) was performed according to a standard protocol as previously reported (12). Test end-points were achievement of target heart rate (85% of maximum age and gender predicted heart rate), maximal dose of dobutamine and atropine, extensive new wall motion abnormalities, >2 mV downsloping ST-segment depression measured 80 ms after the J point compared with baseline, hypertension (blood pressure >240/120 mmHg), a decrease in systolic blood pressure of >40 mmHg compared with at rest, significant arrhythmias, or any intolerable adverse effect considered to be the result of dobutamine or atropine. An intravenous β-blocker (metoprolol 1 to 5 mg) was available to reverse the adverse effects of dobutamine/atropine if these did not reverse spontaneously.

Echocardiographic Imaging and Interpretation. Two-dimensional echocardiographic images were acquired at rest, during dobutamine stress, and recovery. The echocardiograms were recorded in a quad-screen format. Two experienced observers, unaware of the clinical data, scored the echocardiograms using a standard 16-segment model. In case of disagreement, a consensus decision was achieved by a third observer. 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. A biphasic response in an akinetic or severely hypokinetic segment was considered as an ischemic response. Ischemia was not considered to be present when akinetic segments at rest became dyskinetic during stress. For each patient, a wall motion score index (WMSI) was calculated by dividing the sum of scores of visualized segments by the total number of these segments.

Follow-up. Follow-up data collection was performed by contacting the patients, general practitioners and by review of hospital records. The date of the last review or consultation was used to calculate follow-up time. Follow-up events noted were all causes of mortality and hard cardiac events (nonfatal myocardial infarction and cardiac death). Revascularization procedures were also noted. Cardiac death was defined as a death caused by acute myocardial infarction, significant cardiac arrhythmias, or refractory congestive heart failure. Sudden death occurring without another explanation was considered as cardiac death. Nonfatal myocardial infarction was defined by standard criteria of chest pain, cardiac enzymes and electrocardiographic changes.

Statistical Analysis. Continuous data were expressed as mean value ± SD. The Student's t test was used to analyze continuous data. Differences between proportions were compared using the Chi-square test. Univariate and multivariate Cox proportional hazard regression models (BMDP Statistical Software Inc., Los Angeles, California, USA) were used to identify independent predictors of end-points of interest (14). Variables were selected in a stepwise forward selection manner with entry and retention set at a significance level of 0.05. The risk of a variable was expressed as a hazard ratio with a corresponding 95% confidence interval. The incremental value of DSE over the clinical variables in the prediction of events was determined according to two models. In model I, the variable entered was the presence of new wall motion abnormalities during peak stress; in model II, the number of segments with new wall motion abnormalities at peak of DSE (extent of ischemia) was entered as a continuous variable. The probability of survival was calculated using the Kaplan-Meier method, and survival curves were compared using the log-rank test. A p value <0.05 was considered statistically significant.

Results

Patient Characteristics and Hemodynamic Response. The mean age was 72 ± 3 years, 965 (67%) were men, and 440 (31%) were over 75 years (mean 79 ± 3.2 years). Clinical characteristics are presented in Table 1.

Table 1. Clinical Characteristics in Patients with and without Hard Cardiac Events (Cardiac Death or Nonfatal Myocardial Infarction)

	All Patients (n= 1434)	Cardiac Events (n= 294)	No Cardiac Events (n= 1140)	P value
Age (years)	73 ± 5	73 ± 5	72 ± 5	0.04
Men	965 (67 %)	222 (75%)	743 (65%)	0.001
Hypertension	481 (33%)	90 (31%)	391 (34%)	0.3
Hypercholesterolemia	274 (19%)	50 (17%)	224 (20%)	0.3
Smoking	356 (25%)	88 (30%)	268 (23%)	0.03
Diabetes mellitus	151 (11%)	43 (15%)	108 (9%)	0.01
History of heart failure	180 (12%)	67 (23%)	113 (10%)	0.0001
Previous infarction	502 (35%)	148 (50%)	354 (31%)	0.0001
β-blockers	455 (32%)	80 (27%)	375 (33%)	0.07
Calcium channel blockers	366 (26%)	75 (26%)	291 (26%)	1
Nitrates	401 (28%)	121 (41%)	280 (25%)	0.001
Ace-inhibitors	382 (27%)	96 (33%)	286 (25%)	0.01

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

Dobutamine stress test data are presented in Table 2. Heart rate increased significantly from rest to peak stress. The mean maximal dobutamine dose was 35 ± 8 μg/kg/min. Atropine was used in 361 (25%) patients. Side effects were non-sustained ventricular tachycardia (<10 complexes) in 59 patients (4%), atrial fibrillation in 28 patients (2%), severe hypotension (decrease in systolic blood pressure >40 mm Hg compared to baseline) in 10 (0.7%) patients, and ventricular fibrillation in 2 (0.1%). Defibrillation was successful and no ECG or cardiac enzymatic changes suggestive of myocardial infarction were observed in these 2 patients. The test was terminated because of reaching the target heart rate in 1278 (89%) patients, maximal dose of dobutamine and atropine in 45 (3%) patients, ST-segment changes in 38 (3%) patients, minor symptoms in 30 (2%) patients, abnormal blood pressure in 15 (1%), arrhythmias in 14 (1%) and angina in 14 (1%) patients.

Table 2. Hemodynamic and Echocardiographic Data in Patients with and without Hard Cardiac Events

	All Patients (n= 1434)	Cardiac Events (n= 294)	No Cardiac Events (n= 1140)	P value
Heart rate at rest (beats/min)	71 ± 13	72 ± 13	71 ± 13	0.5
Heart rate at peak (beats/min)	122 ± 19	121 ± 20	123 ± 17	0.04
Rest systolic blood pressure (mmHg)	138 ± 25	136 ± 26	139 ± 25	0.06
Peak systolic blood pressure (mmHg)	134 ± 29	131 ± 29	135 ± 30	0.06
Rest rate pressure product	9934 ± 2503	9763±2392	9980±2675	0.2
Peak rate pressure product	16775 ± 4254	16410±4280	16868±4203	0.1
ST-segment depression, patients	348 (24%)	95 (32%)	253 (22%)	0.001
Resting wall motion score index	1.27 ± 0.47	1.55 ± 0.61	1.20 ± 0.37	<0.0001
Abnormal stress echocardiography, patients	928 (65%)	239 (81%)	689 (60%)	<0.0001
New or worsening wall motion abnormalities, patients	675 (47%)	202 (69%)	473 (41%)	<0.0001
Number of ischemic segments (n)	3.1 ± 4.7	4.9 ± 5.5	2.7 ± 4.3	<0.0001

Data are presented as number (%) of patients or mean value ± SD. Legend: n= Number.

Echocardiographic Data. Five hundred-six patients (35%) had a normal study, 253 (18%) patients had fixed wall motion abnormality and 675 (47%) patients had ischemia (new or worsening wall motion abnormalities). Among patients with ischemia, 586 (41%) had resting wall motion abnormalities as well. Among patients with resting wall motion abnormalities, resting WMSI was lower in patients who had no inducible ischemia during DSE as compared to patients who had ischemia (1.39 ± 0.38 vs 1.96 ± 0.62, p<0.0001).

Outcome. During a mean follow-up of 6.5 years (range 6 months-15 years), there were 532 (37%) deaths, of which 249 (17%) were attributed to cardiac causes. Forty-five (3%) patients had nonfatal myocardial infarction and 334 (9%) underwent late revascularization. Clinical, hemodynamic and echocardiographic data of patients with and without hard cardiac events are listed in Table 1 and 2. Patients with cardiac events had a higher incidence of ST-segment depression, a higher WMSI at rest and a higher incidence and extent of ischemia as compared to patients without events.

Predictive Value of Clinical Data and Test Results. Univariate and multivariate predictors of cardiac death/nonfatal myocardial infarction and all causes of mortality are shown in Table 3 and 4. Among clinical variables, age, male gender, smoking, and diabetes were multivariate independent predictors of cardiac death/nonfatal myocardial infarction and of all cause mortality. A history of hypertension was a predictor of all causes of mortality. The presence of rest wall motion abnormalities provided independent prognostic information for hard cardiac events and all cause mortality. Moreover, the presence and the extent of ischemia during DSE provided incremental information for both the end-points (Model I and II).

Table 3. Univariate and multivariate Predictors of Hard Cardiac Events

		Multivariate Analysis	
	Univariate	**Model I**	**Model II**
Clinical characteristics			
Age	1.05 (1.03-1.08)	1.07 (1.05-1.09)	1.05 (1.04-1.08)
Male sex	1.5 (1.2-1.9)	1.3 (1.1-1.7)	1.4 (1.1-1.9)
Smoking	1.3 (1.1-1.6)	1.3 (1.1-1.6)	NS
Diabetes Mellitus	1.5 (1.1-1.9)	1.6 (1.2-2.2)	1.6 (1.2-2.3)
Previous myocardial infarction	1.9 (1.5-2.3)	NS	1.3 (1.1-1.7)
History of heart failure	8.5 (0.8-94)	NS	NS
Stress test results			
Target heart rate	1.4 (1.1-1.8)	—	—
ST-segments changes	1.5 (1.2-1.8)	NS	NS
DSE parameters			
Abnormal segments at rest	1.13 (1.12-1.16)	1.09 (1.07-1.13)	1.06 (1.04-1.08)
New wall motion abnormalities	3.7 (2.8-4.7)	2.1 (1.5-2.8)	—
Number of ischemic segments	1.15 (1.13-1.18)	—	1.13 (1.11-1.16)

Data are presented as risk ratio and 95% confidence intervals.

Table 4. Univariate and multivariate Predictors of All Causes of Mortality

		Multivariate Analysis	
	Univariate	**Model I**	**Model II**
Clinical characteristics			
Age	1.06 (1.04-1.08)	1.06 (1.05-1.08)	1.05 (1.04-1.08)
Male sex	1.6 (1.4-1.9)	1.5 (1.2-1.8)	1.5 (1.3-1.9)
Hypertension	1.01 (0.8-1.2)	1.2 (1.1-1.4)	NS
Smoking	1.4 (1.2-1.6)	1.3 (1.1-1.6)	1.3 (1.1-1.5)
Diabetes mellitus	1.1 (0.9-1.3)	1.4 (1.1-1.8)	1.4 (1.1-1.9)
Previous myocardial infarction	1.3 (1.1-1.5)	NS	NS
History of heart failure	1.8 (1.5-2.1)	NS	NS
DSE parameters			
Abnormal segments at rest	1.07 (1.06-1.09)	1.06 (1.04-1.08)	1.05 (1.04-1.08)
New wall motion abnormalities	1.7 (1.68-1.76)	1.3 (1.1-1.6)	—
Number of ischemic segments	1.08 (1.07-1.10)	—	1.08 (1.06-1.10)

Data are presented as risk ratio and 95% confidence intervals.

Kaplan-Meier survival curves for the end-point of cardiac death/nonfatal myocardial infarction in patients with normal, fixed wall motion abnormalities and ischemia are presented in Figure 1. The combination of rest and inducible wall motion abnormalities identified the group with the highest risk of hard cardiac events ($p<0.0001$). At 5 years of follow-up, the annual hard cardiac events rate was 1.8% in patients with a normal test, 2.1% in patients with fixed wall motion abnormalities, 4.3% in patients with ischemia, and 8% in patients with both resting and inducible wall motion abnormalities.

Among patients with a normal DSE the annual hard cardiac event rate was 1.3% in patients 75 years or younger and 2.8% in patients older than 75 years ($p = 0.1$).

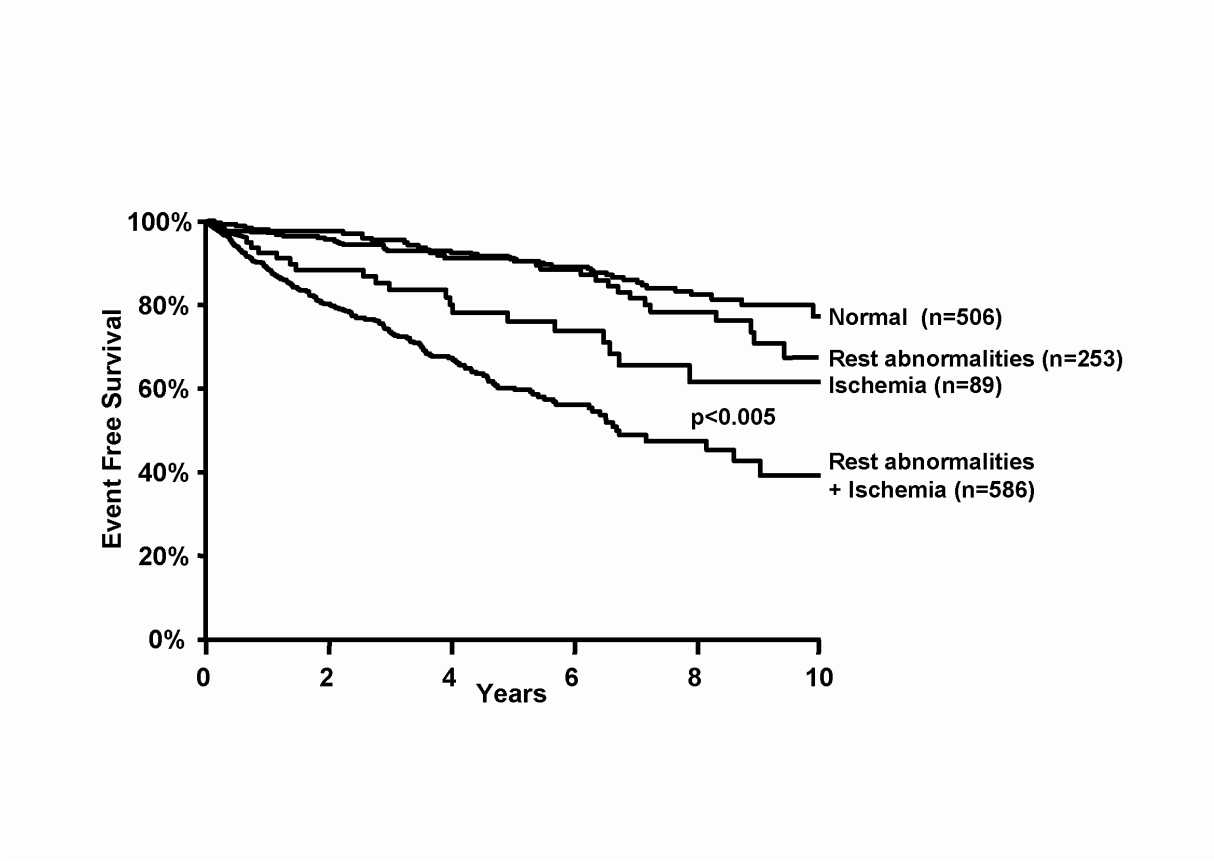

Figure 1. *Kaplan-Meier survival curves (end-point of cardiac death and nonfatal myocardial infarction) based on results of dobutamine stress echocardiography.*

Figure 2 illustrates the incremental contribution of resting wall motion abnormalities and ischemia during DSE to clinical data in predicting hard cardiac events and total mortality. Both resting and dobutamine induced wall motion abnormalities were incremental to clinical data in the prediction of each end-point. The major increment in prognostic information was made by resting left ventricular function.

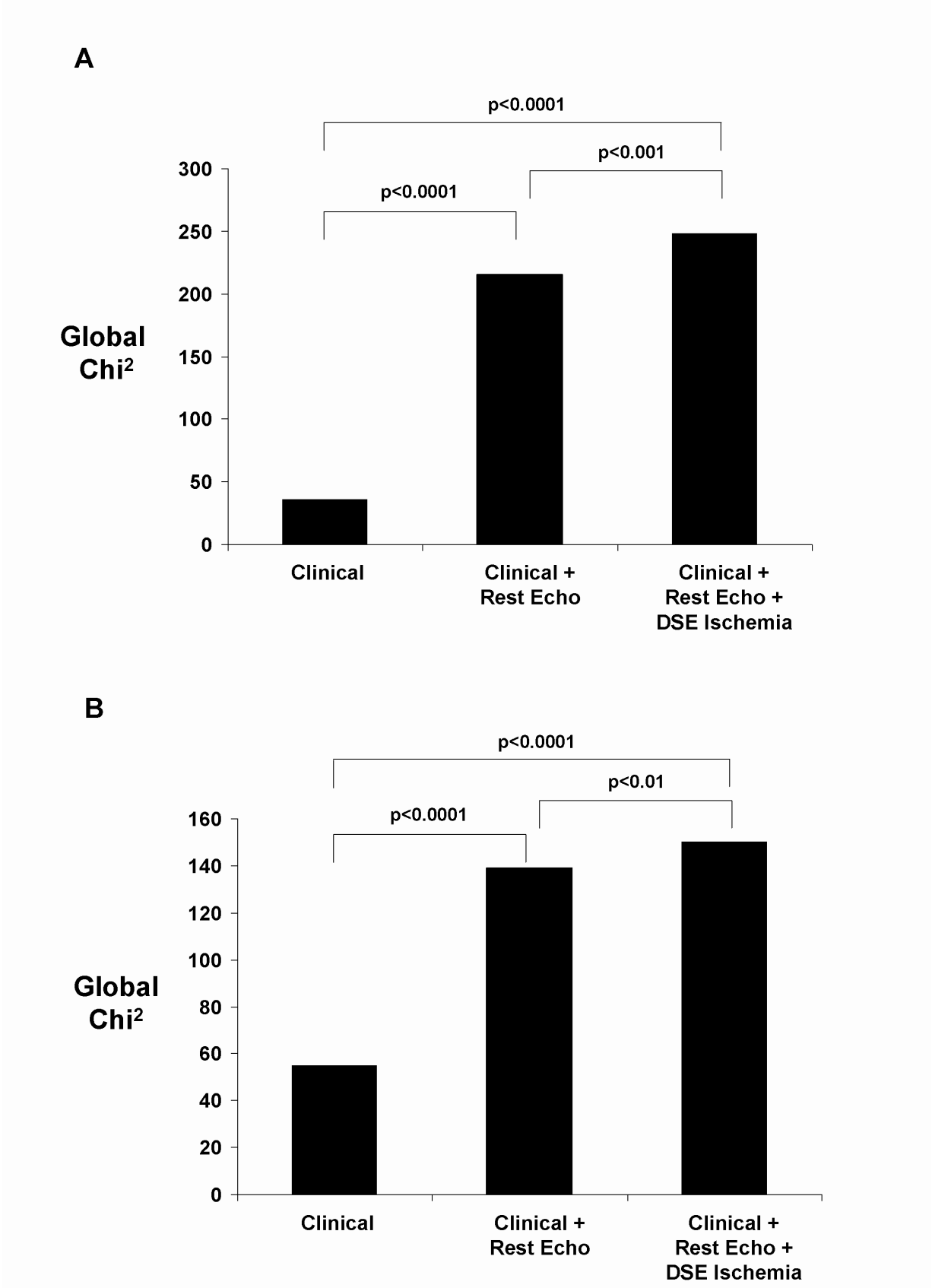

Figure 2. *Incremental prognostic value of ischemia over clinical data and resting left ventricular function for prediction of hard cardiac events (panel A) and all cause mortality (panel B).*

Discussion

This study assessed the incremental value of DSE in the prediction of long-term mortality and hard cardiac events in 1434 elderly patients with known or suspected CAD. During a mean follow-up of 6.5 years, 532 (37%) patients died, of these 249 (17%) died because of cardiac causes. The annual hard cardiac event rate was 1.8% in patients with normal and 5.7% in patents with abnormal DSE. Patients with both resting and dobutamine induced wall motion abnormalities were at highest risk of cardiac events with an annual rate of 8%. Predictors of cardiac death/nonfatal myocardial infarction and all causes of mortality were age, male gender, smoking, diabetes and rest wall motion abnormalities. The presence and the extent of ischemia during DSE provided incremental information in a multivariate analysis over clinical and resting echocardiographic data for the prediction of both hard cardiac events and all cause mortality. Patients with fixed wall motion abnormalities showed a marginally higher event rate than patients with a normal DSE. This could be explained by the fact that the most of these patients had less severe resting left ventricular dysfunction as compared to patients who had both resting and inducible wall motion abnormalities.

Comparison to Previous Studies. To our knowledge, this is the longest-term follow-up study in elderly patients undergoing stress imaging for evaluation of CAD. Additionally this is the first study to document an incremental value for stress imaging in predicting all cause mortality in the elderly.

Feasibility and safety of dobutamine-atropine stress test have been previously reported in elderly patients (15-18). However, prognostic studies are scarce. Anthopoulos et al. (19) studied 120 patients ≥70 years old admitted for chest pain who underwent adenosine and DSE and coronary angiography. During a follow-up of 17 ± 7 months, there were 9 cardiac deaths and 4 nonfatal myocardial infarctions. Predictors of cardiac events were any abnormality on stress echocardiography, cessation of stress test and involvement of two or more coronary vessels disease. Camerieri et al. (20), evaluated 190 patients ≥65 years old by dipyridamole echocardiography early after an acute uncomplicated myocardial infarction. During a follow-up of 14 ± 10 months there were 62 events including 14 cardiac death, 7 nonfatal myocardial infarction, 21 cases of heart failure, and 20 revascularization procedures. Patients with a positive dipyridamole echocardiography test experienced significantly higher myocardial infarction or death (7%) compared with patients with a negative test (4%). Poldermans et al. (21), performed a DSE test in 179 elderly patients (mean age 75 years) referred for chest pain or preoperative risk assessment for major vascular surgery. Ischemia during the test was the only independent predictor of perioperative and cardiac events during short-term follow-up of 16 ± 6 months. Marwick et al. (22), studied 3156 patients (mean age 63 ± 12 years) referred for DSE for a mean follow-up of 3.8 ± 1.9 years. DSE provided independent information for prediction of total and cardiac mortality, incremental to clinical variables. The annual hard cardiac events rate was around 2% in patients with a normal DSE and 6.3% in patients with an abnormal DSE. Age >65 years was associated with an incremental risk of mortality in patients with heart failure but a normal DSE. In particular, patients 65 to 75 years old had a yearly cardiac mortality of 4%, increasing to 6% yearly in patients over 75 years old.

Arruda et al. (8), studied 2632 patients >65 years old who underwent exercise echocardiography. During a follow-up of 2.9 ± 1.7 years, cardiac events included cardiac death in 68 (2%) patients and nonfatal myocardial infarction in 80 (3%) patients. The annual hard cardiac events rate was 2.4% in patients with normal and 5.6% of patients with abnormal exercise echocardiography. Exercise echocardiographic variables provided incremental information to clinical, rest echocardiography and exercise electrocardiogram in predicting

cardiac events. In our study the cardiac death rate was higher than in the exercise study. This may be related to several factors such as a longer and nearly complete (99.5%) follow-up in our study. In general, patients who are able to exercise are considered a lower risk population than patients who are unable to perform exercise stress test. Nevertheless, the event rate was relatively lower for patients with normal DSE in our study as compared to patients with normal exercise echocardiography. In our study, 89% of elderly patients could achieve the target heart rate which may have contributed to a better sensitivity for detecting myocardial ischemia in our study.

Limitations of the study

The population of this study was recruited over 15 years. During the entire follow-up period there has been substantial clinical progress in the treatment of CAD with possible impact on interpretation of the significance of our results. Nevertheless, survival curves for patients with normal and abnormal DSE continued to diverge during the entire follow-up, indicating that the prognostic value of DSE was maintained during follow-up. Exclusion of patients with early revascularization may have reduced the predictive power of an abnormal DSE. This is however an inherent limitation of most prognostic studies which used similar approaches (13).

Clinical Implications and Conclusions

DSE provides independent prognostic information for the prediction of all cause mortality and hard cardiac events in the elderly. Dobutamine induced wall motion abnormalities are independently associated with adverse outcome, particularly in patients with resting left ventricular dysfunction. Patients with a normal DSE have a low cardiac event rate and can be exempted from further non invasive testing if they have a stable clinical course during the 5 years following DSE.

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Chapter 5

Prognostic Stratification Using Dobutamine Stress 99mTc-Tetrofosmin Myocardial Perfusion SPECT in Elderly Patients Unable to Perform Exercise Testing

Schinkel AFL, Elhendy A, Biagini E,
van Domburg RT, Valkema R, Rizzello V,
Pedone C, Simoons ML, Bax JJ, Poldermans D

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Prognostic Stratification Using Dobutamine Stress ^{99m}Tc-Tetrofosmin Myocardial Perfusion SPECT in Elderly Patients Unable to Perform Exercise Testing

Arend F.L. Schinkel, MD, PhD[1]; Abdou Elhendy, MD, PhD[1]; Elena Biagini, MD[1]; Ron T. van Domburg, PhD[1]; Roelf Valkema, MD, PhD[2]; Vittoria Rizello, MD[1]; Chiara Pedone, MD[1]; Maarten Simoons, MD, PhD[1]; Jeroen J. Bax, MD, PhD[3]; and Don Poldermans, MD, PhD[1]

[1]Department of Cardiology, Thoraxcenter, Erasmus Medical Center, Rotterdam, The Netherlands; [2]Department of Nuclear Medicine, Erasmus Medical Center, Rotterdam, The Netherlands; and [3]Department of Cardiology, Leiden University Medical Center, Leiden, The Netherlands

Information on the prognostic value of noninvasive stress imaging techniques in the elderly is relatively scarce. This study assessed the prognostic value of dobutamine stress ^{99m}Tc-tetrofosmin SPECT for the prediction of mortality and cardiac events in elderly patients. **Methods:** Clinical information and SPECT results were analyzed for 272 consecutive patients ≥ 65 y old (mean age, 71 ± 5 y; range, 65–87 y) with limited exercise capacity. Follow-up was complete in 270 patients (99.3%); 23 underwent revascularization within 60 d of the scintigraphy and were excluded. Abnormal findings were defined as the presence of a fixed or reversible perfusion defect. A summed stress score was obtained to estimate the extent and severity of perfusion defects. The incremental prognostic value of SPECT over clinical data was evaluated according to 3 multivariate models, which included any SPECT abnormality, the presence of a fixed or reversible defect, and the summed stress score. **Results:** During the follow-up (3.3 ± 1.4 y), 59 patients died (29 cardiac deaths), 16 had a nonfatal infarction, and 49 underwent late revascularization. Abnormal scan findings were present for 140 patients (57%). The annual event rates for total mortality, cardiac death, and cardiac death or nonfatal infarction were, respectively, 3.2%, 0.2%, and 0.7% when scan findings were normal and, respectively, 9.5%, 4.3%, and 8% when scan findings were abnormal (all $P < 0.0001$). Multivariate analysis showed that abnormal scan findings, the presence of a fixed or reversible defect, and the summed stress score provided incremental prognostic information over clinical data. The presence of abnormal scan findings was independently associated with an increased risk for total mortality, cardiac death, and cardiac death or nonfatal infarction (respectively, hazard ratio 3.4 [95% CI, 1.8–6.5], 12.1 [95% CI, 2.9–51.5], and 9.0 [95% CI, 2.8–29.6]). **Conclusion:** Dobutamine stress ^{99m}Tc-tetrofosmin SPECT provides incremental prognostic information for the prediction of total mortality and cardiac events in elderly patients.

Key Words: ^{99m}Tc-tetrofosmin; scintigraphy; dobutamine; prognosis; elderly

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The population of the Western world is aging, and the proportion of elderly patients in cardiovascular practice will further increase in the next 2 decades (*1*). Cardiovascular disease is the most common cause of morbidity and mortality in patients older than 65 y (*1*). Coronary angioplasty and coronary bypass surgery have become more available for elderly patients and may substantially improve short- and long-term outcome in high-risk patients (*2*). Prognostic evaluation in elderly patients with suspected or known coronary artery disease can distinguish high-risk patients who may benefit from an invasive approach from low-risk patients who do not require invasive procedures. Unfortunately, information on prognostic stratification by noninvasive testing in elderly patients is relatively limited (*3,4*). The feasibility of exercise stress testing in elderly patients is often unsatisfactory because of lack of physical fitness and the presence of comorbid conditions such as degenerative joint disease, claudication, and peripheral neuropathy. Pharmacologic stress myocardial perfusion SPECT is a feasible alternative. However, data on the prognostic value of this technique in elderly patients are scarce (*3,4*). The purpose of this study was to determine the prognostic value of dobutamine ^{99m}Tc-tetrofosmin SPECT for the prediction of total mortality and cardiac events in elderly patients unable to perform exercise testing.

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For correspondence or reprints contact: Arend F.L. Schinkel, MD, PhD, Thoraxcenter Room Ba 302, Erasmus Medical Center, Dr. Molewaterplein 40, 3015 GD Rotterdam, The Netherlands.

E-mail: arendschinkel@hetnet.nl

MATERIALS AND METHODS

Study Population

A total of 272 consecutive patients ≥ 65 y old and unable to perform exercise testing underwent dobutamine stress ^{99m}Tc-tetrofosmin SPECT for the evaluation of suspected or known coronary artery disease. Follow-up was complete for 270 (99.3%) of 272 patients. Twenty-three patients underwent myocardial revascularization within 60 d of the scintigraphy and were excluded from analysis. This exclusion was based on previous data indicating that in the first 60 d after the test, referral for myocardial revascularization tends to be based on the SPECT results, whereas >60 d after testing, referral for myocardial revascularization tends to be based on deterioration of the patient's clinical status (*5*). Accordingly, the prognostic data reported are based on 247 patients. A total of 48 patients (19%) were >75 y old. In 119 patients (48%), the stress myocardial perfusion imaging was performed to evaluate known coronary artery disease; 89 of them had a previous myocardial infarction, and 30 had proven coronary artery disease without previous infarction. The remaining 128 patients (52%) had suspected coronary artery disease and underwent imaging for diagnostic reasons. Ninety-seven patients (39%) had typical angina, 60 (24%) had atypical angina, and 34 (14%) had nonanginal symptoms. All patients gave informed consent before the test. The local Medical Ethics Committee approved the study protocol.

Before dobutamine stress ^{99m}Tc-tetrofosmin SPECT, a structured clinical interview and history were acquired and cardiac risk factors were assessed. Hypertension was defined as a blood pressure ≥ 140/90 mm Hg or treatment with antihypertensive medication. Diabetes mellitus was defined as a fasting glucose level ≥ 7.8 mmol/L or the need for insulin or oral hypoglycemic medication. Hypercholesterolemia was defined as a total cholesterol ≥ 6.4 mmol/L or treatment with lipid-lowering medication.

Dobutamine Stress Testing

Dobutamine stress testing was performed according to a standard protocol as previously reported (*6*). Dobutamine was infused through the antecubital vein, starting at a dose of 10 μg/kg/min for 3 min and increasing by 10 μg/kg/min every 3 min up to a maximum dose of 40 μg/kg/min. If the test endpoint was not reached at a dobutamine dose of 40 μg/kg/min, atropine (up to 1 mg) was given intravenously. Blood pressure and heart rate were monitored and electrocardiography was recorded constantly. Test endpoints were achievement of target heart rate (85% of maximum age- and sex-predicted heart rate); horizontal or downsloping ST-segment depression > 2 mm at an interval of 80 ms after the J-point, compared with baseline; ST-segment elevation > 1 mm in patients without previous myocardial infarction; severe angina; a systolic blood pressure fall > 40 mm Hg, compared with baseline; blood pressure > 240/120 mm Hg; or significant cardiac arrhythmias. Metoprolol was available to reverse the adverse effects of dobutamine/atropine.

SPECT

Approximately 1 min before the termination of the stress test, an intravenous dose of 370 MBq of ^{99m}Tc-tetrofosmin was administered (*6*). For resting studies, 370 MBq of tetrofosmin were injected at least 24 h after the stress study. Image acquisition was performed with a triple-head γ-camera system (Prism 3000 XP; Picker International). For each study, 6 oblique (short axis) slices from the apex to the base and 3 sagittal (vertical long axis) slices were defined. Each of the 6 short-axis slices was divided into 8 equal segments. The septal part of the 2 basal slices was excluded from analysis because this region corresponds to the fibrous portion of the interventricular septum and normally exhibits reduced uptake. Therefore, 47 segments were identified (3 long axis and 44 short axis). The SPECT scoring model has been described previously (*6*) and has been depicted previously by Salustri et al. (*7*). The scan was interpreted semiquantitatively by visual analysis assisted by analysis of the circumferential profiles. Rest and stress images were evaluated by measuring the area between the lower limit of normal and the actual circumferential profile in 6 short-axis slices. Profile curves 2 SDs below normal perfusion were considered abnormal. Stress and rest tomographic views were reviewed side by side by an experienced observer who was unaware of each patient's clinical data. A reversible perfusion defect was defined as a perfusion defect on stress images that partially or completely resolved at rest in ≥2 contiguous segments or slices in the 47-segment model. A fixed perfusion defect was defined as a perfusion defect on stress images in ≥2 contiguous segments or slices that persisted on rest images in the 47-segment model. A study was considered to have abnormal findings if a fixed or reversible perfusion defect (or both) was present. To identify the coronary artery related to the location of the perfusion defect, the 47 segments imaged by SPECT were combined into 6 major regions: anterior, inferior, septal anterior, septal posterior, posterolateral, and apical. This combination provides easily interpretable information for the treating cardiologist. Each of the 6 major left ventricular segments was scored using a 4-grade scoring method (0 = normal, 1 = slightly reduced, 2 = moderately reduced, and 3 = severely reduced or absence of uptake). The perfusion defect score was derived by summing the score of the 6 myocardial segments at stress (summed stress score).

Patient Follow-up

The follow-up data were obtained by reviewing hospital records and by contacting the patient's general practitioner. The date of the last examination or consultation was used to determine follow-up time. Endpoints were overall death, cardiac death, nonfatal myocardial infarction, and late (>60 d) coronary revascularization. Cardiac death was defined as death caused by myocardial infarction, significant cardiac arrhythmias, or refractory congestive heart failure. Sudden death occurring without another explanation was included as cardiac death. Myocardial infarction was defined according to standard criteria (*8*).

Statistical Analysis

Continuous data were expressed as mean ± SD, and percentages were rounded. Statistical analysis was performed with the BMDP statistical software package (BMDP Statistical Software Inc.). Continuous variables were compared using the Student *t* test for unpaired samples. Differences between proportions were compared using the χ^2 test. Univariate and multivariate Cox proportional hazards regression models were used to identify independent predictors of total mortality and cardiac events (*9*). Variables were selected in a stepwise forward-selection manner, with entry and retention set at a significance level of 0.05. The risk of a variable was expressed as a hazard ratio with a corresponding 95% confidence interval. The incremental value of myocardial perfusion scintigraphy over the clinical variables in the prediction of events was determined according to 3 models. In model 1, the incremental value of abnormal scan findings over clinical data and stress test

information was assessed. In model 2, the presence of a fixed or reversible defect was entered. In model 3 the summed stress score was entered. The probability of survival was calculated using the Kaplan–Meier method, and survival curves were compared using the log-rank test. $P < 0.05$ was considered statistically significant.

RESULTS

Demographics and Stress Test Results

Clinical data are presented in Table 1. Dobutamine stress increased heart rate significantly (from 72 ± 15 to 128 ± 16 bpm, $P < 0.001$) and increased systolic blood pressure modestly (from 140 ± 23 to 146 ± 31 mm Hg, $P < 0.001$). The highest dobutamine dose was 10 μg/kg/min in 1 patient (0.4%), 20 μg/kg/min in 44 (18%), 30 μg/kg/min in 45 (18%), and 40 μg/kg/min in 157 (64%). In 88 patients (36%), atropine was added. Patients who were using β-blocker therapy during the dobutamine stress test more frequently received atropine than did patients not receiving β-blocker therapy (54 of 105, 51%, vs. 34 of 142, 24%, $P < 0.001$). Side effects that occurred during dobutamine stress testing were generally self-limiting. These included atrial fibrillation in 5 patients (2.0%), short ventricular tachycardia (<10 complexes) in 6 patients (2.4%), and severe hypotension (decrease in systolic blood pressure > 40 mm Hg) in 4 patients (1.6%). Minor side effects included nausea in 4 (1.6%), flushing in 3 (1.2%), and headache in 13 (5.3%). No patient experienced a myocardial infarction or ventricular fibrillation during or immediately after the stress test.

SPECT and Outcome Events

A total of 107 patients (43%) had normal perfusion, and 140 (57%) had abnormal perfusion. In these 140 patients, perfusion abnormalities were reversible in 20 (14%), fixed in 67 (48%), and both fixed and reversible (or partially reversible) in 53 (38%). During a mean follow-up of 3.3 ± 1.4 y, 59 deaths (24%) occurred, of which 29 (12%) were due to cardiac causes. Nonfatal myocardial infarction occurred in 16 patients (6%). Forty-nine patients (20%) underwent late (>60 d) myocardial revascularization (28 patients had coronary bypass surgery, and 21 had coronary angioplasty).

TABLE 1
Clinical Characteristics

Characteristic	No. of patients	Percentage
Total patients*	247	100
Male patients	129	52
Systemic hypertension	102	41
Diabetes mellitus	47	19
Smoking	52	21
Hypercholesterolemia	74	30
Congestive heart failure	40	16
β-blockers	105	43
Calcium channel blockers	111	45
Angiotensin-converting enzyme inhibitors	69	28
Diuretics	66	27
History of myocardial infarction	89	36
History of coronary angioplasty	44	18
History of coronary artery bypass surgery	48	19

*Age range, 65–87 y; mean ± SD, 71 ± 5 y.

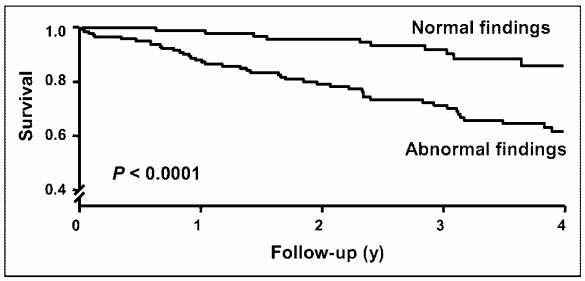

FIGURE 1. Kaplan–Meier survival curves for total mortality according to results of dobutamine stress ^{99m}Tc-tetrofosmin SPECT.

Predictive Value of Clinical Data and Test Results

Kaplan–Meier survival curves and cumulative event rates are presented in Figures 1–3. Patients with normal perfusion had a low event rate. Remarkably, no cardiac deaths occurred during the first 3 y after the test in those whose test results were normal. Survival curves continued to diverge during follow-up, indicating that the prognostic value of dobutamine stress ^{99m}Tc-tetrofosmin SPECT was maintained over time. The annual event rates for total mortality, cardiac death, and cardiac death or nonfatal infarction were, respectively, 3.2%, 0.2%, and 0.7% after a scan with normal findings and, respectively, 9.5%, 4.3%, and 8% after a scan with abnormal findings (all $P < 0.0001$).

Univariate and multivariate predictors of total mortality and cardiac events are presented in Tables 2–4. The

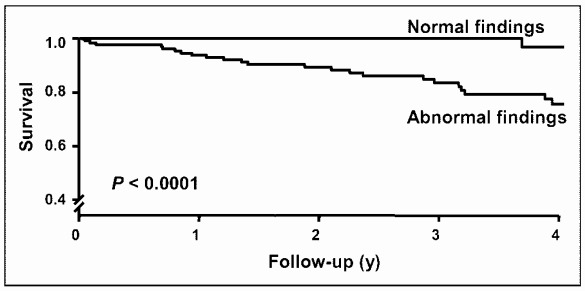

FIGURE 2. Kaplan–Meier survival curves for cardiac death according to results of dobutamine stress ^{99m}Tc-tetrofosmin SPECT.

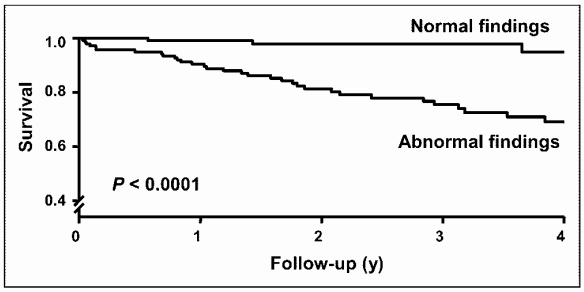

FIGURE 3. Kaplan–Meier survival curves for cardiac death or nonfatal myocardial infarction according to results of dobutamine stress ^{99m}Tc-tetrofosmin SPECT.

incremental prognostic value of dobutamine stress ^{99m}Tc-tetrofosmin SPECT over clinical data was assessed using the 3 models. All models provided incremental information over clinical and stress test data. Model 1, which included any abnormal scan finding, offered the most powerful incremental information for the prediction of total mortality (global $\chi^2 = 26$; $P < 0.05$). Model 2, which included both fixed and reversible perfusion defects, provided the most powerful incremental information for the prediction of cardiac death, as well as of cardiac death or nonfatal infarction (global $\chi^2 = 53$ and 51, respectively; $P < 0.0001$).

DISCUSSION

This study assessed the prognostic value of dobutamine stress ^{99m}Tc-tetrofosmin SPECT in the prediction of mortality and hard cardiac events in elderly patients. Despite their advanced age, patients with normal myocardial perfusion findings had an excellent outcome, with no cardiac deaths during the first 3 y after a normal test. In contrast, patients with abnormal myocardial perfusion findings had an elevated risk of future cardiac events. ^{99m}Tc-Tetrofosmin SPECT provided prognostic information incremental to clinical and stress test parameters for the prediction of total mortality and cardiac events during a nearly complete follow-up of 3.3 ± 1.4 y. Independent clinical predictors of total mortality were smoking and congestive heart failure. Independent clinical predictors of cardiac events were diabetes mellitus, smoking, and congestive heart failure. Furthermore, the presence of a left bundle branch block was predictive of cardiac death. ^{99m}Tc-Tetrofosmin SPECT provided incremental prognostic information over clinical and stress test parameters. The multivariate model that included any scan abnormality provided the most powerful incremental information for the prediction of total mortality. The multivariate model that included both fixed and reversible perfusion defects offered the most powerful incremental information for the prediction of cardiac death, as

TABLE 2
Univariate and Multivariate Predictors of Total Mortality

Parameter	Univariate	Multivariate			
		Clinical data	Model 1	Model 2	Model 3
Clinical characteristics					
Male patient	1.6 (0.9–2.9)	NS	NS	NS	NS
Previous infarction	1.4 (0.8–2.6)	NS	NS	NS	NS
Diabetes mellitus	1.7 (0.8–3.3)	NS	NS	NS	NS
Hypertension	1.3 (0.7–2.3)	NS	NS	NS	NS
Hypercholesterolemia	0.7 (0.4–1.4)	NS	NS	NS	NS
Smoking	3.1 (1.4–7.1)	1.9 (1.1–3.3)	NS	NS	NS
Heart failure	2.9 (1.4–6.0)	2.4 (1.3–4.2)	2.5 (1.4–4.3)	2.5 (1.4–4.4)	2.3 (1.3–4.1)
Left bundle branch block	2.0 (0.7–5.8)	NS	NS	NS	NS
Stress test results					
Angina pectoris	1.0 (0.5–1.9)	—	NS	NS	NS
ST-segment changes	1.4 (0.8–2.7)	—	NS	NS	NS
Peak heart rate	0.9 (0.4–2.1)	—	NS	NS	NS
Scan parameters					
Abnormal findings	3.7 (1.9–7.5)	—	3.4 (1.8–6.5)	—	—
Fixed defect	2.6 (1.4–4.7)	—	—	NS	—
Reversible defect	2.1 (1.2–4.0)	—	—	2.2 (1.3–3.8)	—
Summed stress score/10	5.2 (2.0–12)	—	—	—	4.4 (1.8–11)
Global χ^2		16	26	20	20
Incremental value over clinical data			$P < 0.05$	$P < 0.05$	$P < 0.05$

NS = not significant; — = variable excluded.

Data are Cox proportional hazard ratio, with 95% confidence interval in parentheses. In model 1, the variable entered was the presence of an abnormal scan; in model 2, the presence of a fixed or reversible defect was entered; in model 3, the summed stress score was entered.

TABLE 3
Univariate and Multivariate Predictors of Cardiac Death

Parameter	Univariate	Multivariate			
		Clinical data	Model 1	Model 2	Model 3
Clinical characteristics					
Male patient	1.0 (0.5–2.1)	NS	NS	NS	NS
Previous infarction	1.1 (0.5–2.4)	NS	NS	NS	NS
Diabetes mellitus	3.1 (1.3–7.1)	2.9 (1.4–6.1)	2.8 (1.3–6.3)	2.6 (1.2–6.0)	2.7 (1.2–5.9)
Hypertension	1.6 (0.7–3.5)	NS	NS	NS	NS
Hypercholesterolemia	0.9 (0.4–2.1)	NS	NS	NS	NS
Smoking	3.1 (1.4–7.1)	2.4 (1.1–5.0)	2.3 (1.1–5.2)	2.8 (1.3–6.1)	NS
Heart failure	4.0 (1.7–9.4)	3.4 (1.6–7.4)	3.5 (1.6–7.7)	2.8 (1.3–6.4)	3.1 (1.4–6.8)
Left bundle branch block	5.3 (1.7–16)	NS	3.2 (1.3–8.3)	3.0 (1.2–7.7)	NS
Stress test results					
Angina pectoris	0.8 (0.3–2.1)	—	NS	NS	NS
ST-segment changes	1.2 (0.5–2.7)	—	NS	NS	NS
Peak heart rate	1.1 (0.2–5.0)	—	NS	NS	NS
Scan parameters					
Abnormal findings	11.8 (2.7–51)	—	12.1 (2.9–52)	—	—
Fixed defect	3.2 (1.3–7.4)	—	—	3.1 (1.5–6.8)	—
Reversible defect	3.5 (1.6–7.7)	—	—	4.5 (2.1–9.6)	—
Summed stress score/10	6.7 (2.1–22)	—	—	—	6.7 (2.0–23)
Global χ^2		25	47	53	28
Incremental value over clinical data			$P < 0.0001$	$P < 0.0001$	$P < 0.05$

NS = not significant; — = variable excluded.
Data are Cox proportional hazard ratio, with 95% confidence interval in parentheses. In model 1, the variable entered was the presence of an abnormal scan; in model 2, the presence of a fixed or reversible defect was entered; in model 3, the summed stress score was entered.

well as of cardiac death or nonfatal infarction. Moreover, multivariate analysis showed that the summed stress score, which indicates the extent and severity of perfusion abnormalities, provided incremental prognostic information over clinical data. These results demonstrate that the evaluation of elderly patients using dobutamine stress ^{99m}Tc-tetrofosmin SPECT is a safe and feasible method that provides clinically useful information on clinical outcome.

Previous data indicate that dobutamine stress ^{99m}Tc-tetrofosmin SPECT is safe and feasible in elderly patients (*10*). However, information on the prognostic value of stress myocardial perfusion imaging in the elderly is scarce. Furthermore, there are no data to support a role of stress myocardial perfusion imaging in the prediction of all causes of mortality in the elderly. Currently, prognostic data on sestamibi SPECT in the elderly are not available. Iskandrian et al. (*11*) assessed the use of exercise ^{201}Tl imaging for the prognostic stratification of 404 elderly patients with a mean age of 65 y (range, 60–82 y). During a follow-up of 25 ± 15 mo, 8 (2%) died of cardiac causes, and 10 (2%) had nonfatal myocardial infarction. Patients with abnormal exercise ^{201}Tl findings had higher event rates than did those with normal findings (8% vs. 1%, $P < 0.001$). Steingart et al. (*12*) followed 578 patients aged 65 y or older (range, 65–85 y) using exercise myocardial perfusion imaging. Almost 80% underwent ^{201}Tl SPECT; the remainder underwent ^{99m}Tc-sestamibi imaging. During a follow-up of 4.4 ± 1.3 y, 39 deaths and 17 nonfatal myocardial infarctions occurred. The authors concluded that treadmill exercise is a valuable tool in elderly patients with adequate exercise capacity and that myocardial perfusion imaging added only modest prognostic information. The event rate was lower than for our study, as may be explained by our inclusion of patients unable to perform exercise testing, who are generally recognized as a higher-risk group, compared with patients who can exercise (*13*). Shaw et al. (*14*) studied 348 patients ≥ 70 y old using dipyridamole ^{201}Tl imaging. During a follow-up of 23 ± 15 mo, there were 52 cardiac deaths (15%) and 24 nonfatal myocardial infarctions (7%). The event rate for cardiac death or nonfatal infarction was 2% in patients with normal scan findings and 20% in patients with abnormal scan findings. Abnormal (reversible or fixed perfusion defect) dipyridamole ^{201}Tl findings were the best predictor of cardiac events.

The 0.7% hard cardiac event rate in patients with normal dobutamine stress ^{99m}Tc-tetrofosmin SPECT findings is substantially lower than the hard cardiac event rate in patients with normal ^{201}Tl findings (*11,12,14*). This difference may be related to the better imaging characteristics of ^{99m}Tc-tetrofosmin than of ^{201}Tl. Clinical trials have demon-

TABLE 4
Univariate and Multivariate Predictors of Cardiac Death or Myocardial Infarction

Parameter	Univariate	Multivariate			
		Clinical data	Model 1	Model 2	Model 3
Clinical characteristics					
Male patient	1.8 (0.9–3.6)	NS	NS	NS	NS
Previous infarction	1.5 (0.7–2.9)	NS	NS	NS	NS
Diabetes mellitus	2.6 (1.2–5.5)	2.6 (1.3–5.1)	2.6 (1.3–5.2)	2.3 (1.1–4.8)	2.2 (1.1–4.5)
Hypertension	1.3 (0.6–2.5)	NS	NS	NS	NS
Hypercholesterolemia	0.9 (0.4–1.9)	NS	NS	NS	NS
Smoking	3.3 (1.6–6.9)	2.5 (1.3–4.8)	2.1 (1.1–4.1)	2.7 (1.4–5.2)	NS
Heart failure	3.0 (1.3–6.7)	3.0 (1.5–6.0)	3.2 (1.6–6.4)	2.6 (1.3–5.5)	2.6 (1.3–5.4)
Left bundle branch block	3.7 (1.2–11)	NS	NS	NS	NS
Stress test results					
Angina pectoris	1.2 (0.6–2.6)	—	NS	NS	NS
ST-segment changes	1.0 (0.5–2.1)	—	NS	NS	NS
Peak heart rate	0.8 (0.2–3.6)	—	NS	NS	NS
Scan parameters					
Abnormal findings	7.8 (2.7–23)	—	9.0 (2.8–30)	—	—
Fixed defect	3.2 (1.5–6.8)	—	—	2.9 (1.5–5.8)	—
Reversible defect	2.7 (1.3–5.5)	—	—	3.9 (2.0–7.7)	—
Summed stress score/10	15.1 (5.3–47)	—	—	—	13.1 (4.1–42)
Total χ^2		27	45	51	36
Incremental value over clinical data			$P < 0.0001$	$P < 0.0001$	$P < 0.001$

NS = not significant; — = variable excluded.
Data are Cox proportional hazard ratio, with 95% confidence interval in parentheses. In model 1, the variable entered was the presence of an abnormal scan; in model 2, the presence of a fixed or reversible defect was entered; in model 3, the summed stress score was entered.

strated that ^{99m}Tc-tetrofosmin SPECT provides diagnostic and prognostic information comparable to that derived from traditional ^{201}Tl imaging, with the extra benefit of higher image quality and increased certainty in interpretation (*15–17*). This study expands the body of literature regarding the prognostic utility of this relatively new radioactive isotope in patients with known or suspected coronary artery disease. The study also is, to our knowledge, the first to support a role of stress myocardial perfusion imaging in the prediction of all causes of mortality in the elderly. The present data indicate that elderly patients with normal dobutamine stress ^{99m}Tc-tetrofosmin myocardial perfusion findings have a favorable prognosis during the 3 y after the study if no change in clinical status occurs. There have been several attempts to quantify the low-risk period after a scan with normal findings is obtained (*18*). Prognostic information derived from exercise sestamibi SPECT demonstrates that repeated testing should be not required up to 4 or 5 y after a study with normal findings; however, when symptoms arise or clinical status changes, retesting and subsequent angiography and revascularization may be required (*19*). Further studies are needed to confirm these data in elderly patients. The left ventricular ejection fraction was not available in all patients; this is a limitation of the study.

CONCLUSION

Dobutamine stress ^{99m}Tc-tetrofosmin SPECT provides incremental prognostic information for the prediction of all causes of mortality and hard cardiac events in the elderly. Elderly patients with normal myocardial perfusion findings have a good prognosis and do not require further invasive evaluation during the 3 y after the study if no change in clinical status occurs.

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Chapter 6

Long-term Outcome in Patients with Silent versus Symptomatic Ischemia during Dobutamine Stress Echocardiography

Biagini E, Schinkel AFL, Bax JJ, Rizzello V, van Domburg RT, Krenning BJ, Bountioukos M, Pedone C, Vourvouri EC, Rapezzi C, Branzi A, Roelandt JRTC, Poldermans D

Heart, in press

Abstract

Background. Stress induced ischemia during dobutamine stress echocardiography (DSE) is associated with an increased risk of late cardiac events. The aim of this study was to compare the long-term prognosis of patients having silent versus symptomatic ischemia during DSE.

Methods. Follow-up was completed in 944 patients (99.5%). Thirteen underwent early (<60 days) coronary revascularization and were excluded.

Results. Silent ischemia was present 643 of the 931 remained (69%). The number of dysfunctional segments at rest (9.6±5.1 v 8.8±5.0, p=0.1) and of ischemic segments (3.5±2.2 v 3.8±2.1, p=0.2) was comparable in both groups. During a mean (SD) follow-up of 5.5 (3.3) years, there were 169/931 (18%) cardiac deaths and 86/931 (9%) nonfatal infarctions. Multivariable Cox regression analysis showed age (HR 1.1, 95% CI 1.02-1.05), previous myocardial infarction (HR 1.4, 95% CI 1.1-2.0), and number of ischemic segments (HR 2.0, 95% CI 1.0-3.7) as independent predictors of cardiac death and myocardial infarction. For every additional ischemic segment there was a two-fold increment in risk of late cardiac events. The annual cardiac death or myocardial infarction rate was 3.0% in patients with symptomatic ischemia and 4.6% in patients with silent ischemia (p<0.01). Silent induced ischemia was an independent predictor of cardiac death and myocardial infarction (HR 1.7, 95% CI 1.1-2.0). During follow-up symptomatic patients were treated more often with cardio-protective therapy (p<0.01) and coronary revascularization (145/288 (50%) v 174/643 (27%), p<0.001).

Conclusions. Patients with silent ischemia had a similar extent of myocardial ischemia during DSE, but received less cardio-protective therapy and coronary revascularization, and experienced a higher cardiac event rate compared to patients with symptomatic ischemia.

Introduction

Although angina pectoris is one of the cardinal manifestations of myocardial ischemia, many patients have ischemia during stress testing without associated symptoms (1-3). Studies of stress induced silent ischemia reported discordant results with respect to the extent of ischemia. Some studies reported a similar extent of ischemia in patients with and without angina (4-10), while others report more extensive ischemia in presence of angina (11-16). Dobutamine-atropine stress echocardiography (DSE) is commonly used to assess the extent, location, and severity of coronary artery disease (17, 18). The diagnosis of myocardial ischemia during DSE is based on the detection of new or worsening wall motion abnormalities. The extent of these abnormalities is a powerful predictor of adverse outcome (19, 20). A large number of studies have reported discordant data regarding the prognostic importance of stress induced silent ischemia, the likelihood of future coronary events related to the amount of ischemic myocardium, and the influence of medical treatment or revascularization techniques on the outcome of silent stress induced ischemia. Accordingly, the aim of this study was to compare the long-term prognosis of silent versus symptomatic ischemia in a large group of patients undergoing DSE.

Methods

Patient Selection. Between 1990 and 2002, 949 consecutive patients experienced stress induced myocardial ischemia during DSE. Follow-up was successful in 944 patients (99.5%). A total of 13 patients underwent early coronary revascularization in the first 60 days after the DSE and were excluded from the analysis (21). Data from the remaining 931 patients are reported. The protocol was approved by the Hospital Ethics Committee. All patients gave informed consent before the test. A structured interview and clinical history were taken and cardiac risk factors were assessed before DSE.

Dobutamine Stress Protocol. Dobutamine-atropine stress testing was performed according to a standard protocol as previously reported (19, 22, 23). Dobutamine was administered intravenously, starting at a dose of 5 μg/kg/min for 5 minutes, followed by 10 μg/kg/min for 5 minutes. Subsequently, incremental dobutamine doses of 10 μg/kg/min were given at 3-minute intervals up to a maximum dose of 40 μg/kg/min. If the test end-point was not reached at a dobutamine dose of 40 μg/kg/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), maximal dose of dobutamine and atropine, 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 mm Hg, 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, unaware of the clinical data, scored the echocardiograms using a standard 16-segment model. 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. Symptomatic ischemia was defined as the presence of typical chest pain or anginal equivalent symptoms (epigastric pain, jaw pain, dyspnea) during DSE. Coronary arteries were assigned to myocardial segments based on echocardiographic localization, as previously described (24). The anterior, apical, septal, and anteroseptal walls were assigned to the left anterior descending coronary artery, the posterior and lateral wall to the left circumflex, and inferior and basal septal segments to the right coronary artery. The apical lateral segment was considered an overlapping segment between the left anterior descending coronary artery and the left circumflex and the apical inferior segment was considered an overlapping segment between the left anterior descending coronary artery and the right coronary artery. Overlapping segments were assigned to the regions with concomitant abnormalities.

Follow-up. Follow-up data collection was performed by contacting the patient's general practitioner and by review of hospital records. The date of the last review or consultation was used to calculate follow-up time. Outcome events were overall death, cardiac death, and nonfatal myocardial infarction. Cardiac death was defined as a death caused by acute myocardial infarction, significant cardiac arrhythmias, or refractory congestive heart failure. Sudden death occurring without another explanation was considered as cardiac death. Nonfatal myocardial infarction was defined by two of the following symptoms: typical chest pain, elevated cardiac enzyme levels or typical changes on electrocardiography.

Statistical Analysis. Continuous data were expressed as mean value (standard deviation, SD). The Student's t test was used to analyze continuous data. Differences between proportions were compared using the Chi-square test. Univariate and multivariate Cox proportional hazard regression models (BMDP Statistical Software Inc., Los Angeles, California, USA) were used to identify independent predictors of late cardiac events (25). Variables were selected in a stepwise forward selection manner, including clinical and DSE data, with entry and retention set at a significance level of 0.05. The risk of a variable was expressed as a hazard ratio with a corresponding 95% confidence interval. The probability of survival was calculated using the Kaplan-Meier method, and survival curves were compared using the log-rank test. A p value <0.05 was considered statistically significant.

Results

Patient Characteristics and Hemodynamic Results. Silent myocardial ischemia was present in 643/931 (69%) patients. Clinical risk factors were not significantly different between patients with and without angina during DSE, with the exception of history of angina that was more frequently observed in patients with symptomatic ischemia (Table 1).

Table 1. Clinical Characteristics in Patients With and Without Angina During DSE

	Silent Ischemia (N=643)	Symptomatic Ischemia (N=288)	p value
Age, mean (SD)	61 (13)	61 (11)	0.6
Men (%)	465 (72)	233 (81)	0.009
Previous infarction (%)	330 (51)	161 (56)	0.2
Diabetes Mellitus (%)	78 (12)	29 (10)	0.4
Hypertension (%)	195 (30)	79 (27)	0.4
Hypercholesterolemia (%)	163 (25)	82 (28)	0.3
Smoking (%)	122 (19)	88 (30)	0.3
History of angina (%)	200 (31)	196 (68)	<0.001
History of heart failure(%)	107 (17)	38 (13)	0.2
Previous coronary angiography (%)	219 (34)	112 (39)	0.2
Previous coronary bypass surgery (%)	96 (15)	43 (15)	1
Previous coronary angioplasty (%)	89 (14)	56 (19)	0.04
β-blockers (%)	243 (38)	115 (40)	0.5
Calcium channel blockers (%)	177 (27)	99 (34)	0.04
Nitrates (%)	180 (28)	115 (40)	0.001
Aspirin (%)	302 (47)	158 (55)	0.005
Statins (%)	174 (27)	92 (32)	0.01
Indication for DSE:			
Diagnosis of CAD (%)	350 (54)	211 (73)	<0.0001
Preoperative evaluation before noncardiac surgery (%)	186 (29)	34 (12)	<0.0001
Risk-stratification after myocardial infarction (%)	107 (17)	43 (15)	0.6

DSE characteristics in patients with silent and symptomatic myocardial ischemia are shown in Table 2. There was no significant difference between patients with and without silent ischemia with respect to number of abnormal segments at rest and number of ischemic segments during DSE. No patient experienced a myocardial infarction during the test. Side effects were non-sustained ventricular tachycardia (<10 complexes) in 28/931 patients (3%), sustained ventricular tachycardia (>10 complexes) in 13/931 patients (1%), severe hypotension (decrease in systolic blood pressure >40 mm Hg compared to baseline) in 7/931 (1%), atrial fibrillation in 6/931 patients (1%), and ventricular fibrillation in 1/931 (0.1%).

Table 2. Dobutamine Stress Echocardiographic Data in Patients With and Without Angina During DSE

	Silent Ischemia (N=643)	Symptomatic Ischemia (N=288)	p value
Peak heart rate (betas)	127 ± 21	124 ± 20	0.03
Peak systolic blood pressure (mmHg)	135 ± 31	134 ± 28	0.7
Peak rate pressure product	16573 ± 4290	17119 ± 4767	0.1
Peak dobutamine dose (μg)	37 ± 7	38 ± 5	0.09
Atropine use (%)	230 (36)	96 (33)	0.5
ST-segment depression (%)	248 (38)	179 (62)	<0.001
Number of dysfunctional segments at rest	9.6 ±5.1	8.8 ± 5.0	0.1
Number of ischemic segments	3.5 ± 2.2	3.8 ± 2.1	0.2
Arrhythmias and hypotension during the test (%)	43 (7)	12 (4)	0.2
Reasons for termination of the stress test:			
85% of maximal heart rate (%)	579 (90)	250 (87)	0.2
Maximal dose (%)	36 (5)	14 (5)	0.8
Arrhythmias (%)	12 (2)	2 (1)	0.3
Side effects (%)	11 (2)	1 (0.3)	0.2
ST-segment depression (%)	5 (1)	10 (3)	<0.005
Angina (%)	0 (0)	11 (4)	<0.0001

DSE and Outcome. During a mean (SD) 5.5 (3.3) years follow-up, there were 265/931 (28%) deaths, of which 169/931 (18%) were attributed to cardiac causes. Nonfatal infarction occurred in 86/931 (9%) patients, and late revascularization was performed in 319/931 (34%) patients. The annual cardiac death rate was 2.2% in the group of patients with symptomatic ischemia during DSE and 3.8% in the group with silent ischemia ($p< 0.01$). The annual myocardial infarction or cardiac death rate was 3.0% in patients with symptomatic ischemia and 4.6% in patients with silent ischemia ($p< 0.01$). Late revascularization was more frequently performed in patients with symptomatic ischemia (145/288 (50%) v 174/643 (27%), $p<0.001$). Changes in medical treatment after detection of ischemia by DSE were observed in both groups, but patients with angina during DSE were significantly more often treated with β-blockers, aspirin, and statins (Table 3). On the other hand, the fact that these patients were less treated with nitrates and calcium channel blockers at follow-up is related to the higher incidence of coronary revascularization in this group.

Table 3. Medication Therapy at Follow-up in Patients With and Without Angina During DSE

	Baseline			Follow-up		
	Silent Ischemia (N=643)	**Symptomatic Ischemia (N=288)**	**p value**	**Silent Ischemia (N=643)**	**Symptomatic Ischemia (N=288)**	**p value**
β-blockers (%)	243 (38)	115 (40)	0.5	276 (43)	202 (70)	<0.001
Calcium channel blockers (%)	177 (27)	99 (34)	0.04	193 (30)	89 (31)	0.06
Nitrates (%)	180 (28)	115 (40)	0.001	193 (30)	69 (24)	<0.006
Aspirin (%)	302 (47)	158 (55)	0.005	334 (52)	236 (82)	<0.001
Statins (%)	174 (27)	92 (32)	0.1	263 (41)	245 (85)	<0.001

Kaplan-Meier survival curves for the end-point cardiac death and the combined endpoint cardiac death/nonfatal infarction are presented in Figure 1 and 2, respectively.

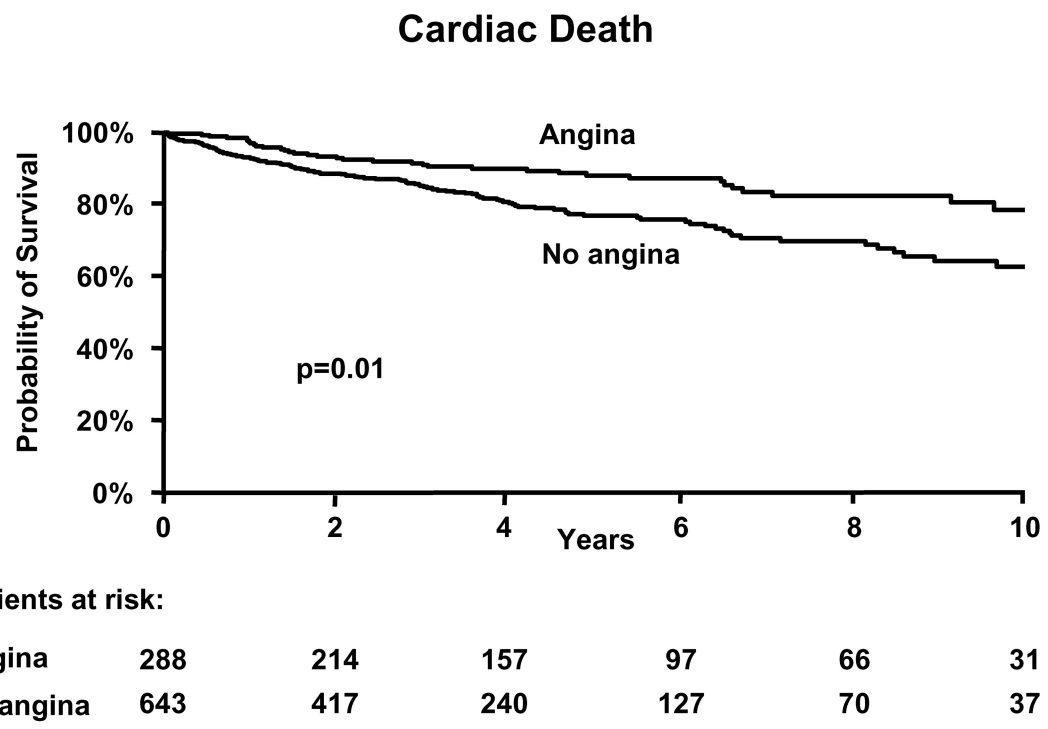

Figure 1. *Kaplan-Meier survival curves (end point of cardiac death) in patients with silent versus patients with symptomatic ischemia during DSE.*

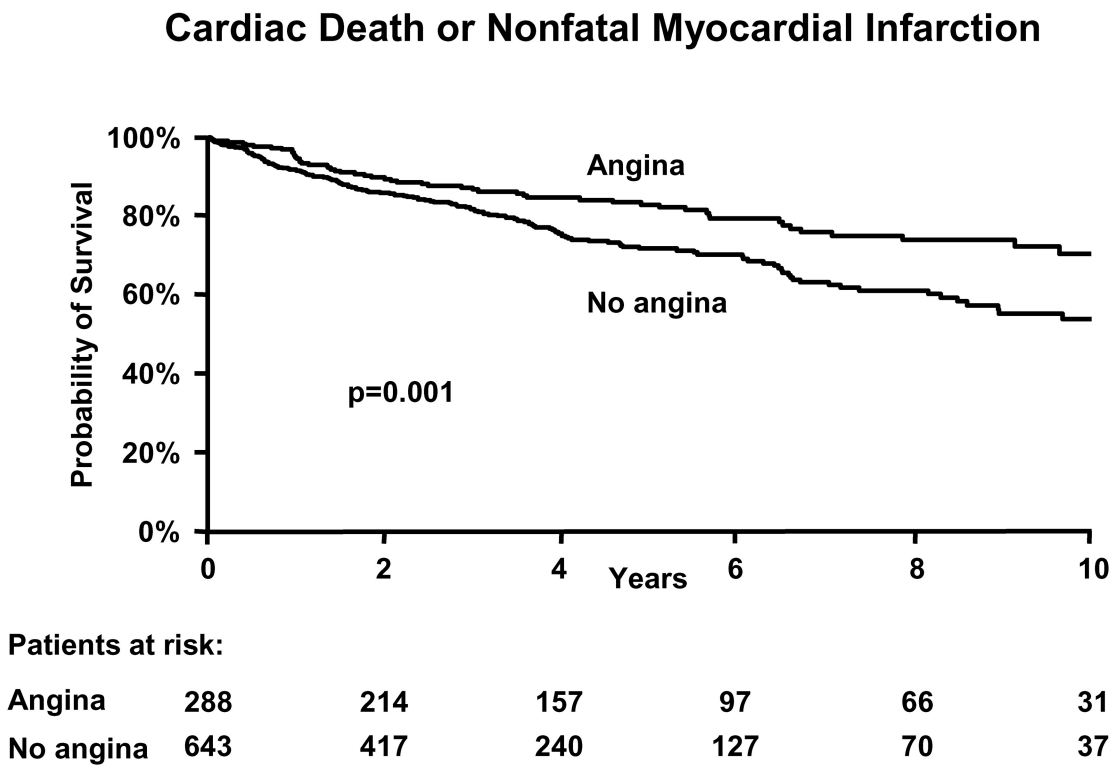

Figure 2. *Kaplan-Meier survival curves (end point of cardiac death and nonfatal myocardial infarction) in patients with silent versus patients with symptomatic ischemia during DSE.*

Patients with silent ischemia had a significantly lower probability of survival during long-term follow-up compared with patients with symptomatic ischemia. Especially, patients with silent ischemia and multivessel disease had a poor long-term prognosis (see Figure 3).

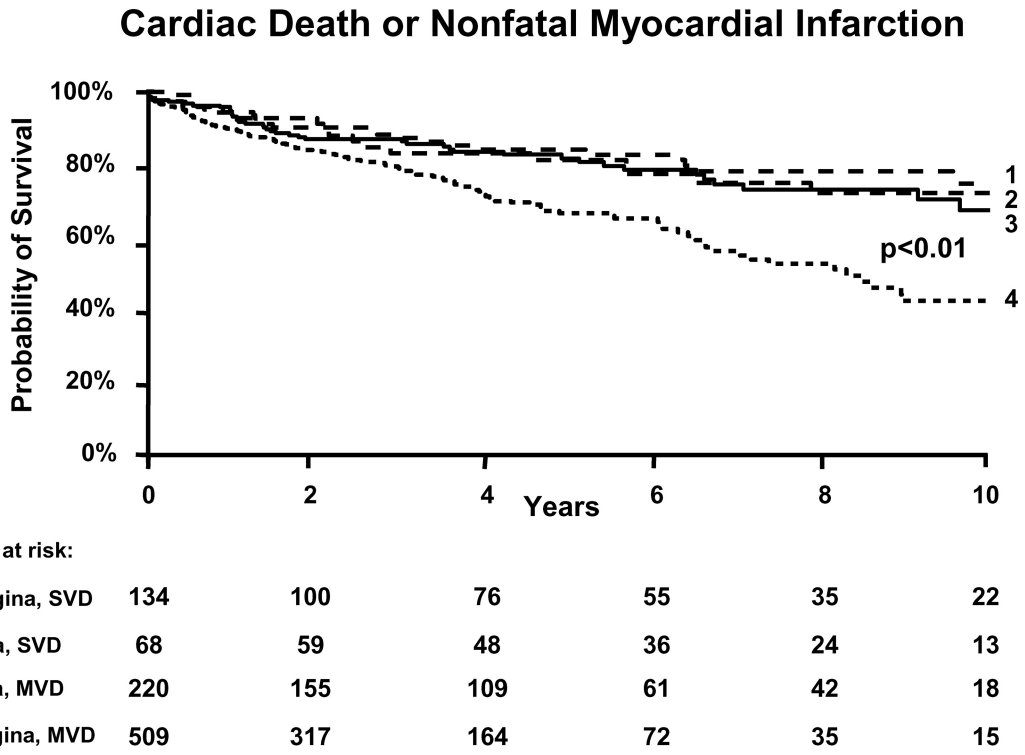

Figure 3. *Kaplan-Meier survival curves showing cardiac event rate in patients with: 1) silent ischemia and single vessel disease; 2) symptomatic ischemia and single vessel disease; 3) symptomatic ischemia and multivessel disease; 4) silent ischemia and multivessel disease.*

This may be related to the fact that patients with symptomatic ischemia and multivessel disease were more often referred for coronary revascularization than patients with silent ischemia and multivessel disease (111/220 (50%) v 141/509 (28%), p<0.0001). Among patients with symptomatic ischemia and multivessel disease, cardiac death occurred in 11/111(11%) patients who were revascularized v 22/109 (20%) patients who were treated by medical therapy (p=0.05). Similarly, in patients with silent ischemia and multivessel disease, cardiac death occurred in 18/141 (13%) patients that were revascularized v 92/368 (25%) patients medically treated (p=0.004).

No gender differences for cardiac death or hard cardiac events were present considering the overall population, as well as separately the two groups of patients with symptomatic or silent ischemia, or the two groups of patients with single or multivessel disease.

Incremental Prognostic Value. Independent predictors of cardiac death in a multivariate analysis were age (HR 1.06, 95% CI 1.04-1.08), male gender (HR 1.8, 95% CI 1.2-2.7), smoking (HR 1.5, 95% CI 1.1-2.0), and number of ischemic segments (HR 2.1, 95% CI 1.1-4.1). Independent predictors of cardiac death or myocardial infarction were age (HR 1.04, 95% CI 1.02-1.05), previous myocardial infarction (HR 1.4, 95% CI 1.1-2.1), and presence of ischemia during DSE (HR 2.0, 95% CI 1.0-3.7). For every ischemic segment there was a two-fold increment in risk of late cardiac events. Silent induced ischemia was also an independent predictor of cardiac death and myocardial infarction (HR 1.7, 95% CI 1.1-2.0). An interaction term between silent induced ischemia and the presence of ischemia was not significant.

Discussion

The current results demonstrate that patients with silent myocardial ischemia during DSE have a higher incidence of long-term cardiac death and myocardial infarction compared to patients with symptomatic myocardial ischemia. This association was observed irrespective of the presence and extent of resting or dobutamine stress induced new wall motion abnormalities.

Significant changes were observed in medical treatment in patients with and without angina during DSE. Patients with silent myocardial ischemia during DSE were less often prescribed β-blockers, aspirin, and statins compared to patients with symptomatic ischemia. In addition, late revascularization was less frequently performed in patients with asymptomatic ischemia during DSE. Moreover, in patients with multivessel disease and symptomatic or silent ischemia during DSE, cardiac death occurred more often in patients medically treated compared with patients who underwent myocardial revascularization.

The worse long-term prognosis of patients with asymptomatic myocardial ischemia could be associated with a less aggressive anti-ischemic medical therapy and coronary revascularization. β-blockers have been unequivocally shown in multiple studies to reduce both angina and the incidence, frequency, and extension of episodes of silent ischemia (26-28). The combination of β-blockers with other anti-ischemic medical therapy such as calcium channel antagonists has been also found to reduce the incidence of myocardial ischemia more than either type of these medications alone (29, 30). Also statin therapy has been shown able to decrease transient myocardial ischemia, probably due to an improved endothelial function (31). Furthermore, myocardial revascularization was previously shown to be associated with a decrease of asymptomatic ischemia and an improvement of clinical outcome compared to angina- or ischemia-guided strategy in a prospective study (32). In this study, the decision to perform coronary angiography was made on clinical grounds by the treating cardiologist. The prescription rate of betablockers or calcium antagonist were relatively low. It seems that in some patients symptoms of angina instead of signs of ischemia on DSE were the reason to prescribe betablockers or calcium antagonists and to perform myocardial revascularization.

Additionally, in this study absence of symptoms during dobutamine stress induced ischemia was frequently observed (69%); this is in line with previous studies (4, 33, 34) and is physiologically explained by the ischemic cascade since systolic dysfunction precedes the development of angina pectoris.

Comparison to Previous Studies. There are only a few studies on the long-term prognostic implications of silent myocardial ischemia during DSE. Bigi et al (35) studied 407 survivors from a first uncomplicated myocardial infarction who had myocardial ischemia during DSE and were followed for a 10 months period. Cardiac death and nonfatal myocardial re-infarction occurred respectively in 6/407 (1%) and 13/407 (3%) of patients. No significant difference in spontaneous event-free survival was observed among patients with silent ischemia. Bonou et al (33) studied 289 patients with advanced age undergoing DSE. During a 35±13 month follow-up period, 15/289 (5%) cardiac deaths and 19/289 (7%) nonfatal myocardial infarctions occurred. There was no significant difference in prognosis between patients with silent or symptomatic myocardial ischemia. In the present study the cardiac event rate was higher than in the previous studies; this may be related to the longer and nearly complete (99.5%) follow-up. Previous data in 224 patients who underwent dobutamine stress myocardial perfusion imaging showed a similar outcome between patients with silent and symptomatic ischemia (34). The different findings in that study may be related to differences in sensitivity between myocardial perfusion imaging and DSE, as well as a possible differences in management of patients following a positive study by these two techniques.

Some previous studies suggested a common pathway for both the electrical and painful response to ischemic stimulus (8). These studies showed that during exercise stress testing a higher incidence of ST-segment changes occurred in patients with symptomatic ischemia (8, 14, 15). However, the extent of ischemia was comparable in patients with and without symptomatic ischemia during dobutamine stress echocardiography. The mechanism underlying the pathogenesis of silent or symptomatic ischemia is complex and may include variations in pain threshold, a central nervous system alteration or a particular biochemical pattern of inflammatory system activation (36, 37). The relation between angina and extent of ischemia is not clear. Several studies have assessed the extent of ischemia in the presence and in absence of symptomatic myocardial ischemia during stress test with contradicting results. Some investigators have reported a greater extent and severity of ischemia in symptomatic patients than in those with silent myocardial ischemia (11-16), while other studies reported no difference in the amount of ischemic myocardium between patients with and without symptomatic myocardial ischemia during exercise or pharmacological stress testing (4-10). In the present study there are no significant differences between dysfunctional segments at rest and number of ischemic segments at peak in patients with and without symptomatic myocardial ischemia. Moreover, the extent of ischemia during DSE was an independent predictor of cardiac death and myocardial infarction so as number of vessels disease was related to an increased rate of cardiac events, particularly in patients with symptomatic ischemia. This is in line with previous studies that show the total amount of ischemic territory at risk is more related to the outcome than the presence of symptoms (3, 18, 19, 38, 39).

Study Limitations

Data on coronary angiography were not available in all patients.

Conclusions

This study showed that patients with asymptomatic myocardial ischemia during DSE had a worse long-term cardiac event-free survival rate as compared to patients with symptomatic myocardial ischemia. Patients with asymptomatic ischemia should be treated with a complete medical therapy or revascularization as patients with symptomatic myocardial ischemia.

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Chapter 7

Clinical and Prognostic Implications of Angina Pectoris Developing during Dobutamine Stress Echocardiography in the Absence of Inducible Wall Motion Abnormalities

Elhendy A, Biagini E, Schinkel AFL, van Domburg RT,

Bax JJ, Rizzello V, Roelandt JRTC, Poldermans D

Am J Cardiol, in press

Abstract

Background. The aim of this study was to assess the incidence, clinical correlates and prognostic significance of angina during dobutamine stress echocardiography (DSE) in patients without inducible wall motion abnormalities.

Methods. We studied 2117 patients (age = 61 ± 13 years, 1149 men) who underwent high dose DSE and had no new or worsening wall motion abnormalities during DSE. Follow up events were hard cardiac events (cardiac death or non-fatal myocardial infarction) and myocardial revascularization.

Results. Angina was induced in 217 (10%) patients during stress. DSE was normal in 1198 (57%) patients, whereas 919 (43%) patients had fixed wall motion abnormalities. During a mean follow up of 5.5 ± 3.7 years, 143 (7%) patients died of cardiac causes and 78 (4%) patients had non fatal myocardial infarction. Patients with angina during DSE were more likely to have a prior history of exertional angina (64% vs 16%, $p<0.001$), and had a higher resting wall motion score index (1.29 ± 0.5 vs 1.17 ± 0.4, $p = 0.01$), compared to patients without angina. The annual hard cardiac event rate was 2.2% in patients with dobutamine induced angina and 2.1% in patients without (p = NS). Myocardial revascularization was performed more frequently in patients with than without dobutamine induced angina (39% vs 14%, $p<0.0001$). In a Cox regression model, independent predictors of hard events were age (risk ratio [RR] 1.03, 95% confidence intervals [CI] 1.02-1.04, male sex (RR 1.6, CI 1.1-2.2), smoking (RR 1.5, CI 1.1-2.9) and resting wall motion score index (RR 2.6, CI 1.8-3.8).

Conclusions. In patients without ischemia by echocardiographic criteria during DSE, inducible angina pectoris is associated with a high incidence of revascularization during follow up. However, the hard cardiac event rate is not different in patients with and without dobutamine induced angina.

Introduction

Exercise induced angina has been reported as a predictor of composite cardiac events among patients with normal left ventricular function who had no inducible wall motion abnormalities with exercise echocardiogram (1). However, the clinical significance and prognostic implications of dobutamine induced angina among patients without echocardiographic ischemia are not known. It is not known whether angina in these patients is a non specific symptom or signifies undetected myocardial ischemia due to a potential shortcoming of the DSE technique. This study assesses the incidence, clinical correlates and prognostic significance of dobutamine induced angina (DIA), in patients without inducible wall motion abnormalities during DSE.

Methods

Patients. The study population consisted of 2129 consecutive patients with limited exercise capacity, referred for DSE between 1990 and 2002 at the Thoraxcenter, Rotterdam, the Netherlands who had no inducible new or worsening wall motion abnormalities or a biphasic response during DSE. Hypertension was defined as a blood pressure ≥140/90 mmHg, or treatment with antihypertensive medication. Diabetes mellitus was defined as a fasting glucose level ≥7.8 mmol/L or the need for insulin or oral hypoglycemic agents. Hypercholesterolemia was defined as a total cholesterol ≥6.4 mmol/L, or treatment with lipid-lowering medication. Follow-up was successful in 2117 patients (99.5%) who represented the population of this study. The protocol was approved by the Hospital Ethics Committee. All patients gave informed consent before the test.

Dobutamine Stress Protocol. Dobutamine-atropine stress testing was performed according to a standard protocol as previously reported (2). Beta blockers were discontinued at least 24 hours before DSE whenever possible. Other medications were not generally discontinued. After obtaining a baseline echocardiogram, dobutamine was administered intravenously, starting at a dose of 10 μg/kg/min for 3 minutes (5 μg/kg/min in patients with resting left ventricular dysfunction). Incremental dobutamine doses of 10 μg/kg/min were given at 3-minute intervals up to a maximum dose of 40 μg/kg/min. If the test end-point was not reached at a dobutamine dose of 40 μg/kg/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 predicted heart rate), maximal dose of dobutamine and atropine, extensive new wall motion abnormalities, >2 mV downsloping ST-segment depression measured 80 ms after the J point compared with baseline, hypertension (blood pressure >240/120 mm Hg), a decrease in systolic blood pressure of >40 mm Hg compared with at rest, significant arrhythmias, severe angina or any intolerable adverse effect considered to be the result of dobutamine or atropine. An intravenous β-blocker (metoprolol 1 to 5 mg) was available to reverse the adverse effects of dobutamine/atropine if needed. DIA was defined as precordial/central chest pain during or immediately after DSE that lasted at least 1 minute and resolved by discontinuation of the stress test or intravenous metoprolol.

Echocardiographic imaging and interpretation. Two-dimensional echocardiographic images were acquired at rest, during dobutamine stress, and recovery using the standard views. The echocardiograms were recorded in a quad-screen format. Two experienced observers, unaware of the clinical data or symptoms during the stress test, scored the echocardiograms using a standard 16-segment model (2,3). In case of disagreement, a consensus decision was achieved by a third observer. 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, or a biphasic response in a dyssynergic segment. Patients with ischemia were not included per enrolment criteria. A normal test was defined as absence of wall motion abnormalities at rest and with stress. For each patient, a wall motion score index was calculated by dividing the sum of segment scores by the total number of interpreted segments.

Follow-up. Follow-up data collection was performed by contacting the patient's general practitioner and by review of hospital records. In addition, the vital status was confirmed through the civil data registry. Patients were contacted if needed after confirmation of their vital status. The date of the last review or consultation was used to calculate follow-up time. Follow-up events noted were overall mortality, hard cardiac events (cardiac death and nonfatal myocardial infarction), and myocardial revascularization. Cardiac death was defined as a death caused by acute myocardial infarction, significant cardiac arrhythmias, or refractory congestive heart failure. Sudden death occurring without another explanation was considered as cardiac death. Nonfatal myocardial infarction was defined by the usual criteria of chest pain, elevated cardiac enzyme levels and electrocardiographic changes.

Statistical Analysis. Continuous data were expressed as mean value ± SD. The Student's t test was used to analyze continuous data. Differences between proportions were compared using the Chi-square test. Univariate and multivariate Cox proportional hazard regression models (BMDP Statistical Software Inc., Los Angeles, California, USA) were used to identify independent predictors of follow up events. Variables were selected in a stepwise forward selection manner with entry and retention set at a significance level of 0.05. The risk of a variable was expressed as a hazard ratio with a corresponding 95% confidence interval. Variables were selected for the multivariate analysis if these were significant or showed a trend in the univariate analysis ($p<0.1$). The probability of survival was calculated using the Kaplan-Meier method, and survival curves were compared using the log-rank test. A p value <0.05 was considered statistically significant.

Results

Patient characteristics and stress test data. Mean age was 61 ± 13 years. There were 1149 (54%) men. Angina during DSE occurred in 217 (10%) patients (31% of the patients with a history of typical angina). Atypical chest pain occurred in 112 (5%) patients. Reasons for termination of DSE were achievement of the target heart rate in 1905 (90%), maximal dose of dobutamine/atropine in 109 (5%), ST segment changes in 33 (1.5%), angina in 13 (1%), arrhythmias in 20 (1%), abnormal blood pressure in 19 (1%), and chills or nausea in 18 (1%) patients. Resting wall motion abnormalities without inducible ischemia were detected in 919 (43%) patients.

Clinical data of patients with and without DIA are presented in Table 1. Patients with angina were younger, received a larger dose of dobutamine, were more frequently treated with calcium channel blockers, beta blockers and nitrates and more often had a history of hypertension, known CAD (previous myocardial infarction, and or revascularization) and exertional angina prior to the DSE.

Table 1. Clinical Characteristics of Patients with and without Dobutamine Induced Angina

Clinical data	**Dobutamine induced angina**		
	Yes (N=217)	**No (N=1900)**	**p value**
Age (years)	59 ± 10	61 ± 13	0.02
Men	141 (65%)	1008 (53%)	0.007
Hypertension	77 (35%)	492 (26%)	0.003
Hypercholesterolemia	40 (18%)	295 (16%)	NS
Smoker	51 (24%)	440 (23%)	NS
History of typical angina	139 (64%)	312 (16%)	0.0001
History of atypical chest pain	46 (21%)	278 (15%)	0.01
Diabetes mellitus	24 (11%)	147 (8%)	NS
Previous myocardial revascularization	58 (27%)	178 (9%)	0.0001
Previous myocardial infarction	84 (39%)	357 (19%)	0.0001
Known coronary artery disease	117 (54%)	463 (24%)	0.0001
β-blockers	76 (35%)	440 (23%)	0.001
Calcium channel blockers	76 (35%)	445 (23%)	0.001
Nitrates	117 (54%)	330 (17%)	0.0001
Indication for stress testing			<0.0001
Chest pain	152 (70%)	590 (31%)	
Multiple risk factors	26 (12%)	1082 (57%)	
Risk-stratification after infarction or revascularization	39 (18%)	228 (12%)	

Hemodynamic data are presented in Table 2. Heart rate and systolic blood pressure increased significantly from rest to peak stress in both groups. ST-segment changes occurred more often in patients with DIA. DSE was normal in 1198 (57%) patients. Resting wall motion score index was higher in patients with DIA.

Table 2. Dobutamine Stress Data in Patients with and without Dobutamine Induced Angina

Stress test data	**Dobutamine induced angina**		
	Yes (N=217)	**No (N=1900)**	**p value**
Resting heart rate (beats/min)	71 ±14	73 ± 13	0.01
Stress heart rate (beats/min)	126 ± 24	127 ± 21	NS
Resting systolic blood pressure (mmHg)	134 ± 21	136 ± 24	NS
Stress systolic blood pressure (mmHg)	139 ± 27	139 ± 29	NS
Maximal dobutamine dose (μg/kg/minute)	37 ± 6	34 ± 9	0.001
Atropine use, patients	68 (31%)	401 (21%)	0.001
Achievement of target heart rate	194 (89%)	1711 (90%)	NS
ST-segment depression, patients	25 (12%)	71 (4%)	0.0001
ST segment elevation, patients	25 (12%)	67 (4%)	0.0001
Resting wall motion score index	1.29 ± 0.5	1.17 ± 0.4	0.01
Normal stress echocardiogram, patients	120 (55%)	1078 (57%)	NS
Resting wall motion abnormalities, patients	97 (45%)	822 (43%)	NS

Dobutamine Stress Echocardiography and Outcome. During a mean follow-up of 5.5 ± 3.7 years, there were 435 (21%) deaths, of which 143 (7%) were attributed to cardiac causes. Seventy eight patients (4%) experienced nonfatal myocardial infarction. Myocardial revascularization was performed in 341 (16%) patients. Events in the groups with and without DIA are presented in table 3.

Table 3. Follow-up Events in Patients with and without Dobutamine Induced Angina

Events	**Dobutamine induced angina**		
	Yes (N=217)	**No (N=1900)**	**p value**
Cardiac death	14 (6.5%)	129 (6.7%)	NS
Non fatal myocardial infarction	12 (5.5%)	66 (3.5%)	0.2
Revascularization	84 (39%)	257 (14%)	<0.0001
Coronary artery bypass	41 (19%)	145 (8%)	
Percutaneous interventions	43 (20%)	112 (6%)	
Early revascularization (within 60 days)	33 (18%)	49 (3%)	0.001
Late revascularization	51 (24%)	208 (11%)	0.001
Unstable angina pectoris	30 (14%)	76 (4%)	0.001

Univariate and multivariate predictors of hard cardiac events and all events are presented in table 4.

Table 4. Predictors of Cardiac Events

	Univariate		Multivariate	
	HR (95% CI)	**p**	**HR (95% CI)**	**p**
Hard cardiac events				
Age	1.04 (1.02-1.05)	0.02	1.03 (1.02-1.04)	0.02
Male gender	1.7 (1.2-2.4)	0.01	1.6 (1.1-2.2)	0.03
Smoker	1.6 (1.1-3)	0.01	1.5 (1.1-2.9)	0.02
Resting wall motion score index	2.9 (1.7-4.1)	0.001	2.6 (1.8-3.8)	0.001
Diabetes mellitus	1.7 (1.1-3)	0.01	1.8 (1.2 -2.8)	0.01
Previous myocardial infarction	3 (1.9-4)	0.01		NS
Previous myocardial revascularization	1.5 (1.1-3.1)	0.02		NS
Hard events + revascularization				
Male gender	1.5 (1.1-1.8)	0.01	1.4 (1.1-1.7)	0.01
Angina pectoris	1.4 (1.2-2.2)	0.01	1.4 (1.2-2)	0.01
Previous myocardial infarction	1.6 (1.1-2)	0.005	1.5 (1.2-1.9)	0.01
Resting wall motion score index	1.9 (1.3-2.8)	0.001	1.9 (1.4-2.7)	0.001
Dobutamine induced angina	1.8 (1.2-2.1)	0.001	1.7 (1.2-1.9)	0.001
Smoker	1.4 (1.1-2.8)	0.03		NS
Diabetes mellitus	1.3 (1.1-2.1)	0.04		NS
Previous myocardial revascularization	1.7 (1.2-5.6)	0.02		NS

Survival curves of patients with and without DIA are shown in Figure 1 (hard event). There was no significant difference among patients with and without DIA regarding annual hard cardiac event rate (2.2% vs. 2.1%). Among patients with normal baseline left ventricular function, the annual hard cardiac event rate was 1.5% in patients with DIA and 1.4% in patients without. Among patients with resting wall motion abnormalities, the hard cardiac event rates were 2.8% and 2.7% respectively.

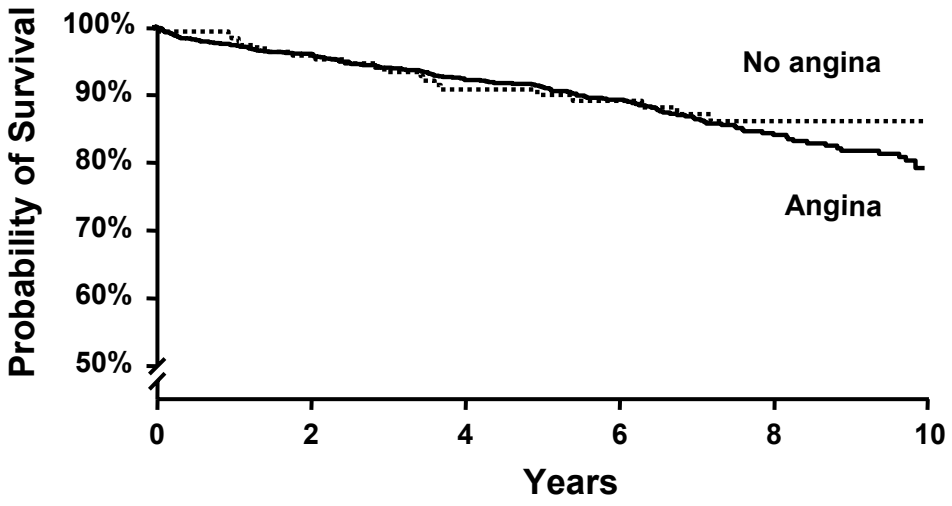

Figure 1. *Kaplan-Meier survival curves (end-point of cardiac death and nonfatal myocardial infarction) in patients with and without angina during dobutamine stress echocardiography.*

Patients with DIA had a higher incidence of unstable angina and revascularization during follow up. Figure 2 presents survival curves (hard events and revascularization) in patients with known versus patients with suspected CAD with and without DIA. Patients with DIA had a higher incidence of the composite end points in the groups with known as well as with suspected CAD. The incidence of cardiac events was higher in patients with known compared to patients with suspected CAD, regardless of DIA.

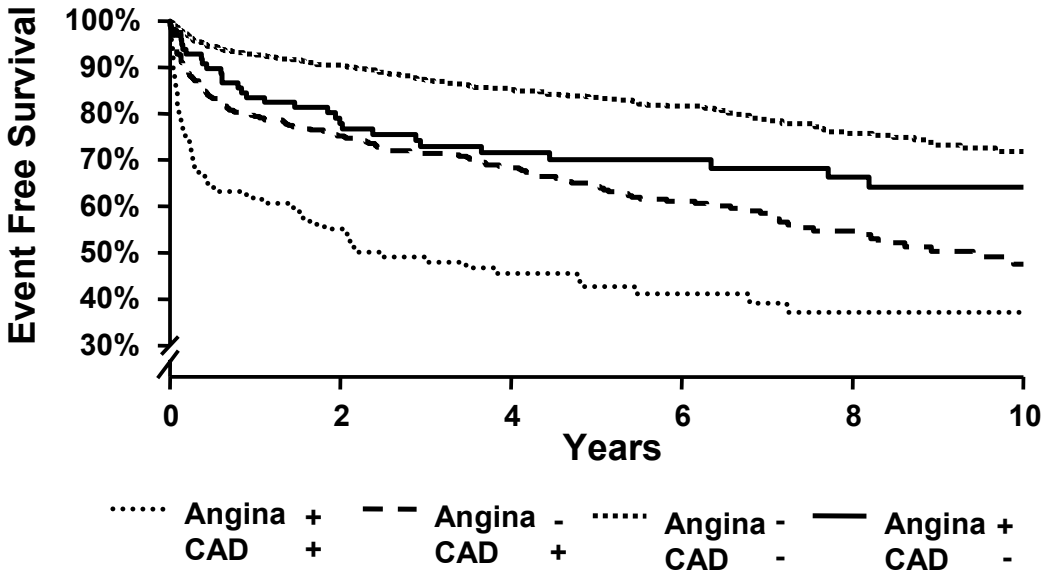

Figure 2. *Kaplan-Meier survival curves (end-point of cardiac death, nonfatal myocardial infarction and revascularization) in patients with and without angina during dobutamine stress echocardiography, with and without a history of coronary artery disease.*

Discussion

The findings of this study are: 1) dobutamine induced angina occurs in 10% of patients who do not demonstrate echocardiographic evidence of ischemia (new or worsened wall motion abnormalities); 2) patients with DIA are more likely to have exertional angina before DSE and history of known CAD; 3) patient with DIA have two to three fold higher incidence of revascularization during follow up as compared to patients without DIA; 4) The higher incidence of revascularization in patients with DIA was observed among patients with known as well as patients with suspected CAD; 5) the annual rate of cardiac death and non fatal myocardial infarction is similar in patients with and without DIA; 6) the hard cardiac event rate is fairly low in this population without inducible wall motion abnormalities, and is strongly related to the baseline left ventricular function.

Transient wall motion abnormalities during DSE are the standard diagnostic markers of myocardial ischemia (4,5). The significance of angina in absence of transient wall motion abnormalities is unclear. A possible mechanism is a non specific response to dobutamine infusion with stimulation of pain receptors due to vigorous myocardial contractility. In our study, patients with angina received higher dose of dobutamine. The second mechanism would be the occurrence of actual myocardial ischemia that could not be depicted by the echocardiogram. Certain methodological limitations may contribute to this such as segmental suboptimal imaging quality, subjective analysis with observer variation, and modest sensitivity in single vessel disease (4,5). It has been demonstrated that some patients with CAD may have ischemia on myocardial perfusion imaging without inducible wall motion abnormalities or a biphasic response with DSE (6-10). A recent study showed that wall motion abnormalities may be demonstrated after administration of beta blockers in the recovery period, in patients without abnormalities at peak dobutamine stress (11). It is possible that administration of beta blockers or applying another imaging technique in these patients could have resulted in eliciting wall motion or perfusion abnormalities in some of them.

According to the ischemic cascade theory, wall motion abnormalities occur before electrocardiographic changes and angina during ischemia (12). In our study, the test was terminated because of angina in only 13 patients. It is unlikely that inadequate stress level was the underlying reason for absence of inducible wall motion abnormalities in patients with DIA, particularly considering the similar stress heart rate in patients with and without DIA. The amount of ischemic myocardium was shown to have no relation with symptoms of angina during dobutamine-induced myocardial ischemia (13-17). Therefore, it is possible (though speculative) that trivial ischemia may have been missed by echocardiographic imaging. The higher incidence of medications with nitrates and calcium channel blockers in the group with DIA can be explained by the higher prevalence of exertional angina and hypertension in this group. Although it is not a common practice to discontinue these medications before DSE, it is possible that these medications have attenuated the ischemic left ventricular dysfunction in some patients (18).

Many findings of this study suggest that myocardial ischemia could be the underlying mechanism of DIA in a significant proportion of patients. These include the higher incidence of ST segment changes, and the higher incidence of unstable angina and revascularization during follow up among patients with than without DIA. Although there is no definite evidence that ischemia was induced in these patients, the fact that 39% of patients with DIA had significant CAD requiring revisualization during follow up makes this possibility likely.

Patients with DIA were more likely to require revascularization during follow up. This was evident in the groups with known as well as with suspected CAD. Most patients had exertional angina and may have required revascularization for relief of angina even without objective evidence of myocardial ischemia. However, both exertional angina and DIA were independent predictors of the composite end point of cardiac events including revascularization, which suggests that DIA was a leading cause for invasive verification irrespective to clinical and echocardiographic data in some patients.

The incidence of cardiac death and non fatal myocardial infarction was not different with and without DIA. Although it is possible that prognosis was improved in some of the high risk patients with DIA because of revascularization, a prognostic impact of revascularization in these patients remains speculative. Resting left ventricular function, expressed as wall motion score index was the most powerful predictor of outcome in this population without objective evidence of ischemia.

Referring patients with DIA without inducible wall motion abnormalities for coronary angiography may be a reasonable clinical decision because of the high prevalence of

exertional angina in these patients prior to DSE, the fact that stress testing reproduced their typical complaints and the potential shortcomings of the DSE. However, because of the similar (and fairly low) hard cardiac event rate in patients with and without DIA, a reasonable alternative to coronary angiography would be the use of another imaging technique such as myocardial perfusion imaging and deferring the coronary angiography if both tests concur on the absence of ischemia. A recent study has demonstrated that up to 50% of patients with classic exertional angina have a normal exercise echocardiogram. These patients had a favourable outcome during the 3 years following the stress test (19). Shaw et al reported that stable chest pain patients who undergo a more aggressive diagnostic strategy have higher diagnostic costs and greater rates of intervention and follow-up costs. The authors concluded that cost differences may reflect a diminished necessity for resource consumption for patients with normal stress test results (20).

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Chapter 8

Risk Stratification of Patients with Classic Angina Pectoris and no History of Coronary Artery Disease by Dobutamine Stress Echocardiography

Biagini E, Elhendy A, Schinkel AFL, Bax JJ, Rizzello V, van Domburg RT, Rapezzi C, Simoons ML, Poldermans D

J Am Coll Cardiol, in press

Abstract

Background. There are currently no available data to suggest a role of dobutamine stress echocardiography (DSE) in the prediction of death among patients with high clinical pre-test probability. The aim of this study was to assess the prognostic value of DSE in patients with classic angina and no history of coronary artery disease (CAD).

Methods. We evaluated 327 patients (63% males, mean age 64±10 years) with typical angina referred for DSE with a pre-test probability of CAD ≥70%. None had previous revascuarization or myocardial infarction. Follow-up events were cardiac and total mortality and hard cardiac events (cardiac mortality and myocardial infarction).

Results. DSE was abnormal in 202 (62%) patients. During a mean follow-up of 6 years, 89 (27%) deaths (52 cardiac death) and 21 (6%) non-fatal myocardial infarction occurred. The annual cardiac death, all cause mortality and hard cardiac events rates at 5 years were 1.5%, 2.6% and 2.3% in patients with a normal DSE respectively. In patients with an abnormal DSE the 5-year event rates were 3.6%, 5.5% and 5.4% respectively. Cox proportional hazards regression analysis identified myocardial ischemia as independent predictor of cardiac death (HR: 2.5, CI [1.3-4.8]), all cause mortality (HR: 2.1, CI [1.1-4.3]) and hard cardiac events (HR: 3.3, CI [1.9-5.7]).

Conclusions. In patients with a high pre-test probability of CAD, DSE yields independent prognostic information. Myocardial ischemia is independently associated with increased risk of death and hard cardiac events. A normal DSE is associated with a low event rate. These patients can be exempted from invasive studies unless there is a change in clinical status.

To the Editor: The incremental value of myocardial ischemia assessed by dobutamine stress echocardiography (DSE), for predicting cardiac events has been demonstrated in various patients group (1-3). The clinical utility of non-invasive stress testing has been mostly established among patients with intermediate pre-test probability of coronary artery disease (CAD). In patients with low pre-test probability of CAD, exercise echocardiography was shown to provide limited prognostic information and was not routinely recommended (4). There are currently insufficient data to suggest a prognostic role of myocardial ischemia assessed by stress echocardiography in patients with typical angina, who are determined to have a high pre-test probability of CAD. According to the Bayes' theorem, a normal stress test in these patients does only modestly reduce the post-test probability of CAD. Therefore, it is not known whether patients with high pre-test probability of CAD would be considered a low risk population if they had a normal stress echocardiogram. We sought to assess the additional value of myocardial ischemia during DSE in predicting mortality and hard cardiac events in patients with angina and no previous history of CAD.

The study population consisted of consecutive patients with typical angina who were considered to have a high pre-test probability of CAD (>0.7) referred for DSE. This was considered in the presence of typical angina pectoris in women ≥50 years of age and in men ≥30 years of age, according to the published data (5, 6). Patients were excluded if they had a previous myocardial infarction, myocardial revascularization or significant coronary artery stenosis by angiography. Criteria were fulfilled in 329 patients. The protocol was approved by the Hospital Ethics Committee. Follow-up was successful in 327 patients (99%), 28 (8%) underwent early coronary revascularization (within 60 days after the DSE).

DSE was performed and interpreted according to a standard protocol as previously reported (1). Ischemia was defined as new or worsening wall motion abnormality or a biphasic response. An abnormal test was defined as resting wall motion abnormality or ischemia. Follow-up was performed by contacting the patient's general practitioner, review of hospital records, review of civil data registry and contacting the patients if needed after confirmation of vital status. Follow-up events were overall mortality and hard cardiac events (nonfatal myocardial infarction and cardiac death). Survival free of the end point of interest was estimated by the Kaplan-Meier method. Comparison between groups was performed using the log rank test. Univariable and multivariable association of clinical and stress echocardiographic variables with events were assessed in the Cox proportional hazards framework (7). Variables were selected in a stepwise forward selection manner with entry and retention set at a significance level of 0.05. The results of these analyses were summarized as risk ratios with corresponding 95% confidence intervals.

Mean age was 64 ± 10 years. There were 205 (63%) men. Thirty-six (11%) patients had a history of diabetes mellitus, 100 (31%) had hypertension and 24 (7%) had a history of heart failure. There was a significant increase of heart rate and systolic blood pressure from rest to peak stress (from 70 ± 14 beats/min to 128 ± 15 beats/min, p=<0.0001 and from 134 ± 23 mmHg to 146 ± 26 mmHg, p<0.0001, respectively). Target heart rate was reached in 262 (80%) patients.

DSE was normal in 125 (38%) patients. Fixed wall motion abnormalities were detected in 53 (16%) and ischemia was detected in 149 (46%) patients. During a mean follow-up of 6 ± 3.8 years, there were 89 (27%) deaths, of which 52 (16%) were attributed to cardiac causes. Twenty-one (6%) patients experienced nonfatal myocardial infarction. Twenty-five patients out of 125 with a normal stress test (20%) underwent to revascularization, whereas 75 out of 202 patients (37%) with an abnormal test were revascularized (p=0.002). Cox proportional hazards regression analysis for the end-points cardiac death, hard cardiac events and all cause mortality is presented in Table 1. The presence of myocardial ischemia was an independent predictor for all end-points.

Table 1. Predictors of Events by Cox Models

	Univariate	Multivariate
Parameter	**RR (CI)**	**RR (CI)**
Cardiac death		
Clinical Model		
Age	1.05 (1.02 – 1.09)	1.06 (1.03 - 1.10
Male gender	1.8 (1.1 – 3.2)	3.2 (1.5 – 6.7)
Heart failure	3.4 (1.7 – 6.8)	—
Systemic hypertension	1.2 (1.1-1.8)	1.9 (1.1 – 3.6)
Stress Echocardiographic Model		
Resting heart rate	1.02 (1.01 – 1.05)	1.03 (1.01 – 1.05)
Resting wall motion abnormalities	1.9 (1.1 – 3.2)	1.9 (1.1 – 3.7)
Ischemia	2.5 (1.4 – 4.2)	2.5 (1.3 – 4.8)
All cause mortality		
Clinical Model		
Age	1.06 (1.03 – 1.09)	1.07 (1.05 – 1.10)
Male gender	1.4 (1.1 – 2.0)	2.1 (1.3 – 3.5)
Heart failure	2.1 (1.3-3.5)	
Systemic hypertension	1.2 (1.1 – 1.7)	1.6 (1.1 – 2.6)
Stress Echocardiographic Model		
Resting heart rate	1.02 (1.01 – 1.12)	1.03 (1.01 – 1.05)
ST depression on ECG during stress	1.2 (1.1 – 2.0)	2.1 (1.1 – 4.3)
Resting wall motion abnormalities	1.3 (1.1 – 1.8)	—
Ischemia	1.5 (1.1 – 2.2)	1.6 (1.1 – 2.6)
Hard cardiac events		
Clinical Model		
Age	1.04 (1.01 – 1.07)	1.04 (1.01 – 1.07)
Male gender	2.0 (1.2 – 3.2)	2.8 (1.5 – 5.3)
Heart failure	2.1 (1.1 – 3.9)	—
Systemic hypertension	1.2 (1.1-1.9)	1.9 (1.1 – 3.3)
Echocardiographic Model		
Resting heart rate	1.01 (1.00 – 1.03)	1.03 (1.01 – 1.05)
Resting wall motion abnormalities	1.5 (1.1 – 2.4)	—
Ischemia	2.4 (1.6 – 3.8)	3.3 (1.9 – 5.7)

Kaplan-Meier survival curves for the end-point cardiac death are presented in Figure 1. Patients with an abnormal DSE had a higher incidence of cardiac death compared to patients with a normal study. The annual cardiac death, all cause mortality and hard cardiac event rates at 5 years were 1.5%, 2.6% and 2.3% in patients with a normal test and 3.6%, 5.5% and 5.4% in patients with abnormal DSE respectively.

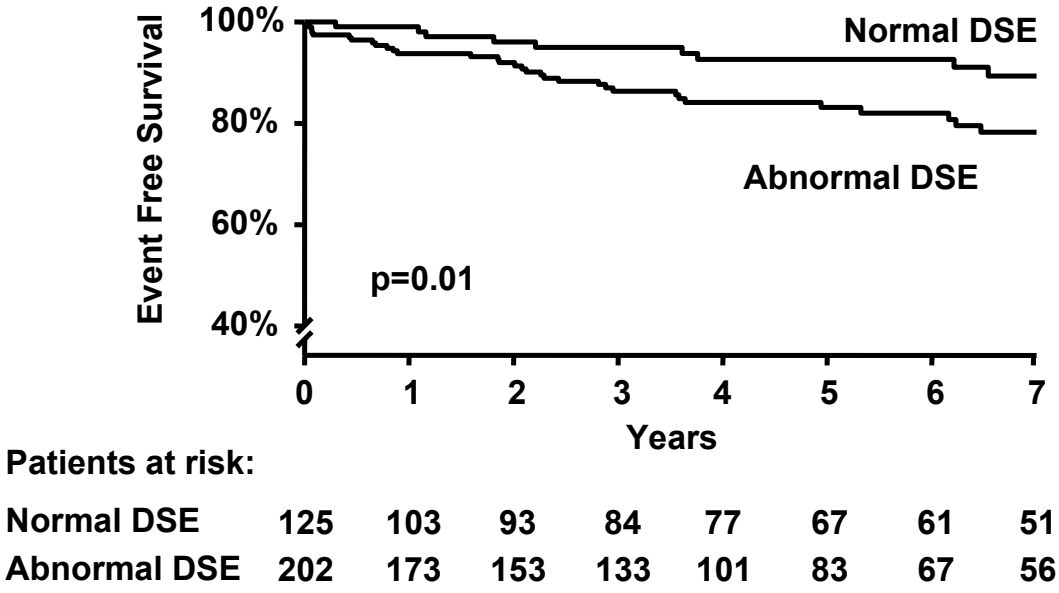

Figure 1. *Kaplan-Meier survival curves (end-point of cardiac death) in patients with high pre-test probability of coronary artery disease.*

An additional analysis was performed excluding patients with early revascularization. This analysis of 299 patients showed that myocardial ischemia was an independent predictor for cardiac death [RR 2.7, CI (1.2-5.7)], all cause mortality [RR 2.3, CI (1.4-3.8)] and hard cardiac events [RR 4.3, CI (2.3-8.1)]. In this group, the annual cardiac death, all cause mortality and hard cardiac event rates at 5 years of follow-up in patients with a normal DSE were 0.9%, 1.8% and 1.2% respectively. In patients with an abnormal DSE event rates were 3.1%, 4.7% and 4.7% respectively.

In this study DSE added independent prognostic information, additional to clinical and hemodynamic parameters in patients with angina and high pre-test probability of CAD. Patients with a normal DSE had a lower risk of death and hard cardiac events, whereas in patients with an abnormal DSE the incidence of all events was substantially higher. The presence of myocardial ischemia was the strongest independent predictor for all end-points and was associated with increased risk of events after adjustment to clinical data.

The prevalence of CAD in patients who present with typical angina is expected to be approximately 90% for men and 70% for women (8). In this study however, DSE was normal in 38% of the population. The results of our study indicate that patients with a normal DSE have a low event rate during intermediate to long term follow up and therefore these patients, who represent a relatively large proportion of the study population, can be exempted from further (invasive) diagnostic evaluation, unless a change in clinical status occurs.

Few studies evaluated the prognostic value of stress echocardiography in patients with high pre-test probability of CAD. These studies used composite endpoints that include soft events such as unstable angina and revascularization (9, 10), or were not powered enough to demonstrate an incremental value of myocardial ischemia alone (11). To our knowledge, the independent association of myocardial ischemia with mortality in these patients has not been established. A recent study by Hachamovitch et al. (12), demonstrated that myocardial perfusion imaging provided incremental prognostic information for predicting cardiac death in 1270 patients with high likelihood of CAD, who underwent exercise or adenosine stress myocardial perfusion tomography.

Although patients were determined to have high pre-test probability of CAD in our study, the annual hard cardiac event rate was moderate (4%). This can be explained by exclusion of patients with previous myocardial infarction, unstable symptoms and history of CAD, which resulted in inclusion of a stable population with preserved left ventricular systolic function. Although this study excluded patients with cardiomyopathy, the possible existence of other cardiac conditions that may be associated with cardiac death without ischemia such as cor pulmonale may have been confounding. However, the incremental significance of myocardial ischemia was demonstrated despite of this potential limitation.

We concluded that in patients with classic angina, determined to have a high pre-test probability of CAD, DSE yields independent prognostic information. A negative DSE is associated with a relatively low event rate for cardiac and all cause mortality as well as for the combined end-point of hard cardiac events. These findings have important clinical implications since these patients can be exempted from invasive studies if they have no change in clinical status. Myocardial ischemia during DSE is independently associated with increased risk of death after adjustment for clinical data.

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Chapter 9

Accuracy of Non-invasive Techniques for Diagnosis of Coronary Artery Disease and Prediction of Cardiac Events in Patients with Left Bundle Branch Block: a Meta-analysis

Biagini E, Shaw LJ, Poldermans D,
Schinkel AFL, Rizzello V, Elhendy A, Bax JJ

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Abstract

Background. Non-invasive evaluation of coronary artery disease in patients with left bundle branch block has limitations inherent to different modalities and the relative merits of the tests are unclear. This meta-analysis assessed the accuracy of the most frequently used non-invasive techniques, including exercise electrocardiography, myocardial perfusion imaging and stress echocardiography, for the detection of coronary artery disease and the prediction of cardiac events in patients with left bundle branch block.

Methods. A systematic review of all reports on detection of coronary artery disease and prediction of cardiac events in patients with left bundle branch block (published between January 1970 and December 2004) revealed 55 diagnostic and 9 prognostic reports with sufficient details for calculating the sensitivity and specificity of each modality. Random effects models were used to calculate summary odds ratios and 95% confidence intervals.

Results. The overall sensitivity was highest for (visually analysed) exercise electrocardiography and myocardial perfusion imaging compared to stress echocardiography (83.4% and 82.1% versus 74.6% respectively, $p<0.0001$); quantitatively analysed myocardial perfusion imaging yielded an even higher sensitivity (88.5%). stress echocardiography had the highest specificity (88.7%) versus myocardial perfusion imaging (41.2%) and exercise electrocardiography (60.1%) ($p<0.0001$). From 8 reports, the relative risk of cardiac death or myocardial infarction with an abnormal stress echocardiography and myocardial perfusion imaging was elevated >7-fold but did not differ by imaging modality ($p=0.9$).

Conclusions. Meta-analysis of non-invasive assessment of coronary artery disease in patients with left bundle branch block shows that exercise electrocardiography and myocardial perfusion imaging have the highest sensitivity (83.4% and 82.1%), while stress echocardiography has the highest specificity (88.7%). Prognostic accuracy of myocardial perfusion imaging and stress echocardiography appears comparable.

Introduction

Left bundle branch block (LBBB) is associated with adverse clinical outcome, in particular in patients with known coronary artery disease (CAD) or after myocardial infarction (1-3). Non-invasive evaluation of CAD in patients with LBBB has several limitations and continues to be a challenge in cardiology. Pre-existent repolarization abnormalities due to abnormal excitation activity with consequent asynchronous ventricular contraction and myocardial perfusion abnormalities hamper the diagnostic accuracy of the available non-invasive techniques, including exercise electrocardiography (ECG), stress echocardiography (SE) and myocardial perfusion imaging (MPI). In particular, a high false-positive rate has been reported for the detection of left anterior descending (LAD) disease. In an attempt to improve the diagnostic accuracy of non-invasive imaging modalities, several investigators have examined the use of pharmacological stress instead of exercise stress, and have adopted different criteria to define myocardial ischemia. In addition to diagnosis of CAD, SE and MPI have been proposed for prognosis and subsequent risk stratification in patients with LBBB. Over the past 30 years, multiple studies have evaluated the diagnostic and prognostic value of both non-invasive techniques in patients with LBBB; however, a direct comparison is not available and the relative merits of the various modalities remains a matter of debate. Therefore, a meta-analysis of the published data on the aforementioned non-invasive techniques has been performed for the detection of CAD and the prediction of (cardiac) events in patients with LBBB.

Methods

Data Sources. The objective of the current meta-analysis was to evaluate the published reports on exercise ECG, MPI and SE in patients with LBBB for: 1. the detection of CAD (diagnostic merit), considering coronary angiography as "the gold standard" and 2. the prediction of cardiac events (prognostic merit). The studies were identified by means of several combined search strategies. 1) A search of the MEDLINE database (January 1970 to December 2004) was conducted. The term LBBB was combined which each of the following terms: exercise ECG, non-invasive imaging, coronary artery disease, radionuclide imaging, SPECT, SE, thallium-201, technetium-99m sestamibi, technetium-99m tetrofosmin, dipyridamole, adenosine, and dobutamine. 2) A manual search of 20 cardiology and nuclear medicine journals from January 1970 to July 2004 was carried out. 3) The reference lists of the reports obtained through these searches were screened for additional articles that may have been missed. Only articles in English and those containing primary data were considered; reviews or abstracts were excluded.

Data Selection. *Inclusion criteria.* For inclusion in the analysis on the diagnosis of significant CAD, the following criteria had to be met: 1) studies were included only if patients underwent coronary angiography; 2) the study contained sufficient details allowing calculation of sensitivity and specificity for detection of CAD. For inclusion in the analysis on the prognostic value, only studies with a minimum of 1 year of mean follow-up data collecting major adverse cardiac events and including $\geq$95% of enrolled patients.

Exclusion criteria. Exclusion criteria for the diagnostic analysis were: 1) studies including patients with intermittent LBBB on the ECG; 2) studies in patients with LBBB and idiopathic dilated cardiomyopathy without angiographically significant CAD; 3) studies only reporting segmental analysis without per patient analysis. Exclusion criteria for the prognostic

analysis were: 1) studies reporting not enough data to calculate 2 x 2 tables for hard cardiac events (cardiac death and myocardial infarction, either individually or combined).

Data Collection and Study Definitions. For each study the following characteristics were noted: the year of publication, the mean or frequency of clinical characteristics including gender, age, cardiac risk factors, the modality (exercise ECG, MPI, SE) to evaluate CAD, the type of stress, the radionuclide tracer (in case of MPI), and the segmental model (number of segments) used for analysis. The gold standard for CAD was $\geq$50% or $\geq$70% coronary artery stenosis on angiography. From each of the prognostic studies, the duration of follow-up, the frequency and events (cardiac death, infarction) were noted.

Nuclear perfusion data were recorded in terms of normal or abnormal findings. Perfusion abnormalities in the LAD territory were noted separately, if available. When more than one stressor (i.e. exercise and pharmacological stress) was used in the same population with independent results, studies were included in the meta-analysis as separate results.

Similarly, stress echocardiographic data were recorded as normal and abnormal findings. Wall motion abnormalities in the LAD territory were also noted, when retrievable.

Angiographic data on coronary arteries were recorded as the presence or absence of angiographically significant CAD and when retrievable LAD disease or single- and multi-vessel disease was noted.

For prognostic purposes, only hard events were noted during follow-up and were recorded as (cardiac) death, non-fatal myocardial infarction, and combined cardiac events (cardiac death or myocardial infarction).

Statistical Analysis. For each of the published reports, we discerned available clinical characteristics for mean age and follow-up time period as well as the relative frequency of men, angiographic coronary disease, hypertension, diabetes, and prior myocardial infarction. From the compilation of this data, the weighted average frequencies or mean was calculated.

Diagnostic value of tests. From each of the selected reports, a 2 x 2 table was constructed that included false-positive and false-negative test results as well as true-negative and true-positive test results. Based upon this 2 x 2 frequency data, sensitivity and specificity were calculated for overall disease, LAD disease, single- and multi-vessel disease for exercise ECG, MPI and SE. In addition, for nuclear imaging, analyses were repeated for visual and quantitative analysis of data. From the combined data, a weighted (by the proportional sample size) average sensitivity (number of true positive tests divided by the total number of patients with angiographically significant CAD) and specificity (number of true negative tests divided by the total number of patients without angiographically significant CAD) was calculated. Overall diagnostic accuracy was defined as the total of true-positive and true-negative tests divided by the total number of patients.

Subanalyses were performed to assess and compare sensitivity/specificity for the different modalities (when data available) for single- versus multi-vessel disease, LAD disease and different stressors. As well, we compared the diagnostic accuracy by the type of stress (pharmacologic versus exercise), when available.

Using Comprehensive Meta-Analysis software, the summary odds ratio of a positive test with CAD versus a negative test with CAD was calculated (www.meta-analysis.com, access date: December 2004). The odds ratio (with 95% confidence intervals, CI) was calculated using a random effects model. A chi-square test for heterogeneity, a measure of the combinability of the reports, was calculated and, for all but the exercise ECG, the p value was >0.05 revealing that the presentation of summary odds ratio data was acceptable.

A summary receiver operating characteristics (ROC) curve was displayed by plotting the false-positive rate on the X-axis by the diagnostic sensitivity values on the Y-axis for

individual reports using the exercise ECG, MPI and SE results. The line of best fit for the scatterplot was calculated using a cubic spline function optimized for the amount of explanatory variance. The concordance (C-) index from the ROC curve was calculated for exercise ECG, MPI and SE.

Prognostic value of tests. A 2 x 2 table was generated separately for the endpoint of cardiac death or myocardial infarction. From the 2 x 2 data, a relative risk ratio (RR) (with 95% CI) was calculated using Comprehensive Meta-Analysis software (www.meta-analysis.com, access date: December 2004). A summary RR ratio (with 95% CI) was calculated for each technique using the random effects model calculation of Mantel-Haenszel. A chi-square test for heterogeneity was calculated to determine the adequacy of combining the individual reports. In each case, the $p>0.70$ such that combining the individual reports was deemed acceptable.

From the summary data, the cardiac death or myocardial infarction rates were calculated within a range of follow-up duration varying from 6 months to 5 years. Accordingly, event-free survival (25th and 75th percentiles) was plotted for 5-year follow-up. The RR ratio (with 95% CI) was calculated at 5-year follow-up.

To compare time-related change in event-free survival for patients with normal MPI findings, we compared the 6-month event rates in those with a normal MPI as compared with similarly-aged event rates in the general population (http://www.nhlbi.nih.gov/resources/docs/04_chtbk.pdf, access date: January 2005). Using this set of comparisons, this defined the time point at which there was an increased risk for those with a low-risk MPI.

Results

Diagnostic Accuracy to Detect CAD. The baseline and clinical characteristics of the different studies focusing on detection of CAD are summarized in Table 1 and divided according to the non-invasive technique used. For exercise ECG, a total of 6 studies (n=182 patients with 177 undergoing coronary angiography) met the inclusion criteria (4-9). In general, patients undergoing exercise ECG were younger, with a higher prevalence of male gender and less risk factors for CAD as compared to patients undergoing MPI or SE ($p<0.05$ for each comparison). For MPI, a total of 43 studies were reported with 1,785 patients (with 1,014 undergoing coronary angiography) (10-43). For SE, 6 studies were reported with 236 patients (all having coronary angiography) (29, 39, 41, 44-46).

Table 1. Baseline Characteristics Classified According to the Non-invasive Technique Used

	Exercise ECG	MPI	SE
Years of enrollment	1974-1998	1993-2004	1995-2001
Total nr of patients	182	1,785	236
Patients with angiography	177	1014	236
Clinical data			
% Male	68.5%	56.2%	58.6%
Mean age (yrs)**	47±9	62±6	60±9
% Prior MI**	26.9%	23.2%	4.7%
% HTN**	8.7%	39.3%	57.5%
% DM	NA	20.1%	16.8%
Mean LVEF (%)	NA	46±14	49±12
Angiography			
Absence of CAD	56.6%	46.8%	42.9%
MVD	32.0%	24.0%	30.7%
Stressor			
Exercise**	100.0%	48.8%	16.7%
Pharmacological stress	NA	41.9%	83.3%
Combined	NA	9.3%	NA

**$p<0.05$

DM: diabetes mellitus; CAD: coronary artery disease; ECG: electrocardiography; HTN: hypertension; LVEF: left ventricular ejection fraction; MI: myocardial infarction; MPI: myocardial perfusion imaging; MVD: multi-vessel disease; NA: not available; SE: stress echocardiography.

Table 2 shows the weighted average (by sample size) diagnostic accuracy for exercise ECG, MPI, and SE. The overall sensitivity was highest for MPI (88.5% when quantitative analysis was used), and both exercise ECG and MPI had a significantly higher sensitivity as compared to SE. The overall specificity was significantly higher for SE as compared to MPI and exercise ECG (88.7% versus 41.2% and 60.1% respectively, $p<0.0001$). The overall accuracy for detection of CAD was 66.4% for exercise ECG, 70.3% for MPI (improving to 78.0% with quantitative analysis), and 84.4% for SE ($p<0.0001$).

Table 2. Weighted Average Diagnostic Accuracy for Detection of CAD

	Exercise ECG	MPI	SE	Overall p-value	Comparative Differences
Sensitivity					
Overall	83.4	82.1 (V)	74.6	<0.01	ECG / MPI vs. SE
	-	88.5 (Q)	-	-	-
Single-vessel CAD	80.5	83.3	53.0	<0.0001	ECG / MPI vs. SE
Multi-vessel CAD	95.4	87.2	93.7	NS	-
LAD	NA	91.9 (V)	79.3	<0.0001	
		89.4 (Q)			-
Specificity					
Overall	60.1	41.2 (V)	88.7	<0.0001	All 3 different
		38.2 (Q)			-
LAD	NA	54.9 (V)	91.5	<0.0001	-
		51.8 (Q)			-
Accuracy	66.4	70.3 (V)	84.4	<0.0001	ECG / MPI vs. SE
		78.0 (Q)			-

CAD: coronary artery disease; ECG: electrocardiography; LAD: left anterior descending; Q: quantitative; MPI: myocardial perfusion imaging; SE: stress echocardiography; V: visual.

Summary Odds Ratio for Positive and Negative Tests with CAD. Figure 1 depicts the odds of a positive versus negative test having CAD at angiography. The odds of a positive echocardiogram were elevated 30.8-fold (95% CI=13.66-62.8, p<0.0001) as compared with a negative study. By comparison, the odds of a positive MPI were only elevated 8.3 (95% CI=5.1-13.64, p<0.0001) when compared with a negative perfusion study. For exercise ECG, the odds ratio was elevated 4.3-fold (95% CI=1.8-10.3, p=0.001) but revealed substantial heterogeneity around this summary measure (p<0.05).

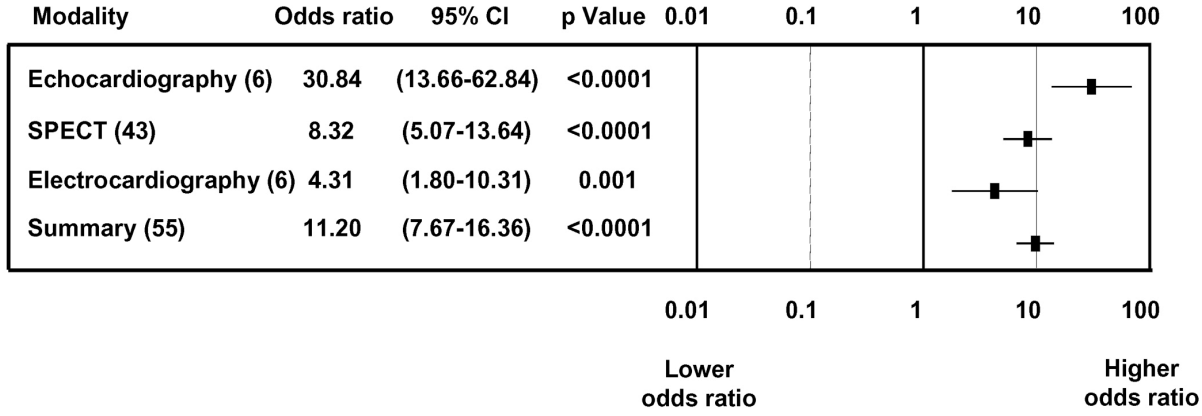

Figure 1. *Diagnostic accuracy expressed as odds ratio and 95% CI of a positive versus negative test for exercise ECG, MPI and SE.*

Summary ROC Curves. Based upon optimal diagnostic accuracy data for exercise ECG, MPI and echocardiography, a plot of the false positive and diagnostic sensitivity revealed variable disease classification rates (Figure 2). The C-index was highest for SE (0.85) when compared with stress MPI (0.72) and exercise ECG (0.66).

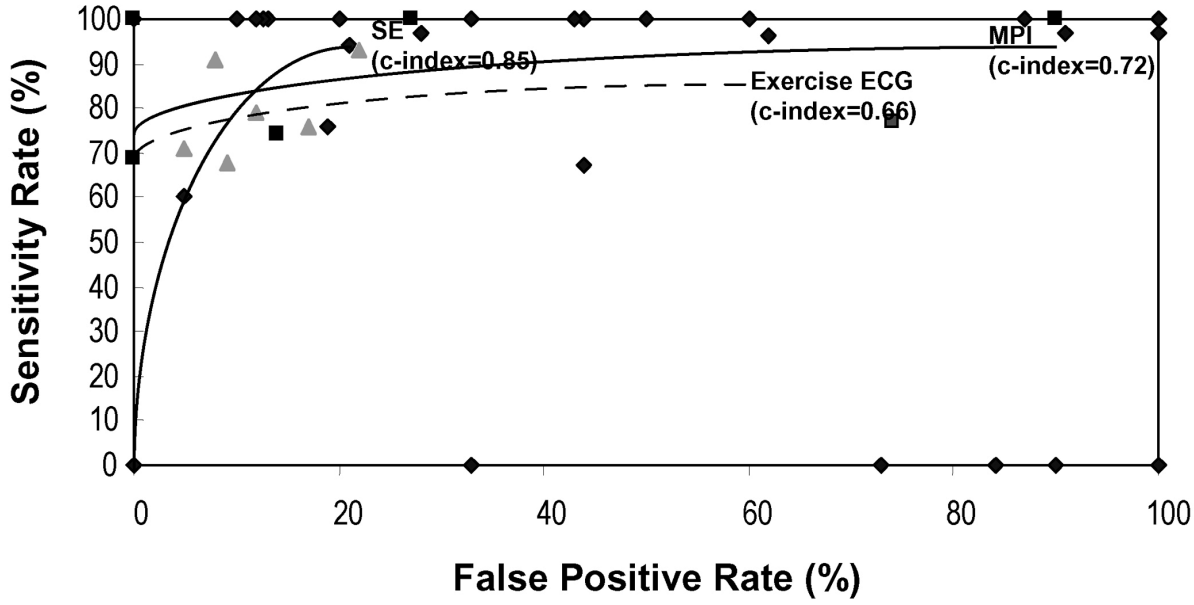

Figure 2. *Summary ROC curves for exercise ECG, MPI, and SE for detection of CAD in patients with LBBB.* ■*= exercise ECG;* ♦*= MPI;* ▲*= SE.*

Diagnostic Accuracy to Detect Single- versus Multi-vessel Disease. For detection of single-vessel disease, MPI had the highest sensitivity when compared to exercise ECG and SE (83.3% versus 80.5% and 53.0% respectively, $p<0.001$, Table 2). For detection of multi-vessel disease, MPI and SE had comparable sensitivities (87.2% and 93.7%, NS), which were also comparable to exercise ECG (95.4%, NS versus MPI and SE, Table 2).

Diagnostic Accuracy of Different Stressors. For MPI, 21 studies used exercise and 18 used pharmacological stress (combined with exercise in 4 studies). The sensitivity was high for both exercise (92.9%) and pharmacological stress (88.5%), while the specificity was significantly lower for exercise stress (23.3%) as compared to pharmacological stress (74.2%, $p<0.01$, Figure 3). For SE, only one study used exercise and 5 used pharmacological stress. In general, SE had a lower sensitivity than MPI (76% for exercise SE and 74% for pharmacological SE, $p<0.01$ vs MPI). Conversely, the specificity of SE was superior to MPI (even for pharmacological MPI).

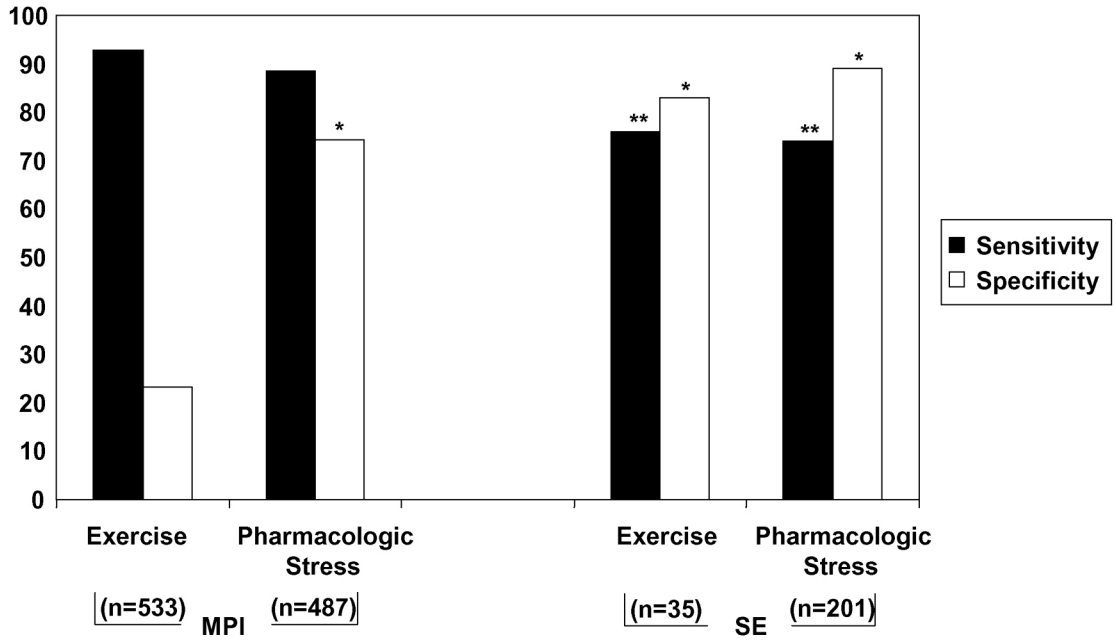

Figure 3. *Diagnostic accuracy according to stressor (exercise vs pharmacological stress) for MPI and SE for detection of coronary artery disease.*

Diagnostic Accuracy to Detect LAD Disease. Detailed information of exercise ECG to detect LAD disease was not available. For MPI, the sensitivity was high, both for exercise and pharmacological stress (Figure 4A). The specificity improved significantly (from 47% to 80%, $p<0.01$) when pharmacological stress was used. For SE, the sensitivity was higher for exercise compared to pharmacological stress ($p= 0.028$), whereas specificity was similar between the two stressors type (Figure 4B). However, only 1 report for exercise SE was available.

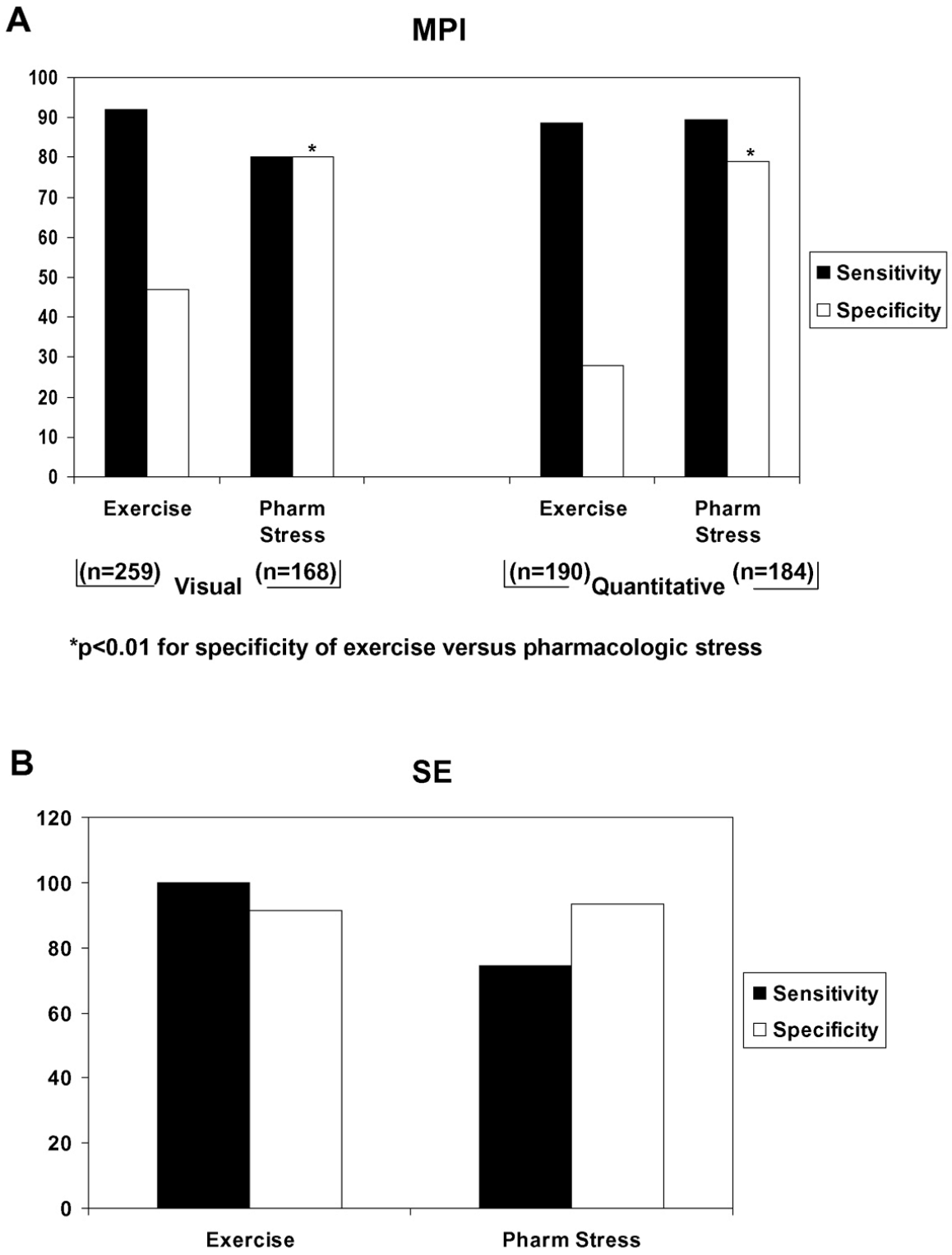

Figure 4. *Sensitivity and specificity according to stressor MPI (Panel A) and SE (Panel B) for detection of LAD coronary artery disease.*

Prognostic Accuracy. No studies on prediction of cardiac events using exercise ECG in patients with LBBB have been reported. Data on prognosis were collected from 9 studies, 7 were performed using MPI, and 2 with SE using dobutamine stress (28, 47-54). All studies were conducted in patients with known or suspected CAD.

Myocardial Perfusion Imaging. A normal MPI was present in 31.5% of patients, whereas any abnormality on MPI was observed in 68.5% of patients. During a mean follow-up of 36 months (range 6 to 60 months), 163 deaths occurred (with 79 cardiac deaths) and 20 myocardial infarctions. The summary RR for predicting any cardiac events (cardiac death or myocardial infarction) with an abnormal MPI was calculated from 6 reports (Figure 5). A report by O'Keefe et al. (28) as excluded from the analysis since available prognostic data were only in normal studies. Analysis of pooled data (n=6 studies, n=997 patients) showed the efficacy of MPI to predict cardiac events (RR of an abnormal versus normal MPI 6.93, 95% CI 4.28 – 11.20, p<0.0001).

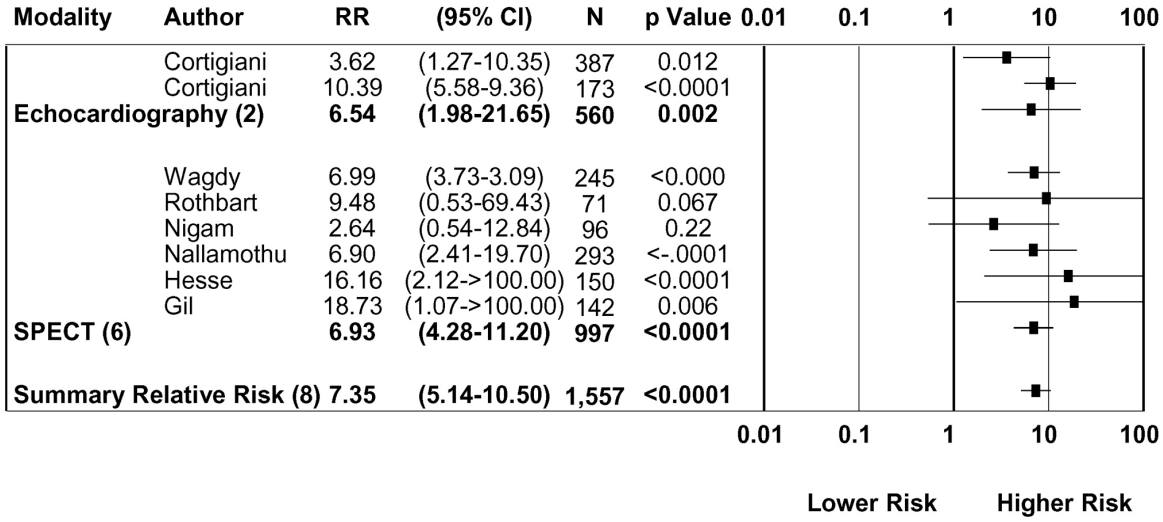

Figure 5. *Prognostic accuracy for MPI and SE expressed as RR and 95% CI of a positive versus negative test.*

Event-free survival curves were constructed based on the data of 7 studies where results on patients with normal or abnormal MPI were reported (Figure 6). Five-year event-free survival rate in patients with a normal MPI was 98.4% (25th-75th percentile 95.3% – 100%), whereas in patients with an abnormal study was 79.8% (25th-75th percentile 58.5% - 94.1%). Thus, for the 5-year follow-up time period, patients with an abnormal MPI had a 13.39-fold (95% CI 8.14-22.03) higher event rate as compared with patients with a normal MPI ($p<0.0001$).

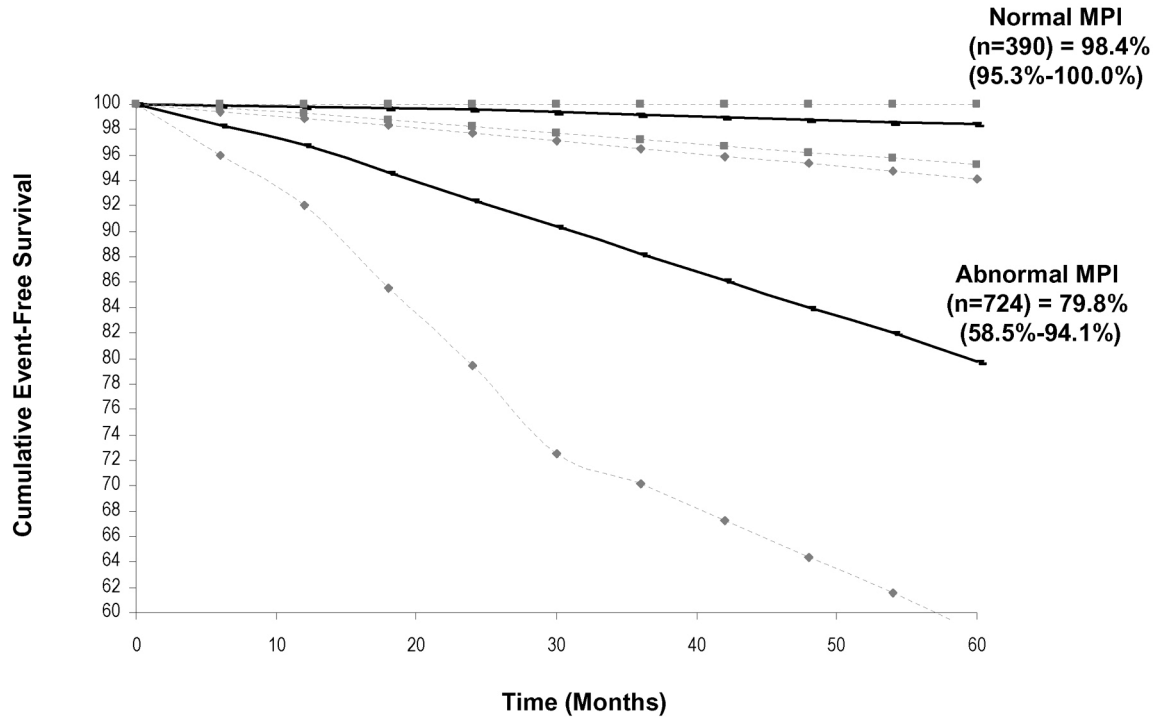

Figure 6. *Summary 5-year event-free [median] survival (25th – 75th %ile) for patients with a normal or abnormal MPI study.*

When plotting the time to increasing risk for patients with a normal MPI (to determine the warranty period for a normal scan), the RR was calculated across a range of follow-up times ranging from 6 to 60 months (Figure 7) and compared to similarly aged event rates from the general population. For follow-up times through 18 months, the event rate for those with a normal MPI were similar to that of the general population ($p>0.40$). However, at 24 months, a non-significant trend was observed ($p=0.18$) that continued to increase until exhibiting a significant increased risk at 36 months of follow-up ($p=0.0225$). At this point, the 95% CI exceeded 1.0.

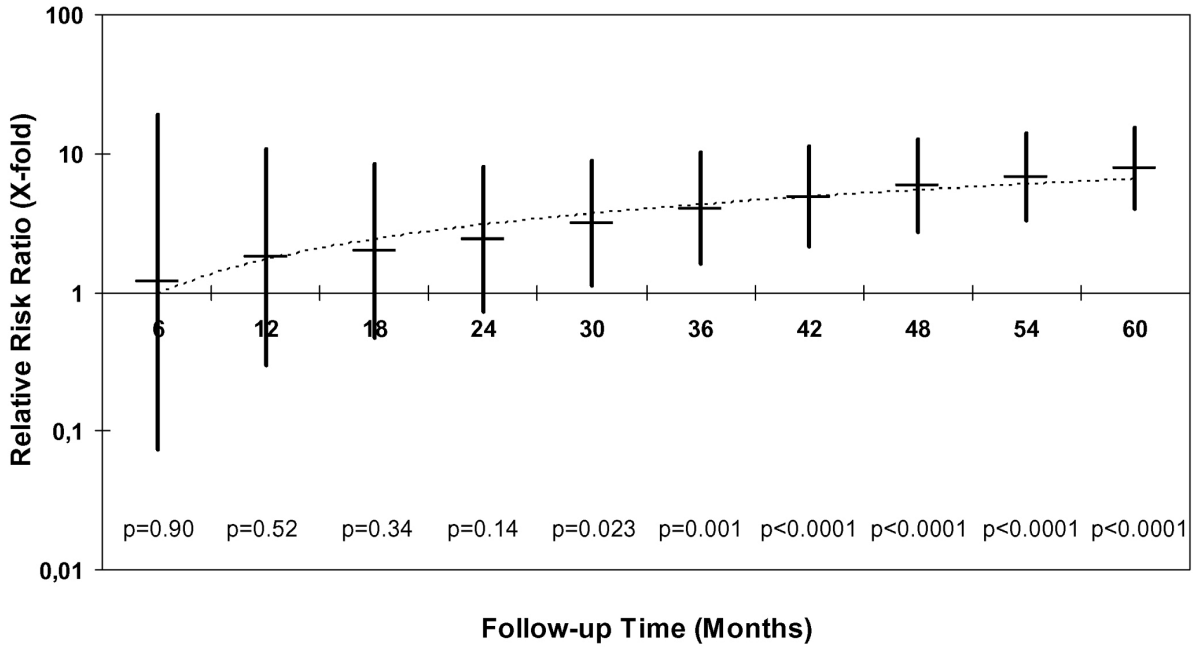

Figure 7. *RR ratio and 95% CI of a cardiac event in patients with a normal MPI study when compared with the cardiovascular event rate in the general population. The RR becomes significant at 30 months after the initial MPI.*

Stress Echocardiography. An abnormal SE was detected in 26% of the patients (n=2 studies, n=560 patients). During a mean follow-up of 35 months, 43 deaths occurred with 21 cardiac deaths and 20 myocardial infarctions. The summary RR for predicting hard cardiac events (cardiac death or myocardial infarction) with an abnormal SE is presented in Figure 5. Analysis of the pooled data showed that an abnormal SE was associated with an increased risk of cardiac events (RR 6.54, 95% CI 1.98-21.65, $p<0.0001$).

Comparison of MPI and SE. No significant differences were present in accuracy between MPI and SE for the prediction of cardiac events ($p=0.9$); wider CI were noted with MPI. Heterogeneity test for both tests revealed no significant differences.

Discussion

The current meta-analysis of non-randomized reports on the detection of CAD and the prediction of cardiac events in patients with LBBB focused on the most frequently used non-invasive techniques: exercise ECG, MPI and SE. The main findings of the current study are that the sensitivity for the detection of CAD in patients with LBBB is higher for MPI (in particular when quantitative analysis is used) and exercise ECG as compared to SE. Sensitivity for LAD disease in particular is poor with MPI when exercise is used, but improved significantly when pharmacological stress was used. Conversely, the overall specificity for the detection of CAD is significantly higher for SE as compared to MPI and exercise ECG. The overall accuracy for detection of CAD is comparable for SE and MPI (when quantitative analysis is used) and significantly higher compared to exercise ECG. The prognostic accuracy for the prediction of hard cardiac events is comparable between MPI and SE.

Detection of CAD in Patients with LBBB. The Framingham study showed that the onset of LBBB in patients with known CAD is associated with an increased cumulative cardiovascular mortality (2, 3), whereas other studies reported that patients with LBBB without clinical evidence of CAD have a good long-term prognosis (1, 54). Thus, accurate non-invasive evaluation is clinically important in patients with LBBB and has prognostic implications. Non-invasive evaluation of CAD in patients with LBBB is challenging. The commonly used non-invasive tests (exercise ECG, MPI, and SE) generally have lower sensitivity and specificity values in patients with LBBB as compared to patients without LBBB. This is related to the fact that the interpretation of exercise ECG, MPI, and SE in the presence of LBBB is limited. First, evaluation of myocardial ischemia by exercise ECG is complicated by pre-existent repolarization abnormalities secondary to the altered depolarization, and exercise-induced ST-segment changes are non-specific for detection of ischemia in the presence of LBBB. Second, the ability of MPI to detect CAD in patients with LBBB suffers from the high incidence of false positive perfusion defects in the interventricular septum in the absence of LAD disease. Because of the electrical conduction defect, septal blood flow (and flow reserve) may be decreased during physiological stress (55), which does not necessarily reflect ischemia. Third, SE relies on detection of stress-induced wall motion/thickening abnormalities. In patients with LBBB, mechanical asynchrony between left and right ventricle results in abnormal septal motion, thereby hampering interpretation of induction of septal wall motion abnormalities.

This meta-analysis of currently available data shows that MPI and exercise ECG have the highest sensitivity as compared to SE for detection of CAD. However, SE showed a higher overall specificity compared to MPI and exercise ECG. The specificity of MPI could be improved using quantitative analysis instead of visual interpretation. These data support the use of either MPI or SE as first line technique for non-invasive detection of CAD in patients with LBBB.

A specific comparison between exercise and pharmacological stress supported the use of pharmacological stress with MPI, imaging confirmed the higher sensitivity for MPI (both stressor types) compared to SE, whereas the specificity was higher for SE compared to MPI. In particular, exercise MPI had a very low specificity (23%), which increased significantly when pharmacological stress was used (74%), and supports the ACC/AHA guidelines in that patients with LBBB referred for MPI should undergo pharmacological (in particular vasodilator) stress (56, 57). The low specificity of exercise MPI is related to a combination of shortened diastolic relaxation time and asynchronous contraction which are worsened by exercise (or dobutamine) stress (10, 13, 55, 58). For SE it is less clear what stressor is

preferred: currently only 1 report on exercise SE is available (46), whereas the remaining studies have used pharmacological stress.

In addition, similar results were obtained for detection of LAD disease: sensitivity was high for both MPI and SE using either exercise or pharmacological stress. The specificity however was lower for exercise MPI (47%), which could be improved by pharmacological stress (80%).

Prognostic Value of MPI and SE to Predict Cardiac Events. Prognostic data on exercise ECG in patients with LBBB are not available. The current meta-analysis shows that, despite the aforementioned diagnostic limitations, both MPI and SE have additional prognostic value over clinical data. The data on prognosis after SE are limited, with only 2 studies and 560 patients. However, the available data indicate that both modalities are equally useful in patients with LBBB to distinguish low- and high-risk patients. The prognosis of patients with LBBB and a normal MPI study is comparable to the prognosis of patients without LBBB with a normal test (59). An abnormal MPI or SE was associated with a 6.9 or 6.5-fold higher risk for cardiac death or myocardial infarction. The RR varied substantially between studies (Figure 5) and is probably related mostly to differences in sample size but varying casemix and study methodology difference would also be contributory. Importantly, no differences were present between the 2 techniques for prediction of cardiac events.

Finally, the warranty-period of a normal MPI study was evaluated as was previously described by Hachamovitch et al for patients with known or suspected CAD (60). The current pooled analysis shows that patients with a normal test have a similar prognosis to the general population until 1 year and half, whereas a trend to a higher incidence of cardiac events begins at two years and becomes significant at three years. This observation suggests that after 2-3 years non-invasive testing should be repeated to define the patient's risk.

Limitations

This meta-analysis of published data reveals some of the shortcomings of the currently available data. First of all, consistency in the imaging interpretation is needed. For MPI, not all studies used both fixed and reversible defects as markers for CAD, and for SE not all studies used resting and stress-induced wall motion abnormalities. Second, the available diagnostic and prognostic data series are relatively small when compared to the available evidence in patients without LBBB (59-61). More diagnostic data are needed in patients with an intermediate likelihood of CAD; the majority of studies have focused on patients with a relatively high likelihood of CAD. Third, more studies are needed to clearly define the prognostic role of imaging in patients with LBBB, in particular more SE data are needed.

Conclusions and Clinical Implications

Meta-analysis of available data on non-invasive testing in patients with LBBB showed that accuracy for detection of CAD is comparable for SE and MPI (preferably using quantitative analysis of data) and significantly higher as compared to exercise ECG. The prognostic accuracy for the prediction of hard cardiac events is comparable between MPI and SE. Thus, the available evidence favours the use of SE or MPI (using quantitative analysis) as first-line techniques for diagnostic and prognostic purposes in patients with LBBB with known or suspected CAD.

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Chapter 10

Prognostic Stratification of Patients with Right Bundle Branch Block Using Dobutamine Stress Echocardiography

Biagini E, Schinkel AFL, Rizzello V, van Domburg RT, Pedone C, Elhendy A, Krenning BJ, Bountioukos M, Vourvouri EC, Branzi A, Rapezzi C, Simoons ML, Bax JJ, and Poldermans D

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Prognostic Stratification of Patients With Right Bundle Branch Block Using *Dobutamine* Stress Echocardiography

Elena Biagini, MD, Arend F.L. Schinkel, MD, Vittoria Rizzello, MD, Ron T. van Domburg, PhD, Chiara Pedone, MD, Abdou Elhendy, MD, Boudewijn J. Krenning, MD, Manolis Bountioukos, MD, Eleni C. Vourvouri, MD, Angelo Branzi, MD, Claudio Rapezzi, MD, Maarten L. Simoons, MD, Jeroen J. Bax, MD, and Don Poldermans, MD

The presence of a right bundle branch block (RBBB) is associated with increased mortality. We studied the role of dobutamine stress echocardiography for the prognostic stratification of patients with RBBB. The presence of an abnormal dobutamine stress echocardiography was the strongest predictor of cardiac events and provided incremental prognostic information to clinical and stress test data. ©2004 by Excerpta Medica, Inc.

(Am J Cardiol 2004;94:954–957)

Patients with a right bundle branch block (RBBB) have an increased risk of cardiac events, particularly those with previous myocardial infarction.[1–3] Therefore, it is clinically important to assess the prognosis in these patients to select the appropriate management strategy. Exercise testing is often inadequate in patients with RBBB because of preexisting repolarization abnormalities that impede the identification of myocardial ischemia.[4,5] Information on the role of pharmacologic stress echocardiography for the prognostic stratification of these patients is limited. Assessment of prognosis may be challenging because extensive wall motion abnormalities in patients with RBBB do not always suggest more severe or extensive coronary disease.[6] The aim of this study was to assess the incremental prognostic value of dobutamine stress echocardiography relative to clinical data in a large subset of patients with RBBB during a long-term follow-up.

From the Department of Cardiology, Thoraxcenter, Erasmus MC, Rotterdam, The Netherlands; Department of Cardiology, Leiden University Medical Center, Leiden, The Netherlands; and Institute of Cardiology, S.Orsola, Bologna, Italy. Dr. Poldermans' address is: Thoraxcenter Room Ba 300, Department of Cardiology, Erasmus Medical Center, Dr. Molewaterplein 40, 3015 GD Rotterdam, The Netherlands. E-mail: d.poldermans@erasmusmc.nl. Manuscript received April 5, 2004; revised manuscript received and accepted June 25, 2004.

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The study population consisted of 176 consecutive patients with RBBB referred for dobutamine stress echocardiography for the evaluation of suspected or known coronary artery disease. All patients underwent surface electrocardiography with simultaneous 12-lead recordings. An experienced observer, unaware of any other data, read the surface electrocardiograms, using a dedicated computer system (Mortara Instruments, Bilthoven, The Netherlands). RBBB was defined as a QRS duration ≥120 ms, broad notched R wave in leads V_1 and V_2 and wide and deep S waves in leads V_5 and V_6.[7] Follow-up was successful in 173 patients (98%). Ten patients who underwent coronary revascularization within 60 days of the test were excluded from the analysis.[8] Data from the remaining 163 patients are reported. All patients gave informed consent before testing. The hospital medical ethics committee approved the study protocol.

Before the test, a structured interview and clinical history were obtained, including assessment of cardiac risk factors. Hypertension was defined as blood pressure ≥140/90 mm Hg or treatment with antihypertensive medication. Hypercholesterolemia was defined as total cholesterol ≥6.4mmol/L or treatment with lipid-lowering medication. Diabetes was defined as a fasting blood glucose level >140 mg/dl or the need for insulin or oral hypoglycemic agents.

Dobutamine–atropine stress testing was performed according to a standard protocol as previously reported.[9] Dobutamine was administered intravenously, starting at a dose of 10 μg/kg/min for 3 minutes, increasing by 10 μg/kg/min every 3 minutes, up to a maximum dose of 40 μg/kg/min. If the test end point was not reached at a dobutamine dose of 40 μg/kg/min, atropine (up to 2 mg) was given. Blood pressure, heart rate, and electrocardiography were constantly monitored. Test end points were achievement of target

TABLE 1 Baseline Characteristics (n = 163)

	No. (%)
Age (yrs)	64 ± 11
Men	131 (80%)
Systemic hypertension	52 (32%)
Hypercholesterolemia	38 (23%)
Smoker	58 (35%)
Diabetes mellitus	22 (13%)
Previous myocardial infarction	54 (33%)
Previous heart failure	26 (16%)
Previous myocardial revascularization	40 (24%)
β blockers	56 (34%)
Diuretics	40 (24%)
Angiotensin-converting enzyme inhibitors	49 (30%)
Calcium antagonists	51 (31%)

TABLE 2 Outcome in Patients With Normal and Abnormal Dobutamine Stress Echocardiography

	Normal Test (n = 53)	Abnormal Test (n = 110)	p Value
Cardiac death	6 (11%)	31 (28%)	0.02
Cardiac death or nonfatal infarction	9 (17%)	37 (34%)	0.04
All cardiac events	12 (22%)	49 (44%)	0.007
Late revascularization	5 (9%)	43 (39%)	0.0001

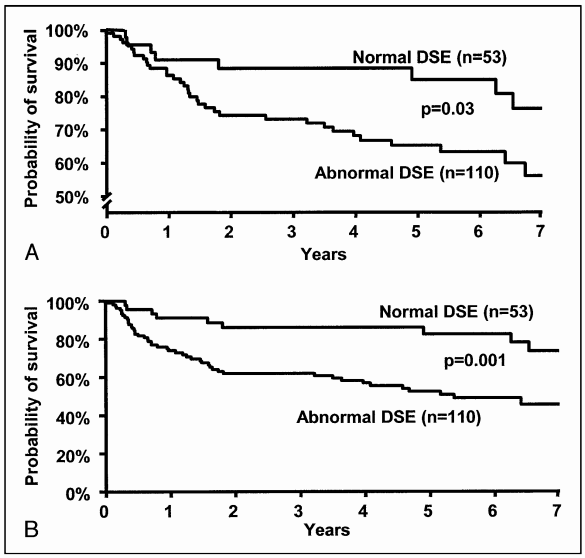

FIGURE 1. Kaplan-Meier survival curves for hard cardiac events *(A)* and all cardiac events *(B)* in patients with RBBB. A significant difference in event-free survival exists between patients with a normal and abnormal dobutamine stress echocardiogram (DSE).

heart rate (85% of maximum age- and gender-predicted heart rate), severe angina, a decrease in systolic blood pressure of >40 mm Hg, blood pressure >240/120 mm Hg, or significant cardiac arrhythmia. Metoprolol was available to reverse the (side) effects of dobutamine–atropine.

Two-dimensional echocardiography was performed at rest, during dobutamine stress, and during recovery. The echocardiograms were recorded in a quad-screen format. Two experienced observers, unaware of the clinical data, scored the echocardiograms using a standard 16-segment model. 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 worsening wall motion abnormalities during stress as indicated by an increase of wall motion score ≥1 grade in ≥1 segment. Ischemia was not considered present when akinetic segments at rest became dyskinetic during stress. An abnormal study was considered in the presence of dysfunctional segments at rest or ischemic segments during the test.

Follow-up data were obtained by review of hospital records and/or contacting the patient's general practitioner. The median follow-up period was 4.3 years (25th to 75th percentiles 1.5 to 6.6). End points comprised hard cardiac events (cardiac death and nonfatal myocardial infarction) and all cardiac events (hard cardiac events and late coronary revascularization). Cardiac death was defined as a death caused by acute myocardial infarction, significant cardiac arrhythmia, or refractory congestive heart failure. Sudden death occurring without another explanation was included as cardiac death. Myocardial infarction was defined according to the standard criteria.[10]

Values are expressed as mean value ± SD or number and compared using Student's *t* test or chi-square test. Univariate and multivariate Cox proportional hazard regression models (BMDP statistical software, Los Angeles, California) were used to identify independent predictors of late cardiac events.[11] Variables were selected in a stepwise forward selection manner with entry, and retention was set at a significance level of 0.05. The risk of a variable was expressed as a hazard ratio (HR) with a corresponding 95% confidence interval (CI). The probability of survival was calculated using the Kaplan-Meier method, and survival curves were compared using the log-rank test. A p value <0.05 was considered statistically significant.

Baseline data are listed in Table 1. During the stress test, heart rate increased from 74 ± 15 to 131 ± 12 beats/min (p <0.0001) and systolic blood pressure from 131 ± 20 to 144 ± 24 mm Hg (p <0.001). In 42 patients (26%) atropine was added. Typical angina occurred in 19 patients (12%). Side effects during the test were ventricular tachycardia (>10 beats) in 1 patient (0.6%), short ventricular tachycardia (<10 beats) in 7 patients (4%), atrial fibrillation in 2 patients (1%), nausea in 4 (2%), and headache in 3 patients (2%). No patient experienced a myocardial infarction or fatal complication.

A total of 110 patients (67%) had an abnormal dobutamine stress echocardiogram. Thirty-one patients (19%) had wall motion abnormalities at rest, 6

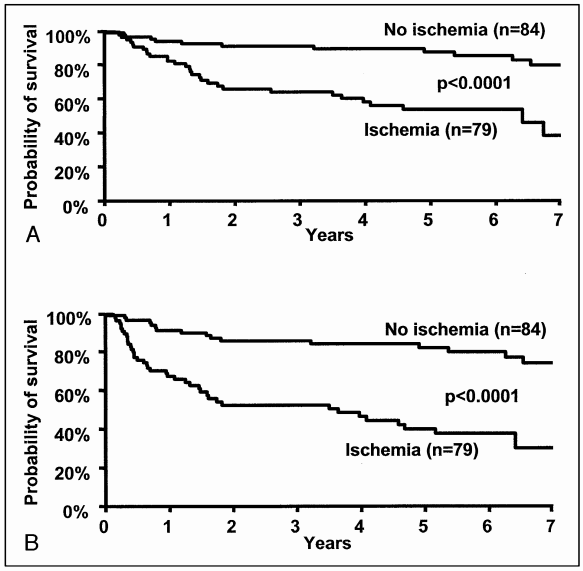

FIGURE 2. Kaplan-Meier survival curves for hard cardiac events *(A)* and all cardiac events *(B)* in patients with RBBB. Event-free survival is significantly better in patients without stress-induced ischemia compared with patients with ischemia during the test.

(4%) had an ischemic wall motion pattern, and 73 (45%) had both wall motion abnormalities and myocardial ischemia at rest. During the 4.3 year follow-up, patients with RBBB and an abnormal study had a significant higher incidence of cardiac death, hard cardiac events, and all cardiac events compared with patients with RBBB and normal dobutamine stress echocardiography (Table 2).

Independent predictors of hard cardiac events in a multivariable analysis model were age (HR 1.04, 95% CI 1.01 to 1.08), heart failure (HR 2.3, 95% CI 1.1 to 5.1), and the presence of an abnormal dobutamine stress echocardiogram (HR 3.0, 95% CI 1.2 to 7.4). Kaplan-Meier survival curves are presented in Figures 1 and 2. Event-free survival was significantly better for patients with a normal stress test compared with those with an abnormal dobutamine stress echocardiogram (Figure 1). Patients who did not show stress-induced ischemia had a better outcome compared with patients who showed ischemia during the test (Figure 2).

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The main finding of this study is that dobutamine stress echocardiography provides incremental prognostic information for the prediction of cardiac events in patients with RBBB. During a follow-up of 4.3 years, 57 deaths (35%) occurred, of which 37 (23%) were caused by cardiac causes. Nonfatal myocardial infarction occurred in 9 patients (5%) and 48 patients (29%) underwent late coronary revascularization. An abnormal dobutamine test and the presence of stress-induced ischemia were associated with a significantly increased risk of cardiac death and nonfatal myocardial infarction in patients with RBBB. Clinical predictors of hard cardiac events were age and heart failure. The presence of an abnormal dobutamine stress echocardiogram was the strongest predictor of subsequent cardiac events. Dobutamine stress echocardiography provided clinically useful information in patients with RBBB.

Information on the prognostic value of noninvasive imaging in patients with RBBB is scarce. Hesse et al[12] studied 190 patients with complete RBBB (3%) of 7,073 patients referred for nuclear exercise testing. After a mean follow-up of 6.7 years, 825 deaths (12%) occurred. Mortality was significantly higher in patients with complete RBBB than in those without a bundle branch block. Moreover, after adjustment for exercise capacity, nuclear perfusion defects, and other risk factors, complete RBBB was equally predictive for mortality compared with left bundle branch block. Ciaroni et al[13] studied 158 patients with an abnormal electrocardiogram at rest who underwent dobutamine stress echocardiography. Sixty-five patients (41%) had a RBBB, 36 patients (23%) had a left bundle branch block, and 57 (36%) had repolarization abnormalities. During a mean follow-up of 24 ± 13 months, an abnormal dobutamine stress echocardiogram was the most predictive independent parameter for the onset of nonfatal cardiac events. Recently, Cortigiani et al[14] reported on 343 patients with RBBB who underwent pharmacologic stress echocardiography (231 dipyridamole, 112 dobutamine) for the evaluation of suspected or known coronary artery disease. Overall mortality was the only end point. Stress echocardiography was abnormal in 109 patients (32%). During follow-up (38 ± 32 months), 36 deaths occurred. An abnormal stress echocardiogram was predictive of all-cause mortality.

The present study shows that dobutamine stress echocardiography is predictive of hard cardiac events and all cardiac events, which is a finding that has not been previously shown. This may have been related to the higher risk profile of the present population (46 hard cardiac events), more patients who underwent dobutamine stress echocardiography, and a longer, nearly complete follow-up compared with previous studies.

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Chapter 11

Pacemaker Stress Echocardiography Predicts Cardiac Events in Patients with Permanent Pacemaker and Known or Suspected Coronary Artery Disease

Biagini E, Schinkel AFL, Elhendy A, Bax JJ, Rizzello V,
van Domburg RT, Krenning BJ, Schouten O,
Branzi A, Rocchi G, Simoons ML, Poldermans D

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Abstract

Background. Non-invasive pacemaker stress echocardiography is a newly introduced method for the diagnosis of coronary artery disease in patients with a permanent pacemaker. The prognostic value of pacemaker stress echocardiography has not been previously studied.

Methods. We studied 136 patients (mean age 64±12 years) with a permanent pacemaker who underwent pacemaker stress echocardiography for evaluation of coronary artery disease. All patients underwent pacemaker stress echocardiography by external programming (pacing heart rate up to ischemia or target heart rate).

Results. Thirty-one patients (23%) had a normal study. Ischemia was detected in 75 (55%) patients. During a mean follow-up of 3.5±2.4 years, 35 (26%) deaths (20 due to cardiac causes) and 2 (1%) nonfatal myocardial infarction occurred. The annual cardiac death rate was 1.3% in patients without ischemia and 4.6% in patients with ischemia (p=0.01), whereas the annual all cause mortality rate was 3.1% in patients without ischemia and 7% in patients with ischemia (p=0.004). The presence of ischemia during pacemaker stress echocardiography was the strongest independent predictor of cardiac death (hazard ratio 4.1 CI 1.2-14.5) and all cause mortality (hazard ratio 2.7 CI 1.2-6.0) in a multivariable model.

Conclusions. Myocardial ischemia during pacemaker stress echocardiography is an independent predictor of cardiac death and all cause mortality in patients with a permanent pacemaker.

Introduction

The number of permanent pacemaker implantations has exponentially increased in the last decades and may be related to the increase of the elderly population as well as to the expanding indications for pacing (1). Coronary artery disease may concomitantly exist in patients with pacemaker or may be the underlying cause of conduction defects in some cases (2-5). Non-invasive evaluation of coronary artery disease is challenging in these patients, since the electrocardiogram is often uninterpretable (6). Myocardial perfusion abnormalities in the septum and apex have been reported in the absence of coronary artery disease in patients with paced rhythm (7). Non-invasive pacemaker stress echocardiography has been recently introduced as a feasible method to increase heart rate and to induce myocardial ischemia in these patients (8, 9). There are currently no data to define the prognostic value of pacemaker stress echocardiography. The aim of this study was to assess the value of pacemaker stress echocardiography for prediction of cardiac death and all cause mortality in patients with known or suspected coronary artery disease who have a permanent right ventricular pacemaker.

Methods

Patients. The study population comprised 140 consecutive patients with a permanent right ventricular pacemaker referred to the Thoraxcenter, Rotterdam, The Netherlands, between 1998 and 2004 for evaluation of myocardial ischemia. Follow-up was successful in 138 patients (99%). Two patients underwent coronary revascularization in the first 60 days after pacemaker stress echocardiography. These patients were excluded from the analysis, because referral to myocardial revascularization in the first 60 days after stress testing tends to be based on the results of the test, whereas referral to revascularization >60 days after testing tends to be based on worsening of the patients clinical status (10). Data on the remaining 136 patients are reported. The protocol was approved by the Hospital Ethics Committee. All patients gave informed consent before the test. A structured interview and clinical history were taken and cardiac risk factors were assessed before pacemaker stress echocardiography.

Hypertension was defined as a blood pressure ≥140/90 mmHg, or treatment with antihypertensive medication. Diabetes mellitus was defined as a fasting glucose level ≥7.8 mmol/L or the need for insulin or oral hypoglycemic agents. Hypercholesterolemia was defined as a total cholesterol ≥6.4 mmol/L, or treatment with lipid-lowering medication.

Pacemaker Stress Echocardiography. Echocardiography was performed with standard equipment (Sonos 5500, Andover, Massachusetts, USA) using second harmonic imaging (1.8MHz/3.6MHz). Images were obtained with the patient in the left lateral decubitus position and were acquired before the stress test and every 3 min throughout the stress test, using the standard parasternal and apical views. Continuous ventricular pacing was started at the rate of 100 beats/minute and was increased by 10 beats every three minutes until test end-point was reached. In patients with a dual chamber pacemaker, the pacemaker stress test was started with atrial pacing, if target heart rate or other test end-points were not reached with this approach the pacemaker was programmed to ventricular pacing. Test end-points were achievement of target heart rate (85% of maximum age predicted heart rate), pacemaker maximal programmable heart rate, severe angina, systolic blood pressure fall >40 mmHg,

blood pressure >240/120 mmHg, or significant cardiac arrhythmia. The echocardiograms were recorded in a quad-screen format. Two experienced observers, unaware of the clinical data, scored the echocardiograms using a standard 16-segment model as suggested by the American Society of Echocardiography (11). In case of disagreement, a consensus decision was achieved by a third observer. 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. Myocardial septal and apical function was evaluated based on systolic thickening because wall motion could be influenced by ventricular pacing.

Follow-up. Follow-up data collection was performed by contacting the patient's general practitioner and by review of hospital records. The date of the last review or consultation was used to calculate follow-up time. Follow-up events noted were cardiac and all cause mortality. Cardiac death was defined as a death caused by acute myocardial infarction, significant cardiac arrhythmias, or refractory congestive heart failure. Sudden death occurring without another explanation was considered as cardiac death. Myocardial revascularization procedures were registered.

Statistical Analysis. Values were expressed as means (± SD) or number, and compared using the Student t test or chi-squared test. Univariate and multivariate Cox proportional hazard models (BMDP Statistical Software Inc., Los Angeles, California) were used to identify variables that were independently predictive of cardiac death and all cause mortality 12. Variables were selected in a stepwise forward selection manner with entry and retention set at a significance level of 0.05. The risk of a variable was expressed as hazard ratios with corresponding 95% confidence intervals. Clinical data, stress test variables, and noninvasive imaging data were incorporated into the analysis. The incremental value of dobutamine stress echocardiography over the clinical value in the prediction of cardiac death and all cause mortality was performed according to 2 models. In model 1, only clinical data were entered; in model 2 dobutamine echocardiographic variables including resting wall motion abnormalities and myocardial ischemia were added to the clinical variables. The probability of survival was calculated using the Kaplan-Meier method, and survival curves were compared using the log-rank test. P values <0.05 were considered statistically significant.

Results

Clinical data are presented in Table 1. Ninety-eight (72%) patients had a dual-chamber pacemaker, and 38 (28%) had a single-lead right ventricular pacemaker. In patients with a dual-chamber pacemaker, pacemaker stress echocardiography using atrial pacing was performed in 82 (84 %) patients and ventricular pacemaker stress testing was performed in 16 (16%).

Table 1. Baseline Characteristics (136 patients)

	Number (%)
Age (years)	64 ± 12
Men	94 (69%)
Systemic hypertension	28 (20%)
Hypercholesterolemia	87 (64%)
Smoker	10 (7%)
Diabetes mellitus	27 (20%)
Prior myocardial infarction	44 (32%)
Prior heart failure	48 (35%)
Beta blockers	57 (42%)
Diuretics	34 (25%)
Angiotensin converting enzyme inhibitors	43 (32%)
Nitrates	49 (36%)
Calcium channel blockers	28 (20%)
Indications for pacemaker implantation:	
Atrioventricular block	53 (39%)
Sick sinus syndrome	43 (32%)
Bradycardia	40 (29%)

Hemodynamic data are presented in Table 2. During the pacing there was a mild increase of systolic blood pressure (119 ± 24 mmHg to 123 ± 26 mmHg, $p<0.05$). No major adverse effects were observed during the test. Thirty-one patients (23%) had angina during pacemaker stress echocardiography, Angina was the reason for the test termination in 3 of these patients. Other causes of test termination were achievement of the target heart rate in 126 (93%) patients, and achievement of pacemaker maximal programmable heart rate in 5 (4%). Two (1%) patients experienced nausea during pacemaker stress echocardiography.

Table 2. Pacemaker Stress Echocardiographic Data

Heart rate at rest (beats/min)	73 ± 18
Heart rate at peak (beats/min)	124 ± 17
Rest systolic blood pressure (mmHg)	119 ± 24
Peak systolic blood pressure (mmHg)	123 ± 26
Rest rate pressure product	9456 ± 2863
Peak rate pressure product	15423 ± 4627
Angina during stress	31 (23%)
Resting wall motion score index	2.1 ± 0.7
Ischemia (patients)	75 (55%)
Number of ischemic segments	6.4 ± 5.7

Pacemaker Stress Echocardiography and Outcome. Thirty (22%) patients had a normal pacing stress echocardiogram. Fixed wall motion abnormalities were detected in 31 (23%) patients and ischemia was induced in 75 (55%) patients. Eighteen (13%) patients showed ischemia only in the septum and/or apex. During a mean follow-up of 3.5 ± 2.4 years, there were 35 (26%) deaths, of which 20 (15%) were due to cardiac causes. Nonfatal myocardial infarction occurred in 2 (1%) patients. Forty-one (30%) patients underwent coronary angiography, within 6 months from the stress test. Late revascularization was performed in 36 (26%) patients, of these 17 (12%) underwent percutaneous interventions and 19 (14%) underwent coronary bypass surgery.

Predictors of Events. Predictors of cardiac death and all cause mortality in univariable and multivariable models are presented in Table 3. Ischemia was the strongest independent predictor of cardiac and all cause mortality, with incremental value to the clinical variables (log-likelihood, -75 to -72, $p< 0.05$ for cardiac death, and -140 to -136, $p< 0.05$ for all cause mortality).

Table 3. Predictors of events by Cox models

	Univariate	Multivariate Model 1	Multivariate Model 2
Parameter	RR (CI)	RR (CI)	RR (CI)
Cardiac Death			
Age	1.03 (1.01-1.06)		
Previous myocardial infarction	1.5 (1.0-2.1)		
Diabetes mellitus	4.6 (1.2-18.0)	3.0 (1.1-9.2)	3.1 (1.1-9.6)
Smoking	3.4 (1.2-9.4)	2.9 (1.1-7.3)	2.9 (1.2-7.4)
Resting wall motion abnormalities	2.4 (0.7-8.9)		
Ischemia	3.9 (1.2-12.2)		4.1 (1.2-14.9)
All cause mortality			
Age	1.03 (1.01-1.06)		
Male gender	2.1 (0.8-5.3)	2.1 (1.1-6.2)	2.1 (1.1-5.2)
Previous myocardial infarction	1.4 (1.0-2.1)		
Diabetes mellitus	5.0 (1.3-19.0)	2.4 (1.1-6.0)	2.4 (1.1-5.8)
Resting wall motion abnormalities	1.6 (0.6-4.3)		
Ischemia	3.1 (1.3-7.2)		2.7 (1.2-6.0)

Kaplan-Meier survival curves for the end-points cardiac death and all cause mortality are presented in Figures 1 and 2. Event-free survival was significantly better for patients without ischemia as compared to patients with ischemia. The annual cardiac death rate was 1.3% in patients without ischemia and 4.6% in patients with ischemia ($p=0.01$). The annual all cause mortality rate was 3.1% in patients without ischemia and 7% in patients with ischemia ($p=0.004$). Patients with ischemia involving only the septum and/or the apex had a comparable prognosis as patients with ischemia in other regions (Figure 3).

The annual cardiac death rate was 5.4% in patients with ischemia involving only the septum and/or the apex and 7.6% in patients with ischemia in other regions ($p=0.9$). The annual all cause mortality rate was 6.4% in patients with ischemia involving only the septum and/or the apex and 9.5% in patients with ischemia in other regions ($p=0.9$).

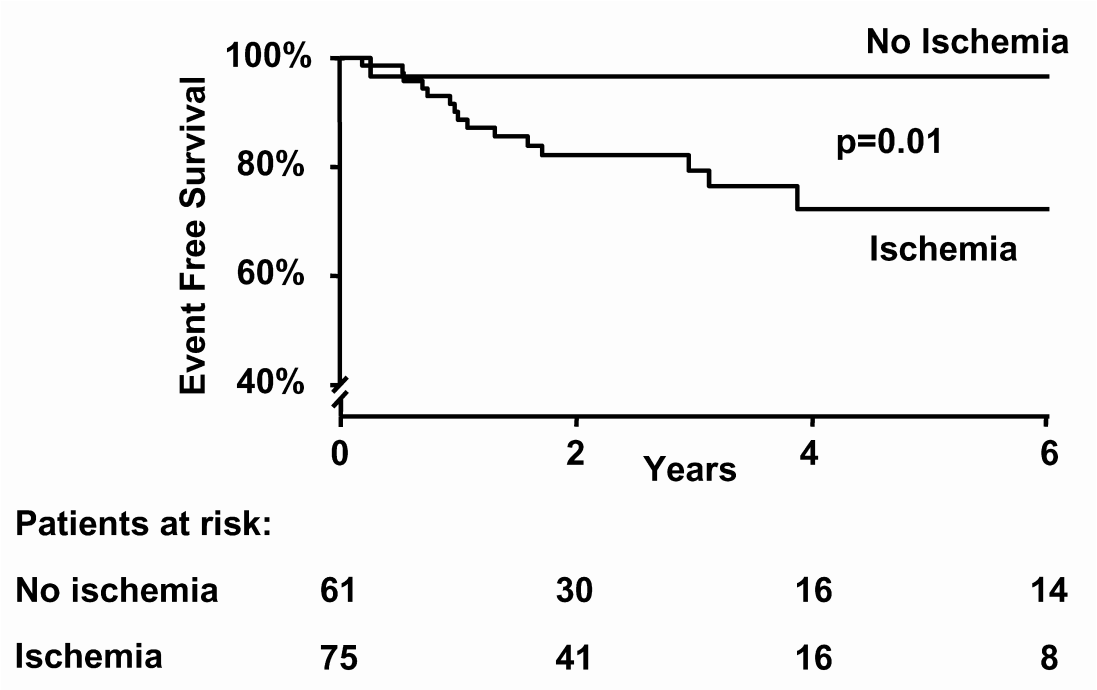

Figure 1. *Kaplan-Meier survival curves (end-point cardiac death) in patients without ischemia during pacing stress echocardiography versus patients with ischemia.*

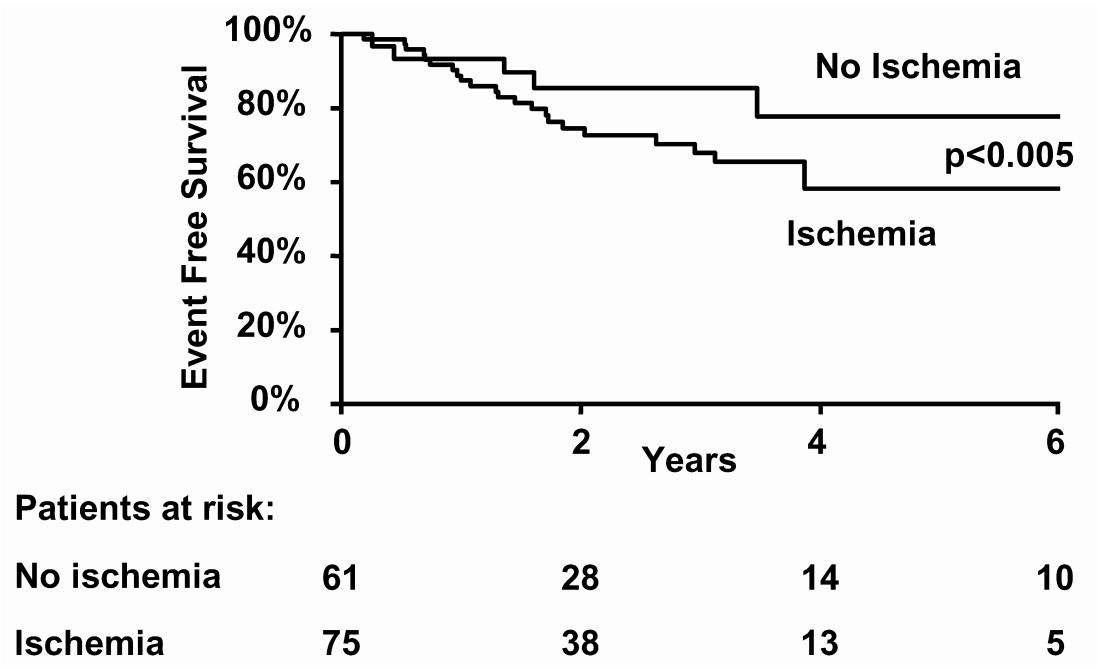

Figure 2. *Kaplan-Meier survival curves (end-point all cause mortality) in patients without ischemia during pacing stress echocardiography versus patients with ischemia.*

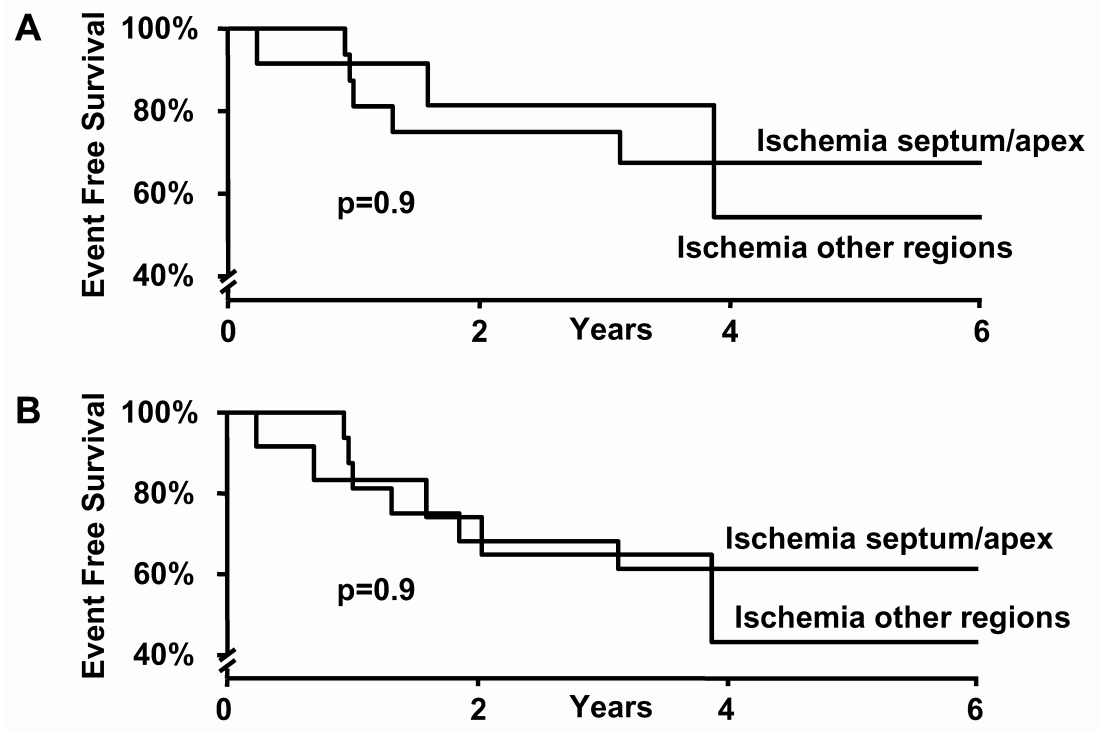

Figure 3. *Kaplan-Meier survival curves for end-point cardiac death (panel A) and all cause mortality (panel B) in patients with ischemia involving only the septum and/or the apex versus patients with ischemia in the other regions.*

Discussion

In the present study, the prognostic value of pacemaker stress echocardiography was evaluated in 136 patients with a permanent pacemaker and known or suspected coronary artery disease. During a follow-up period of 3.5 ± 2.4 years, 35 (36%) deaths occurred of which 20 (15%) were due to cardiac causes. The presence of ischemia during pacemaker stress echocardiography was associated with a significantly increased risk of cardiac and all cause mortality, incremental to the clinical variables. Patients without ischemia during pacemaker stress echocardiography had an annual cardiac death rate of 1.3%, identifying a lower-risk group of patients who do not need further invasive evaluation. Conversely, in patients with ischemia the annual cardiac death rate was 4.6%, identifying a high-risk group of patients who can potentially benefit from invasive evaluation. pacemaker stress echocardiography provided independent prognostic information for the prediction of cardiac death and all cause mortality. Patients with ischemia involving the septum or the apex had a worse outcome compared to patients without ischemia and a similar prognosis compared to patients with ischemia in other regions.

There were no significant differences in mortality between patients with myocardial ischemia only located in the septum and/or apex compared to those with ischemia in other myocardial regions. This finding suggests that interpretation of (changes in) function in these regions is reliable for the detection of myocardial ischemia. The presence of resting wall motion abnormalities was not associated with cardiac death or all cause mortality. This could

be explained by the fact that the abnormal function at rest of the interventricular septum can be present in patients with permanent pacemaker and is not related to the presence of coronary artery disease.

The high number of abnormal tests in this study (77%), is probably related to the prevalence of comorbidity in the population. Table 1 shows that a large number of patients had diabetes mellitus, prior myocardial infarction, prior heart failure, and obviously, conduction abnormalities.

Previous studies showed that pharmacological stress echocardiography is a feasible and accurate alternative for the detection of coronary artery disease in pacemaker-dependent patients (13). However, this examination can be time-consuming and may be associated with a varying hemodynamic response and side-effects (14-16). Pooled data have shown that approximately 10% of patients fail to achieve the target heart rate during dobutamine stress echocardiography (14). Transesophageal atrial pacing has been proposed as an effective alternative technique for the detection of coronary artery disease in the general population (17-22). A controlled increase of heart rate can be used to assess impaired regional wall thickening independently from regional myocardial dysfunction due to abnormal electrical activation. Nevertheless transesophageal pacing is an invasive procedure and its efficacy has been limited by patient intolerance. Moreover, intact atrioventricular conduction and absence of esophageal diseases are preliminary conditions to perform the test.

In patients with permanent pacemakers, pacemaker stress echocardiography has been reported as a safe, rapid and effective non-invasive tool to detect coronary artery disease (8, 9). Picano et al (8) evaluated the feasibility, safety and diagnostic accuracy of pacemaker stress echocardiography in 46 consecutive patients with a permanent pacemaker with suspected or known coronary artery disease. Sensitivity for detection of significant coronary artery disease was 70%, specificity 90% and accuracy 78%. Forty-two of 46 patients (91%) achieved the target heart rate or positive test end-point. Four patients (9%) had a submaximal test. In the present study, 93% of patients with a permanent pacemaker reached the target heart rate, which is comparable to previous studies performed by dobutamine stress echocardiography (23).

Pacemaker echocardiography is a simple, rapid, safe test for the assessment of prognosis in patients with permanent pacemaker and suspected or known coronary artery disease. Although no study directly has compared pacemaker and dobutamine stress echocardiography; pacemaker stress seems less time-consuming and is associated with less side effects. Therefore, when information on myocardial ischemia and/or prognosis is required, pacemaker stress echocardiography is a reasonable choice. One limitation of pacemaker stress echocardiography is to assess myocardial viability. Therefore, when information on myocardial viability is needed, dobutamine stress echocardiography should be preferred.

Clinical Implications and Conclusions

Pacemaker stress echocardiography is a safe and feasible method for the risk stratification of patients with permanent pacemakers. The presence of ischemia during pacemaker stress echocardiography is independently associated with an increased risk of cardiac death and all cause mortality. Pacemaker stress echocardiography identifies high-risk patients in whom aggressive evaluation and/or therapy is required.

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Chapter 12

Prognostic Significance of Left Anterior Hemiblock in Patients with Suspected Coronary Artery Disease

Biagini E, Elhendy A, Schinkel AFL, Nelwan S,
Rizzello V, van Domburg RT, Rapezzi C,
Rocchi G, Simoons ML, Bax JJ, Poldermans D

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Abstract

Background. The significance of isolated left anterior hemiblock (LAHB) in patients with suspected coronary artery disease (CAD) is unclear. The aim of this study was to assess the functional and prognostic significance of LAHB in patients with no history of myocardial infarction referred for dobutamine stress echocardiography (DSE).

Methods. We studied 1187 patients with suspected CAD and no history of previous myocardial infarction, who underwent DSE and were followed for occurrence of cardiac death.

Results. LAHB was detected on baseline electrocardiogram (ECG) in 159 (13%) patients. Ischemia occurred more frequently in patients with LAHB (43% vs 33%, $p = 0.02$). During a mean follow-up of 5.0 ± 2.5 years, 125 (11%) patients died of cardiac causes. The annual cardiac death rate was 4.9% in patients with LAHB and 1.9% for patients without ($p<0.0001$). Patients with both LAHB and an abnormal DSE had the highest cardiac death rate (6.3%). In a Cox multivariable analysis, independent predictors of cardiac death were age, smoking, history of heart failure, diabetes and inducible myocardial ischemia. LAHB was independently associated with increased risk of cardiac death among patients with normal DSE (HR= 1.8, 95% CI=1.1-3.8) as well as in patients with abnormal DSE (HR= 1.7, 95% CI=1.1-2.7).

Conclusions. In patients with suspected CAD referred for stress testing, LAHB is associated with increased risk of cardiac death. This risk is persistent after adjustment for major clinical data and abnormalities on the stress echocardiogram. Therefore, isolated LAHB should not be considered a benign ECG abnormality in these patients.

Introduction

Data on prognostic significance of left anterior hemiblock (LAHB) are scarce, particularly among patients without history of myocardial infarction (1). In subjects with no evidence of cardiac disease some authors found a marginally increased incidence of coronary artery disease (CAD) in patients with LAHB (2). No association has been found between the presence of LAHB and an increased risk of cardiac death (3-5). However data in literature are limited by including small number of patients and the short term follow-up. LAHB is a well recognized complication that occurs in 3-5% of patients after acute myocardial infarction. In these patients, LAHB is believed to be due to ischemic injury of the anterior fascicle of the left conduction system. In patients with acute inferior myocardial infarction, LAHB was associated with a larger infarct extension and left anterior descending CAD (6). However, its occurrence in patients after acute myocardial infarction has not been related to a higher mortality rate (7-10). We sought to study the association of LAHB with abnormalities on the stress echocardiogram and prognosis in patients with suspected CAD who have no history of myocardial infarction.

Patients. The study population consisted of consecutive patients with suspected CAD referred for DSE at the Thoraxcenter, Rotterdam, the Netherlands. Exclusion criteria were history of previous myocardial infarction, cardiac pacemaker, pathological Q wave, and complete left or right bundle branch block on baseline electrocardiogram (ECG). Criteria were fulfilled in 1199 patients. Follow-up was successful in 1187 patients (99%) who represented the final population of the study. Patients were divided in two groups according to the presence or absence of LAHB on baseline ECG. Criteria for LAHB were leftward QRS axis of -30° to -90°, with rS patterns in leads II, III, and aVF, and Q waves in aVL (11, 12). Left ventricular hypertrophy (LVH) was defined using the Cornell voltage-duration product, which was calculated as follows: RaVL ± SV3 (with 6 mm added in women) × QRS duration. A threshold of 2440 mm x msec was used to identify left ventricular hypertrophy (13, 14). The duration of the QRS complex was electronically measured by 12 lead ECG performed in the resting supine position ("Escribe" v15.25, Mortara Instruments, Milwaukee, USA). QRS detection by this system used a filter and template matching technique to identify a median QRS complex, which was then aligned in all leads simultaneously. QRS duration was measured from the earliest onset in any lead to the latest detection in any lead. The protocol was approved by the Hospital Ethics Committee. All patients gave informed consent before the test. Clinical characteristics and indications for testing were entered in a computerized database before DSE and were defined as previously described (15).

Dobutamine Stress Test. Dobutamine-atropine stress testing was performed according to a standard protocol as previously reported (16). After obtaining a baseline echocardiogram, dobutamine was administered intravenously, starting at a dose of 5-10 μg/kg/min for 3 minutes. Incremental dobutamine doses of 10 μg/kg/min were given at 3-minute intervals up to a maximum dose of 40 μg/kg/min. If the test end-point was not reached at a dobutamine dose of 40 μg/kg/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), maximal dose of dobutamine and atropine, extensive new wall motion abnormalities, >2 mV downsloping ST-segment depression measured 80 ms after the J point compared with baseline, hypertension (blood pressure >240/120 mm Hg), a decrease in systolic blood pressure of >40 mm Hg compared with at rest, significant arrhythmias, or any intolerable

adverse effect considered to be the result of dobutamine or atropine. An intravenous β-blocker (metoprolol 1 to 5 mg) was available to reverse the adverse effects of dobutamine/atropine.

Echocardiographic imaging and interpretation. Two-dimensional echocardiographic images were acquired at rest, during dobutamine stress, and recovery using the standard views. The echocardiograms were recorded in a quad-screen format. The interpretation of DSE studies was performed off-line from cineloops, by 2 experienced observers blinded to the clinical and electrocardiographic data. In case of disagreement, a consensus decision was achieved by a third observer. Regional function was scored using a 16-segment 5-point scoring model (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. A biphasic response in an akinetic or severely hypokinetic segment was considered as an ischemic response. An abnormal DSE was defined as resting or inducible wall motion abnormalities. The wall motion score index (WMSI) was calculated by dividing the sum of regional wall motion scores by the total number of interpreted segments.

Follow-up. Follow-up data collection was performed by contacting the patient's general practitioner and by review of hospital records. The date of the last review or consultation was used to calculate follow-up time. Follow-up events noted were overall mortality and hard cardiac events (nonfatal myocardial infarction and cardiac death). Cardiac death was defined as a death caused by acute myocardial infarction, significant cardiac arrhythmias, or refractory congestive heart failure. Sudden death occurring without another explanation was considered as cardiac death. Nonfatal myocardial infarction was defined based on criteria of typical chest pain, elevated cardiac enzyme levels and typical changes on electrocardiography. Myocardial revascularization procedures were also noted.

Statistical Analysis. Continuous data were expressed as mean value ± SD. The Student's t test was used to analyze continuous data. Differences between proportions were compared using the Chi-square test. The following major clinical and stress test data were used in a Cox regression model to identify independent predictors of cardiac events: age, gender, smoking, hypertension, diabetes mellitus, history of heart failure, angina, LAHB, QRS duration, LVH on baseline ECG, ST segment depression during stress, peak stress rate pressure product, peak wall motion score index, and myocardial ischemia on DSE. The risk of a variable was expressed as a hazard ratio with a corresponding 95% confidence interval. The probability of survival was calculated using the Kaplan-Meier method, and survival curves were compared using the log-rank test. A p value <0.05 was considered statistically significant.

Results

Clinical and stress test data. Clinical characteristics are presented in Table 1. Patients with LAHB were older and more often had a history of hypertension and heart failure.

Table 1. Clinical Characteristics of Patients with and without LAHB

	LAHB		p value
	Yes (N=159)	No (N=1028)	
Age (years, standard deviation)	66 ± 11	60 ± 13	<0.0001
Male	95 (60%)	581 (56%)	0.5
Hypertension	70 (44%)	363 (35%)	0.04
Hypercholesterolemia	32 (20%)	275 (27%)	0.09
Smoking	40 (25%)	252 (24%)	0.9
Diabetes mellitus	15 (9%)	140 (14%)	0.2
History of typical angina	25 (16%)	215 (21%)	0.2
Atypical chest pain	33 (21%)	281 (27%)	0.1
History of heart failure	16 (10%)	56 (5%)	0.04
LVH	14 (9%)	90 (9%)	1.0
QRS duration	109 ± 26	95 ± 14	<0.0001
β-blockers	52 (33%)	338 (33%)	1.0
Calcium channel blockers	45 (28 %)	262 (25%)	0.5
ACE-inhibitors	44 (28%)	212 (21%)	0.06
Nitrates	32 (20%)	167 (16%)	0.3

Dobutamine stress data are presented in Table 2. Peak heart rate was lower in patients with LAHB, reflecting the lower maximal predicted heart rate due to older age in patients with than without LAHB. Ischemia (new or worsened wall motion abnormalities) occurred more frequently in patients with than without LAHB. Resting WMSI was comparable between the two groups, whereas the peak WMSI was significantly higher in patients with LAHB.

Table 2. Dobutamine Stress Hemodynamic and Echocardiographic Data

	LAHB		p value
	Yes (N=159)	No (N=1028)	
Heart rate at rest (beats/min)	72 ± 13	74 ± 14	0.2
Heart rate at peak (beats/min)	126 ± 16	130 ± 17	0.002
Patients who achieved target heart rate	140 (88%)	888 (86%)	0.6
Rest systolic blood pressure (mmHg)	136 ± 16	133 ± 23	0.2
Peak systolic blood pressure (mmHg)	140 ± 24	138 ± 25	0.5
Rest rate pressure product	9914 ± 2648	9877 ± 2501	0.9
Peak rate pressure product	16796 ± 4262	17506 ± 4299	0.07
Maximal dobutamine dose (μg/kg/minute)	33 ± 9	34 ± 8	0.1
Atropine use, patients	54 (6%)	391 (9%)	0.4
ST-segment depression	9 (6%)	98 (9%)	0.2
Resting WMSI	1.1 ± 0.2	1.1 ± 0.3	0.2
Peak WMSI	1.3 ± 0.5	1.2 ± 0.4	0.02
Normal DSE, patients	69 (43%)	497 (48%)	0.3
Fixed abnormalities, patients	21 (13%)	188 (18%)	0.1
New or worsening wall motion abnormalities, patients	69 (43%)	343 (33%)	0.02

Regional distributions of stress wall motion abnormalities in patients with and without LAHB are presented in Figure 1. Patients with LAHB had a higher incidence of abnormalities in the anterior, apical and lateral walls compared to patients without LAHB.

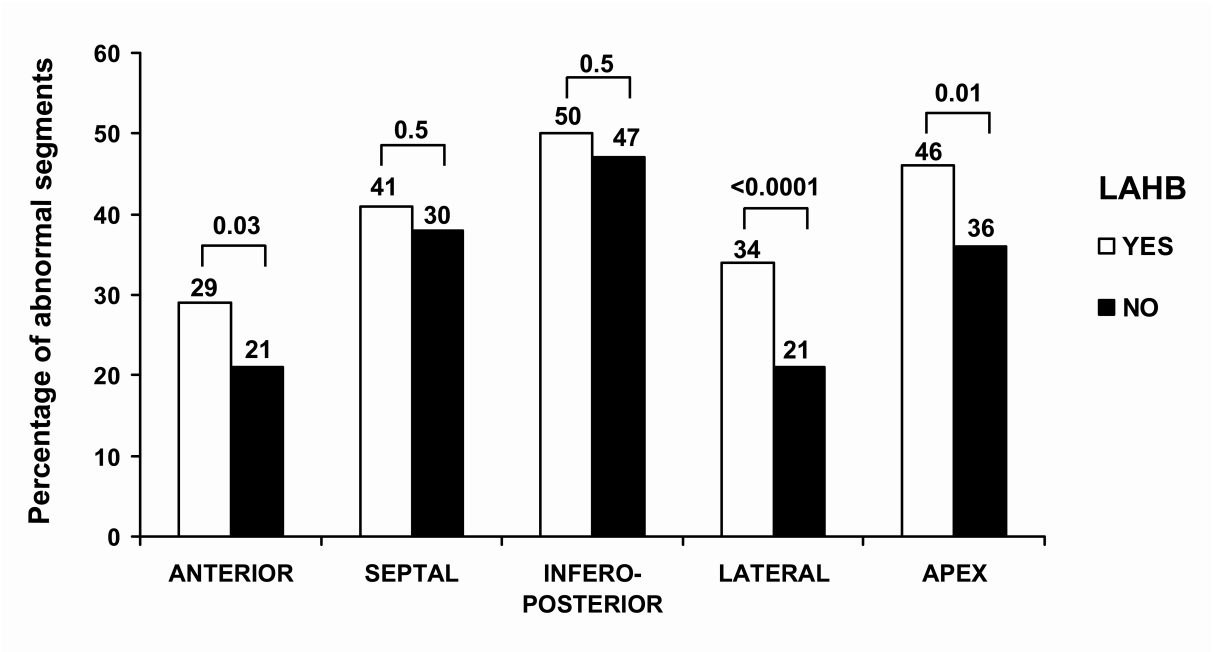

Figure 1. *Regional distribution of abnormalities on the dobutamine stress echocardiogram in patients with and without LAHB.*

Follow-up data. During a mean follow-up of 5.0 ± 2.5 years, 283 (24%) patients died, 125 (11%) due to cardiac causes. Non-fatal myocardial infarction occurred in 54 patients (5%); revascularization was performed in 177 (15%) patients. Patients with LAHB had a higher incidence of overall mortality [53 (33%) versus 230 (22%), p=0.004] and cardiac mortality [32 (20%) versus 93 (9%), p<0.0001] compared to patients without LAHB. Non fatal myocardial infarction occurred in 11 (7%) patients with LAHB and in 43 (4%) patients without (p=0.1). Among patients with normal DSE, myocardial infarction occurred in 4 (6%) of 69 patients with LAHB, and in 19 (4%) of 497 patients without LAHB (P=0.6). Six (9%) out of 69 patients with LAHB and a normal DSE underwent subsequent coronary angiography during follow up. CAD was detected in 4 (6%) of these patients. Cardiac death occurred in 11 (16%) of 69 patients with LAHB and a normal DSE, and in 33 (7%) of 497 patients without LAHB and a normal DSE (P=0.01).

Table 3 and Table 4 present predictors of cardiac death and all cause mortality, respectively. Age, smoking, history of heart failure and myocardial ischemia during DSE were independent predictors of cardiac death. Age, gender, smoking, history of heart failure, LVH and myocardial ischemia during DSE were independent predictors of all cause mortality. LAHB was an independent predictor of both cardiac death and all cause mortality after adjustment for clinical and stress echocardiographic data. LAHB was independently associated with increased risk of cardiac death among patients with normal DSE (HR = 1.8,

95% CI = 1.1-3.8) as well as in patients with abnormal DSE (HR = 1.7, 95% CI = 1.1-2.7). The annual cardiac death rate was 1.9% for patients without LAHB and 4.9% for patients with LAHB ($p<0.0001$). The hard event rate was 2.5% for patients without LAHB and 5.9% for patients with LAHB ($p<0.0001$).

Table 3. Univariate and Multivariate Association of Clinical and Echocardiographic Data with Cardiac Death

	Univariate	Multivariate
Parameter	**Hazard Ratio (95%CI)**	**Hazard Ratio (95%CI)**
Age	1.06 (1.04-1.07)	1.05 (1.03-1.08)
Gender	1.9 (1.4-2.6)	1.4 (0.9-2.1)
Smoking	2.1 (1.6-2.8)	2.0 (1.3-3.1)
Hypertension	0.9 (0.7-1.3)	1.2 (0.7-1.8)
History of heart failure	4.2 (2.5-6.8)	1.8 (1.1-3.3)
Diabetes mellitus	1.4 (0.9-2.1)	1.4 (1.1-2.4)
History of typical angina	0.8 (0.5-1.2)	0.4 (0.2-1.0)
LAHB	2.5 (1.6–4.0)	1.7 (1.1-2.8)
QRS duration (msec)	4.84 (2.12-10.9)	1.16 (0.32-4.22)
LVH by EcG criteria	1.6 (0.9-2.8)	1.3 (0.7-2.5)
ST depression	0.8 (0.4-1.4)	1.0 (0.5-2.1)
Peak rate pressure product	0.97 (0.94-1.00)	0.01 (0.95-1.07)
Peak wall motion score index	3.04 (2.39-3.86)	2.13 (0.94-4.85)
Myocardial ischemia	1.9 (1.2-2.7)	1.8 (1.1-2.9)

Table 4. Univariate and Multivariate Association of Clinical, Electrocardiographic and Echocardiographic Data with All Cause Mortality

	Univariate	Multivariate
Parameter	**Hazard Ratio (95%CI)**	**Hazard Ratio (95%CI)**
Age	1.03 (1.02-1.04)	1.04 (1.02-1.06)
Gender	1.9 (1.5-2.4)	1.9 (1.4-2.7)
Smoking	1.6 (1.3-2.1)	1.7 (1.3-2.3)
Hypertension	0.9 (0.8-1.2)	1.1 (0.9-1.5)
History of heart failure	3.8 (2.5-5.9)	1.9 (1.3-3.0)
Diabetes mellitus	1.1 (0.8-1.6)	1.3 (0.9-2.0)
History of typical angina	0.8 (0.6-1.1)	0.8 (0.5-1.2)
LAHB	1.7 (1.2–2.5)	1.4 (1.1-2.0)
QRS duration (msec)	0.64 (0.26-1.58)	0.71 (0.30-41.64)
LVH by ECG criteria	1.8 (1.5-2.6)	1.5 (1.1-2.3)
ST depression	0.6 (0.4-1.0)	0.9 (0.6-1.6)
Peak rate pressure product	0.95 (0.92-0.99)	0.93 (0.90-0.97)
Peak wall motion score index	1.39 (0.76-2.59)	1.38 (0.75-2.57)
Myocardial ischemia	1.8 (1.2-2.6)	1.5 (1.1-2.2)

Kaplan-Meyer survival curves in patients with normal DSE (figure 2a) and in patients with abnormal DSE (Figure 2b) demonstrated a lower event free survival among patients with LAHB in both groups.

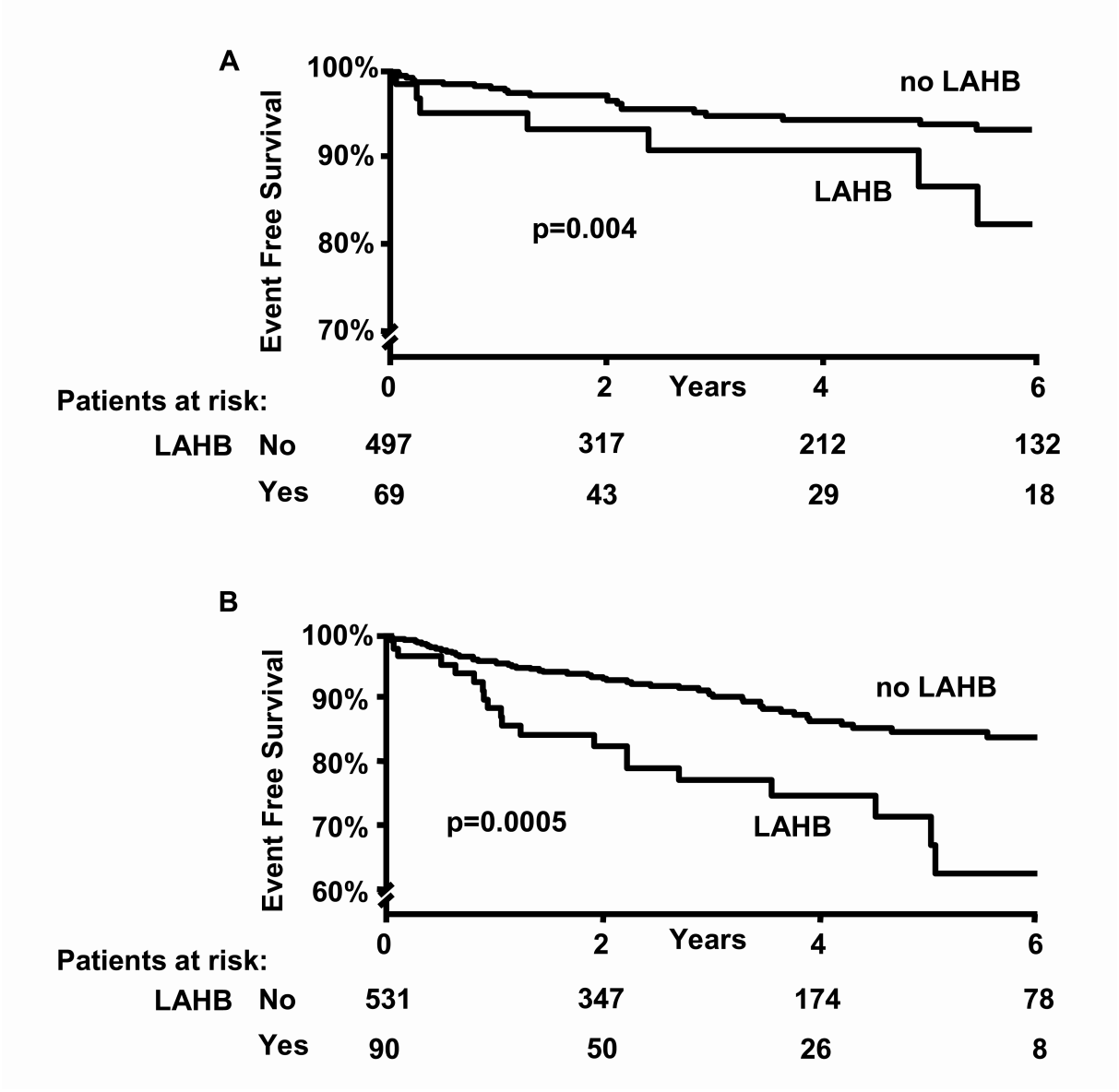

Figure 2. *Kaplan-Meier survival curves (end point of cardiac death) in the presence and in the absence of LAHB in patients with normal dobutamine stress echocardiogram (Panel A) and in patients with abnormal dobutamine stress echocardiogram (panel B).*

The annual cardiac event rates according to combination of LAHB and abnormalities on DSE are presented in Figure 3. The presence of LAHB in both groups of patients with normal and abnormal DSE identified a significantly higher risk population for cardiac death and hard cardiac events. Patients with both LAHB and abnormal DSE were at the highest risk.

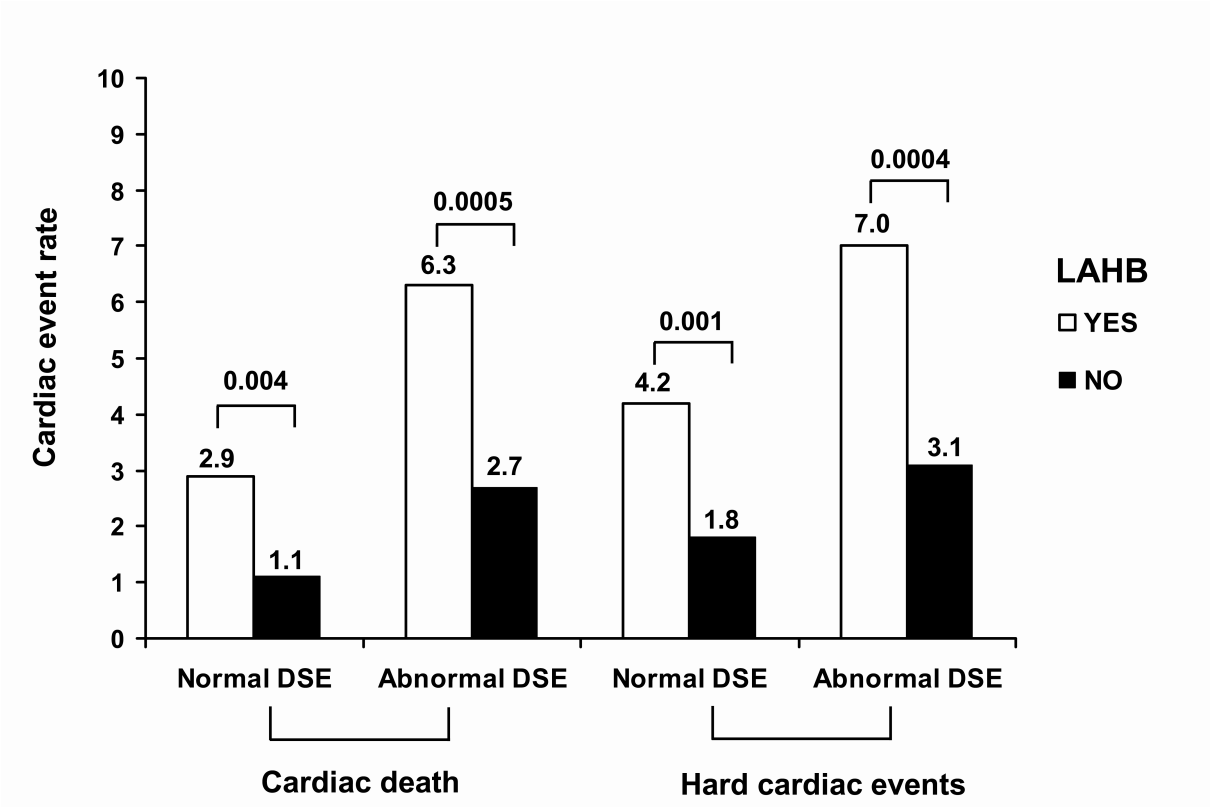

Figure 3. *Annual cardiac event rates according to combinations of ECG and stress echocardiographic findings.*

Discussion

In this study we assessed the functional and prognostic significance of LAHB on resting 12 lead ECG in patients with suspected CAD, who had no history or ECG evidence of prior myocardial infarction. LAHB was detected in 159 patients (13%). Patients with LAHB had 2.5 fold higher incidence of cardiac death and 1.5 fold higher incidence of all cause mortality as compared to patients without LAHB during a mean follow-up of 5 years. The associated risk of death was independent of clinical parameters, QRS duration, LVH on the ECG, and abnormalities on the DSE. The higher incidence of cardiac death in association with LAHB was observed among patients with normal as well as patients with abnormal DSE. The combination of LAHB and abnormal DSE identified patients with the highest incidence of cardiac death and hard cardiac events.

Echocardiographic data and prognosis. Patients with LAHB had 10% higher incidence of ischemia on DSE. This indicated that LAHB is associated with higher prevalence of significant CAD. However, this modest difference does not alone explain the large difference in cardiac mortality, particularly with the similar resting WMSI in both groups and the fact that Cox model adjusted for myocardial ischemia. The reason for the independent association of LAHB with cardiac mortality after adjustment for DSE data is unclear. It is possible that LAHB is associated with ultrastructural myocardial damage that can not be grossly identified by echocardiographic imaging. Because of the small size of the left anterior fascicle, it is vulnerable for blockage in the presence of trivial ischemia in the region of its course. Another explanation could be higher propensity for fatal arrhythmias in the presence of a substrate of myocardial dysfunction, LHAB and triggering ischemia. Another possibility

would be a higher rate of false negative DSE in patients with LAHB. However, because of the very small number of patients who underwent coronary angiography during follow up, a lower sensitivity of DSE in patients with LAHB remains speculative.

LAHB and LVH were independent predictors of all cause mortality, whereas QRS duration was not. The lack of independent association of QRS duration with outcome may be explained by exclusion of patients with complete bundle branch block and patients with previous myocardial infarction and thereby including a population with preserved left ventricular function.

Regional abnormalities with LAHB. The occurrence of LAHB in association with myocardial ischemia is thought to be related to left anterior descending CAD (17, 18). However, there are no previous reports on tomographic localization of functional abnormalities in these patients.

Analysis for regional distribution of stress wall motion abnormalities in our study showed a higher incidence of abnormalities in the anterior and apical regions in patients with compared to patients without LAHB. This is in concordance with anatomic studies showing that the left anterior division of the left bundle branch block runs across the septal surface towards the antero-lateral aspect of the free wall of the left ventricle and is supplied by the left anterior descending coronary artery. The higher incidence of abnormalities in the lateral wall among patients with LAHB, with a similar incidence of abnormalities in the posterior and inferior walls, suggest that abnormalities noted in the lateral wall in some of these patients are due to diagonal rather than left circumflex CAD.

Previous studies. Previous data on the correlation between LAHB and cardiac disease in the general population are scarce (2-4). Corne et al. (2), found a relation with systemic hypertension and cardiac disease in 390 men of 30 years and over with LAHB compared with age and sex matched control group. Studies of the prognostic significance of isolated LAHB in the general population or in subjects without clinical evidence of cardiac disease are limited but have reported no effect on mortality (3, 4). Yano et al. (3), followed 70 clinically normal subjects with LAHB for periods ranging from 3 to 6 years and found no increase in the mortality risk ratio compared with normal controls. Ostrander et al. (4), analysed data from the Tecumseh Communities Health Study and found that 102 subjects with left axis deviation and no other findings suggestive of heart disease had no excess of morbidity or mortality during an average observation of 4 years.

LAHB is not uncommonly observed in patients with acute myocardial infarction. Development of LAHB during inferior acute myocardial infarction has been correlated with significant stenosis in left anterior descending coronary artery and multivessel disease (6-19). Assali et al. (6), studied 87 patients with an first inferior wall acute myocardial infarction. Seventeen (19%) developed a LAHB. Significant stenosis of the left anterior descending artery was found in 82% of patients with LAHB and in 21% of patients without LAHB ($p= 0.001$). By logistic regression analysis, the odds ratio for development of LAHB was 27.5 ($p=0.0001$) for left anterior descending artery stenosis compared with 2.92 ($p=0.053$) and 0.3 ($p= 0.3$) for circumflex and right coronary artery. However, LAHB after acute myocardial infarction has not been found to be related to an increased mortality (7-10).

Information regarding the prognostic significance of LAHB in patients referred for stress test is limited. In the study by Cortigiani et al. (20), the prognostic implication of intraventricular conduction defects in patients with suspected CAD referred for pharmacologic stress echocardiography was evaluated during a mean follow-up of 3 years. Out of a total of 1230 patients, 173 had complete left bundle branch block, 98 isolated right bundle branch block, 43 right bundle branch block plus LAHB and 106 isolated LAHB. The

presence of right bundle branch block together with left anterior hemiblock was associated with a poor prognosis and was an independent predictor of mortality. The presence of isolated LAHB was not associated with all-cause mortality in a multivariate analysis.

Limitations

LVH was evaluated by ECG criteria, with possible underestimation of incidence of LVH by echocardiographic criteria (21). Nevertheless, LVH as defined by ECG was an independent predictor of mortality in this study despite possible underestimation of the true incidence of LVH. The ECG has been generally used as an acceptable method to define LVH in outcome trials (22) Finally, this study could not determine whether the increased risk in association with LAHB is related to a lower sensitivity of DSE in patients with LAHB or not, since only a small number of patients underwent coronary angiography. Further studies are needed to assess the diagnostic performance of DSE in patients with LAHB.

Conclusions

Isolated LAHB is an independent predictor of total and cardiac mortality in patients with suspected CAD who have no history of myocardial infarction. The increased risk of mortality is persistent after adjustment for clinical data, left ventricular function and inducible ischemia on DSE. Among patients with a normal DSE, the presence of LAHB is associated with a worse prognosis. Patients with both LAHB and abnormal DSE had the worst outcome. Therefore, isolated LAHB should not be considered a benign ECG abnormality in these patients and should be considered along with other clinical and stress test data in estimating the risk of cardiac events.

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Chapter 13

Opposite Patterns of Left Ventricular Remodeling after Coronary Revascularization in Patients with Ischemic Cardiomyopathy. Role of Myocardial Viability

Rizzello V, Poldermans D, Boersma E, Biagini E,
Schinkel AFL, Boudewijn JK, Elhendy A, Vourvouri EC,
Sozzi FB, Maat A, Crea F, Roelandt JRTC, Bax JJ

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Opposite Patterns of Left Ventricular Remodeling After Coronary Revascularization in Patients With Ischemic Cardiomyopathy

Role of Myocardial Viability

Vittoria Rizzello, MD; Don Poldermans, MD; Eric Boersma, PhD; Elena Biagini, MD; Arend F.L. Schinkel, MD; Boudewijn Krenning, MD; Abdou Elhendy, MD; Eleni C. Vourvouri, MD; Fabiola B. Sozzi, MD; Alexander Maat, MD; Filippo Crea, MD; Jos R.T.C. Roelandt, MD; Jeroen J. Bax, MD

Background—In patients with ischemic cardiomyopathy, left ventricular (LV) remodeling is an important prognostic indicator. The precise relation between viable myocardium, revascularization, and ongoing or reversed remodeling is unknown and was evaluated in the present study.

Methods and Results—A total of 100 patients with ischemic cardiomyopathy underwent dobutamine stress echocardiography to assess myocardial viability and LV geometry (volumes and shape). At a mean of 10.2 months and 4.5 years after revascularization, resting echocardiography was repeated to evaluate LV remodeling. Long-term follow-up (mean 5±2 years) data were obtained. According to dobutamine stress echocardiography, 44 patients (44%) were defined as viable (≥4 viable segments) and 56 as nonviable. After revascularization, 40 patients (43%) had ongoing LV remodeling and 53 (57%) did not (in 7 patients who died early after revascularization, postoperative echocardiographic evaluation was not available). On multivariable analysis, the number of viable segments was the only predictor of ongoing LV remodeling (OR 0.60, 95% CI 0.48 to 0.75; $P<0.0001$). The likelihood of LV remodeling decreased as the number of viable segments increased. During the follow-up, reverse remodeling was present in viable patients, whereas in nonviable patients, LV volumes significantly increased, which indicates ongoing LV remodeling. At follow-up, viable patients also showed a persistent improvement of heart failure symptoms and fewer cardiac events than nonviable patients ($P<0.05$).

Conclusions—In patients with ischemic cardiomyopathy, a substantial amount of viable myocardium prevents ongoing LV remodeling after revascularization and is associated with persistent improvement of symptoms and better outcome. **(*Circulation*. 2004;110:2383-2388.)**

Key Words: remodeling ■ revascularization ■ cardiomyopathy

In patients with ischemic cardiomyopathy coronary revascularization is a therapeutic option that may improve left ventricular (LV) function and prognosis.[1–10] A substantial amount of viable myocardium is necessary to obtain improvement of LV ejection fraction (LVEF), symptoms and prognosis.[2–10] It has been suggested that the preservation of LV geometry in patients with ischemic cardiomyopathy may also be an important end point after revascularization.[11] The restoration of adequate flow to viable myocardium may prevent LV distortion and ongoing LV remodeling, and thus prevent progressive heart failure and death. Some studies showed that revascularization can prevent the LV remodeling process in patients with recent myocardial infarction and residual viability.[12,13] Information on the effect of viability and revascularization on LV remodeling in patients with chronic LV dysfunction is scarce.[14,15] Accordingly, in the present study, the role of myocardial viability in the LV remodeling process after revascularization has been evaluated in a large cohort of patients with ischemic cardiomyopathy. In addition, long-term clinical follow-up has been obtained.

Methods

Study Population

The study population existed of 106 patients (89 men, age 61±10 years) with ischemic cardiomyopathy and heart failure symptoms already scheduled for revascularization according to clinical criteria (symptoms, presence/absence of ischemia, and angiographic findings). Sinus rhythm was present in all patients. Ninety-eight patients (93%) had a history of myocardial infarction that had occurred >6 months before study entrance (median 3 years, range 0.8 to 23 years). Patients with moderate to severe valvular disease were excluded.

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From the Department of Cardiology, The Catholic University of the Sacred Heart (V.R., F.C.), Rome, Italy; Department of Cardiology, Thoraxcenter (D.P., E. Boersma, E. Biagini, A.F.L.S., B.K., A.E., E.C.V., F.B.S., A.M., J.R.T.C.R.), Erasmus MC, Rotterdam, Netherlands; and the Department of Cardiology, Leiden University Medical Center (J.J.B.), Leiden, Netherlands.

Correspondence to Don Poldermans, MD, PhD, Department of Cardiology, Thoraxcenter Room Ba 300, Erasmus MC, Dr. Molewaterplein 40, 3015 GD Rotterdam, Netherlands. E-mail d.poldermans@erasmusmc.nl

Study Protocol

Patients with ischemic cardiomyopathy were studied prospectively to evaluate LV remodeling, LV ejection fraction (LVEF), and cardiac events during a long-term follow-up after revascularization and their relation to myocardial viability. Before revascularization (study 1, baseline) resting 2D echocardiography was performed to assess regional wall-motion abnormalities and LV geometry, followed by dobutamine stress echocardiography (DSE) to evaluate myocardial viability. After revascularization, resting 2D echocardiography was repeated at a mean of 10.2 months (study 2) and 4.5 years (study 3) to assess changes in LV geometry. Within 2 weeks of each echocardiographic study, radionuclide ventriculography (RNV) was performed to assess LVEF by an independent technique. Before and sequentially after revascularization, functional status was evaluated by structured clinical interviews. Cardiac events were obtained during a 5±2-year follow-up. The local ethics committee approved the protocol, and all patients gave informed consent.

Echocardiographic Studies

All echocardiograms were performed with a Sonos-5500 device (Hewlett-Packard, PMS) equipped with a second-harmonic 1.8- to 3.6-MHz transducer. Standard views of the LV were obtained.[14]

Myocardial Viability

Low- to high-dose DSE (up to 40 $\mu g \cdot kg^{-1} \cdot min^{-1}$ plus 2 mg of atropine, if necessary) was performed as described previously.[6] Interpretation of DSE studies was performed offline from cine loops by 2 experienced observers blinded to the clinical data. Interobserver and intraobserver agreement for analysis of DSE studies was 92% and 94%, respectively.[16] Regional function was scored with a 16-segment, 5-point scoring model as follows: 1=normal, 2=mildly hypokinetic, 3=severely hypokinetic, 4=akinetic, and 5=dyskinetic.[6] The wall-motion score index (WMSI) was calculated by dividing the summed wall-motion score by the number of segments. Myocardial viability was evaluated only in severely dysfunctional segments (score 3 to 5). Segments showing a sustained improvement in wall motion up to the high dose and segments with an ischemic pattern (biphasic response or worsening of the wall motion) during DSE were considered viable.[4,6,11] Segments with unchanged wall motion or with akinesia that became dyskinesia were considered nonviable.[4,6] A patient was defined as viable in the presence of ≥4 viable segments and as nonviable in the presence of <4 viable segments.[6] This definition is based on previous work with receiver operator characteristic curve analysis that showed that recovery of function may be predicted in the presence of ≥4 viable segments.[6]

LV Geometry (Volumes and Sphericity)

LV volumes and LV sphericity index (LVSI) were measured from the resting echocardiography (before and sequentially after revascularization). All measurements were performed offline in random order by 2 experienced readers blinded to patient data and study time. LV volumes were measured with the biplane Simpson's rule.[17] The end-diastolic and end-systolic volumes were indexed (LVEDVI and LVESVI, respectively) by the body surface area. LVEDVI ≤55.5±8.7 mL/m^2 and LVESVI ≤22.1±4.9 mL/m^2 were considered normal values.[18,19] Interobserver and intraobserver variability for the measurement of LV volumes was 5% and 7%, respectively. An increase >15% in the LVEDVI or LVESVI after revascularization defined ongoing LV remodeling. Absolute changes in LVEDVI and LVESVI were expressed as the change (Δ) between the volume late after revascularization (at 4.5 years) and the baseline volume. The LVSI was derived by the ratio of LV short- to long-axis dimensions in the end-systolic apical 4-chamber view.[16] The higher the LVSI, the more spherical the shape. Intraobserver and interobserver agreement for assessment of LVSI was 95% and 91%, respectively.

Assessment of Improvement in LVEF

RNV was performed at rest with the patient in the supine position after administration of 740 MBq of ^{99m}Tc. Images were acquired with a small-field-of-view gamma camera (Orbiter, Siemens Corp) oriented in the 45° left anterior oblique position with a 5° to 10° caudal tilt. LVEF was calculated from the 45° left anterior oblique view by an automated technique. An improvement in LVEF ≥5% at study 2 or 3 was considered clinically significant.[6]

Symptoms and Long-Term Follow-Up

At each study point, patients' New York Heart Association (NYHA; for heart failure symptoms) and Canadian Cardiovascular Society (CCS) class (for angina) were defined by an independent physician blinded to all data. Long-term follow-up was obtained by chart review and telephone contact. Events included cardiac death, myocardial infarction, hospitalization for heart failure, and major ventricular arrhythmias (ventricular tachycardia/fibrillation). Moreover, the duration of stay in the intensive care unit after surgery was noted, as was the presence of low-output syndrome (defined as the need for high dosages of inotropic medication and/or intra-aortic balloon pumping to sustain adequate hemodynamic status).

Statistical Analysis

Continuous data were expressed as mean±SD and compared with the Student's t test for (un)paired samples, as indicated. Proportions for dichotomous data were compared by χ^2 analysis. Repeated measurements were analyzed by 2-way ANOVA to evaluate differences across time and between different groups. Univariable and multivariable logistic regression analyses were performed to characterize predictors of ongoing LV remodeling. Categorical variables included diabetes, anterior/inferior Q-wave myocardial infarction, persistent ST-segment elevation, ACE inhibitor and/or β-blocker therapy, and mode and completeness of revascularization. Continuous variables included age, WMSI at rest, baseline LV volumes and LVEF, and number of viable and nonviable segments. To define the predictive value for LV remodeling of each DSE pattern that indicated viable myocardium, the numbers of segments with sustained improvement, biphasic response, or worsening of the wall motion were included in the analyses. All variables entered the multivariable stage, regardless of the results of univariable analyses. Multivariable regression was then performed by stepwise backward deletion. All variables with a probability value <0.25 remained in the final model. Linear regression analysis was performed to evaluate the relation between the amount of viable myocardium and the changes (Δs) in LV volumes. Cardiac event rate was evaluated by Kaplan-Meier analysis. Differences between curves were tested with log-rank χ^2 statistics. For all tests, a probability value <0.05 was considered significant.

Results

Study Population

CABG was performed in 85 patients (80%) and PTCA in 21 patients (20%). Revascularization procedures were performed within 1 month of the DSE and were complete in all but 1 patient, who had perioperative myocardial infarction (peak creatine kinase level of 2640 IU/L). Five patients who underwent associated procedures influencing LV remodeling (aneurysmectomy [n=3] and mitral valve repair [n=2]) were subsequently excluded. One patient was lost to follow-up. Cardiac death occurred early after revascularization in 6 patients, and 1 patient died of progressive heart failure at 6 months after revascularization. These patients were included in the follow-up analysis, but sequential evaluations after revascularization were not available in these 7 patients. One patient had an acute myocardial infarction 5 months after study 2. In this patient, ongoing LV remodeling was already present at study 2. Study 3 (at 4.5 years) was not performed in 8 patients who died (3 noncardiac deaths) during the follow-up period.

TABLE 1. WMSI, Systolic Blood Pressure/End-Systolic Volume Ratio, and LVEF at Different Study Points

	Group 1 (Remodeling)				Group 2 (No Remodeling)			
	Study 1	Study 2	Study 3	*P*	Study 1	Study 2	Study 3	*P*
WMSI*	2.7±0.6	2.7±0.7	2.8±0.61	NS	2.8±0.7	2.6±0.7	2.5±0.5	<0.01
SBP/ESV*	1.5±0.8	1.6±0.7	1.5±0.7	NS	1.6±0.6	2.6±1.6	2.7±0.6 1.4	<0.001
LVEF, % *	32±8	31±10	31±9	NS	32±9	38±11	41±11	<0.001

SBP/ESVI indicates systolic blood pressure/end-systolic volume ratio.
*P<0.001, group 1 vs group 2 by ANOVA.

Baseline Echocardiographic Data

All patients presented with moderate to severe LV dilatation. LVEDVI and LVESVI were on average 108±34 and 71±31 mL/m^2, respectively. Analysis of wall motion showed that 939 segments (59%) were severely dysfunctional. On average, patients had 9.3±4.7 severely dysfunctional segments. During DSE, 392 segments (42%) were viable: 176 (19%) had a biphasic response, 185 (20%) had sustained improvement, and 31 (3%) had worsening of wall motion. The remaining 597 segments (58%) were nonviable. Forty-four patients (44%) had ≥4 viable segments (viable patients), whereas 56 patients had <4 viable segments (nonviable patients).

LV Geometry After Revascularization

After revascularization, patients were divided into group 1 (40 patients [43%] with ongoing LV remodeling) and group 2 (53 patients [57%] without ongoing LV remodeling). Overall, WMSI and LVEF improved significantly after revascularization in group 2 but remained unchanged in group 1 (Table 1). Table 2 summarizes the baseline characteristics of the 2 groups. Q-wave anterior myocardial infarction was more frequent in group 1 (P<0.04). In addition, a trend toward a higher prevalence of persistent ST elevation was present in group 1. Finally, the number of viable and nonviable segments was significantly different between the 2 groups. At baseline, in groups 1 and 2, medications included ACE inhibitors in 67% and 64% of the patients, respectively (P=NS) and β-blockers in 48% and 66% of the patients, respectively (P=NS). At study 2 and 3, groups 1 and 2 were comparable for use of ACE inhibitors (82% versus 75% and 74% versus 79%, respectively, both P=NS) and β-blockers (25% versus 38% and 49% versus 52%, respectively,

TABLE 2. Baseline Characteristics

	Group 1 (Remodeling)	Group 2 (No Remodeling)	*P*
Age, y	60±11	61±10	NS
Male, n (%)	35 (87)	42 (80)	NS
CCS class	2.8±0.6	2.7±0.6	NS
NYHA class	2.6±1.2	2.9±0.9	NS
Hypertension, n (%)	29 (72)	38 (73)	NS
Hypercholesterolemia, n (%)	18 (45)	23 (43)	NS
Smoking, n (%)	20 (50)	23 (57)	NS
Family history of CAD, n (%)	24 (60)	28 (53)	NS
Diabetes, n (%)	4 (10)	4 (7)	NS
History of myocardial infarction, n (%)	39 (97)	51 (92)	NS
Q-wave myocardial infarction, n (%)	36 (90)	40 (75)	NS
Anterior	26 (65)	22 (41)	0.04
Septal	14 (35)	13 (24)	NS
Lateral	7 (17)	6 (11)	NS
Inferoposterior	16 (40)	28 (53)	NS
Persistent ST elevation, n (%)	21 (52)	17 (32)	0.08
Stenotic vessels, n	2.5±0.7	2.6±0.6	NS
LVEF, %	32±9	33±9	NS
Severely dysfunctional segments, n	8.6±4.2	9.6±5.1	NS
Viable segments, n	2.2±2.2	6.1±3.3	<0.001
Biphasic response, n	1±1.6	2.4±2.7	<0.01
Sustained improvement, n	0.9±1.7	2.7±2.4	<0.001
Worsening, n	0.3±0.7	0.4±0.9	NS
Unchanged, n	6.4±4.2	4.2±3.4	<0.01

CAD indicates coronary artery disease.
All values are presented as mean±SD or percentage (%).

TABLE 3. Predictors of LV Remodeling

	Univariable Analysis			Multivariable Analysis		
	OR	CI	*P*	OR	CI	*P*
LVEDVI	1.01	0.9–1.1	0.82	...	...	...
LVESVI	1.00	0.9–1.1	1	...	...	...
Viable segments, n	0.61	0.5–0.7	<0.0001	0.6	0.4–0.7	<0.0001
Nonviable segments, n	1.16	1.1–1.3	<0.05	1.11	0.9–1.3	0.13
Biphasic response, n	0.73	0.5–0.9	<0.01	...	...	...
Sustained improvement, n	0.66	0.5–0.8	<0.001	...	...	...
Worsening, n	0.86	0.5–1.5	0.6	...	...	...
LVEF	0.98	0.9–1.1	0.45	...	...	...
Inferior Q wave	0.61	0.2–1.4	0.26	...	...	...
Anterior Q wave	2.50	1.1–5.8	0.03	0.96	0.8–7.2	0.11
Persistent ST elevation	1.83	0.7–4.5	0.18	...	...	...
Mode of revascularization	1.99	0.6–6.2	0.23	...	...	...
Diabetes	2.88	0.5–16.6	0.28	...	...	...
WMSI	1.03	0.5–1.9	0.9	...	...	...
ACE inhibitors	1.12	0.4–2.6	0.78	...	...	...
β-Blockers	0.49	0.2–1.1	0.09	0.48	0.2–1.4	0.19
Age	0.99	0.9–1.1	0.78	...	...	...

both *P*=NS). In addition, 55% of patients in group 1 and 49% of patients in group 2 were taking lipid-lowering drugs at baseline (*P*=NS). The proportion of patients taking lipid-lowering drugs in the 2 groups was similar at study 2 (48% and 53%) and at study 3 (both 66%).

Predictors of Ongoing LV Remodeling After Revascularization

The presence of anterior Q-wave myocardial infarction and the number of scar segments were positively related to ongoing LV remodeling. The sustained improvement pattern was significantly more related to the occurrence of no remodeling (OR 0.66, 95% CI 0.5 to 0.8, $\chi^2=10.9$, $P<0.0001$) than was the biphasic response (OR 0.73, 95% CI 0.5 to 0.9, $\chi^2=6.7$, $P<0.01$). The worsening pattern was not related to LV remodeling. The total number of viable segments (showing sustained improvement, biphasic response, or worsening) was the strongest univariable predictor (OR 0.62, 95% CI 0.50 to 0.76, $\chi^2=20.3$, $P<0.0001$) and the only multivariable predictor of ongoing LV remodeling (OR 0.60 for each additional viable segment, 95% CI 0.48 to 0.75, $\chi^2=18.7$, $P<0.0001$; Table 3). The likelihood of ongoing LV remodeling decreased for each additional viable segment. When normal (not only dysfunctional) segments were included in the number of viable segments, this variable remained predictive of LV remodeling. Moreover, the Δs in LV volumes were inversely related to the number of viable segments (LVEDVI $P<0.001$; LVESVI $P<0.001$; Figure 1).

Myocardial Viability, Remodeling, and Long-Term Follow-Up

After revascularization, the duration of stay in the intensive care unit was 1.4±2 and 3.5±2 days for viable and nonviable patients, respectively ($P<0.005$). Low-output syndrome occurred in 12 viable (27%) and 29 (52%) nonviable patients ($P<0.05$). In 2 nonviable patients, an intra-aortic balloon pump was placed.

After revascularization, the majority of viable patients (88%) showed preserved LV volumes. Conversely, ongoing LV remodeling occurred in the majority of nonviable patients (72%, $P<0.0001$ versus viable patients). On average, in viable patients, LVEDVI did not change significantly during follow-up (from 105±37 to 102±35 up to 98±48 mL, *P*=NS by ANOVA), whereas LVESVI decreased significantly (from 70±34 to 65±31 up to 61±39 mL, $P<0.05$ by ANOVA). In nonviable

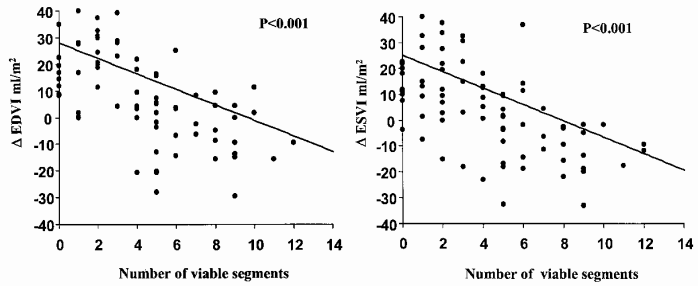

Figure 1. Relation between extent of viability and changes (Δs) in LV volumes after revascularization. Δs in LVEDVI (A) and LVESVI (B) decreased as number of viable segments increased.

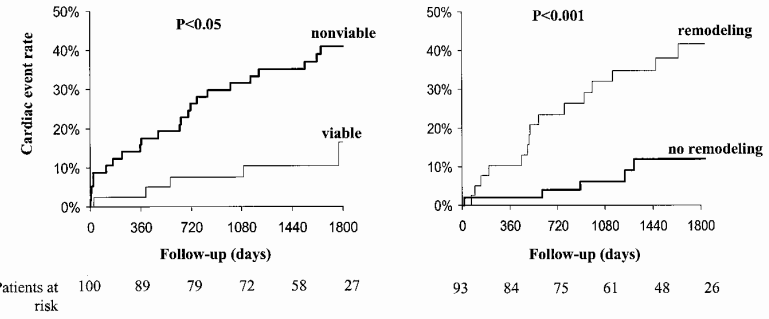

Figure 2. Kaplan-Meier curves showing cardiac event rate in viable and nonviable patients (A) and in patients with and without remodeling (B).

patients, LV volumes significantly increased over the follow-up period (ongoing LV remodeling; LVEDVI from 105±28 to 121±36 up to 131±50 mL/m^2, LVESVI from 65±24 to 80±32 up to 88±45 mL/m^2, both $P<0.001$ by ANOVA). Also, LVSI improved in viable patients (from 0.60±0.09 to 0.57±0.1, $P<0.01$ by ANOVA), whereas it worsened significantly in nonviable patients (from 0.59±0.09 to 0.65±0.1, $P<0.01$ by ANOVA). LVEF significantly improved in 65% of viable patients compared with 25% of nonviable patients ($P<0.001$). Changes in LVEF were inversely related to changes in LVEDVI ($P<0.01$). In addition, viable patients showed persistent improvement of symptoms during follow-up (CCS from 2.6±0.6 to 1.2±0.7 and NYHA from 3.1±0.8 to 1.5±0.5, both $P<0.001$ by ANOVA). In nonviable patients, although CCS class improved persistently (from 2.8±0.6 to 1.1±0.9, $P<0.001$ by ANOVA), NYHA class did not improve over the follow-up (from 2.9±0.9 to 2.9±0.7, P=NS by ANOVA). During the long-term follow-up, 1 nonviable patient underwent cardiac resynchronization therapy, and 2 patients (1 viable and 1 nonviable) received an intracardiac defibrillator.

Overall cardiac events were significantly less frequent in viable than in nonviable patients (16% versus 41%, $P<0.05$; Figure 2A). A trend toward a lower frequency of cardiac death was observed in viable patients (7% versus 21%, $P=0.08$). Also, cardiac events were less common in patients without LV remodeling than in those with ongoing LV remodeling (12% versus 42%, $P<0.001$; Figure 2B). Cardiac death occurred less frequently in patients without remodeling (4% versus 17%, $P=0.06$).

Discussion

Improvement in LV function, symptoms, and prognosis is likely to occur after revascularization in patients with ischemic cardiomyopathy and viable myocardium.[2,6–10] The findings in the present study indicate that in these patients, substantial myocardial viability prevents ongoing LV remodeling after revascularization and is associated with improvement of symptoms and favorable long-term prognosis.

Beneficial Effects of Revascularization in Patients With Viable Myocardium

Several studies have demonstrated that revascularization in patients with ischemic cardiomyopathy and viable myocardium improves regional and global LV function.[2,6, 20,21] A substantial amount (≥25% of the LV) of viable myocardium is necessary to result in improvement in LVEF.[6–10] However, it has been stated that the improvement in LV function may underestimate the benefit of revascularization and that improvement of symptoms and prognosis need to be considered.[11] In particular, a recent meta-analysis demonstrated that in patients with viable myocardium, revascularization is associated with a good prognosis.[22] Initial data suggested that in patients with ischemic cardiomyopathy, preservation of LV geometry and prevention of ongoing LV remodeling after revascularization can be an additional end point.[14,15] Accordingly, in the present study, coronary revascularization resulted in improvement in LVEF only in 65% of viable patients, whereas ongoing LV remodeling was prevented in 88% of viable patients. Hence, after revascularization, some viable patients did improve in terms of LV remodeling, although they failed to improve in LVEF. It is known that LV remodeling after acute myocardial infarction is a major determinant of poor prognosis.[23,24] In the present study, ongoing LV remodeling after revascularization of patients with ischemic cardiomyopathy was associated with a higher cardiac event rate (42%) than for patients with no remodeling (13%, $P<0.001$).

LV Remodeling After Revascularization

Senior and coworkers[14] demonstrated that coronary revascularization resulted in a significant reduction of LV volume in 32 patients with ischemic cardiomyopathy and viable myocardium. Conversely, ongoing LV remodeling occurred in viable patients treated medically.[14] Dalle Mule et al[15] showed a decrease in LV volumes 3 months after revascularization only in patients with substantial viability during ^{201}Tl imaging. Interestingly, an increase in LV volumes was observed in 24 nonviable patients undergone revascularization.[15] In the present study, a large number of patients were included, and more importantly, serial measurements of LV volumes were performed at different time points after revascularization. It appeared that LV volumes changed in different directions in relation to myocardial viability. In patients with minimal or absent viability, LV volumes continued to increase, which indicates ongoing LV remodeling, whereas in viable patients, attenuation or even reversion of LV dilatation occurred. Uniquely, the present study demonstrated that the extent of viable myocardium was related to the occurrence and extent of LV remodeling. In the individual patient, the likelihood of LV remodeling and the absolute changes in LV volumes decreased for each additional viable segment. Among the different patterns of response to dobutamine that indicated viable myocardium, the sustained-improvement pattern was a stronger univariable predictor of no LV remodeling

(χ^2=10.9) than the biphasic response (χ^2=6.7). It may well be that the duration of hibernation before study entrance affected the predictive power of the biphasic response. Also, the extent of nonviable myocardium was a univariable predictor of ongoing LV remodeling, whereas baseline volumes and resting WMSI failed to predict LV remodeling. The inclusion of only patients with moderate to severe LV dilatation and extensive wall-motion abnormalities at rest may explain this finding. Finally, β-blocker therapy before revascularization showed a trend toward a lower occurrence of LV remodeling, and the presence of anterior Q-wave myocardial infarction was a univariable predictor of ongoing LV remodeling. However, only the total number of viable segments remained predictive of LV remodeling in multivariable analysis. The beneficial effect of revascularization of viable myocardium on LV remodeling may have important prognostic implications. In the present study, patients with a substantial amount of viable myocardium, together with an improvement in LV geometry, had persistent improvement in heart failure symptoms and fewer cardiac events during the long-term follow-up. In addition, a trend toward a lower frequency of cardiac death was observed. Conversely, nonviable patients demonstrated ongoing LV remodeling without an improvement in heart failure symptoms after revascularization. Moreover, the cardiac event rate was higher in these patients (Figure 2A). Previous studies have already shown the beneficial effect of revascularization on early and mid-term prognosis.[6–10] These findings further extend previous observations to a long-term follow-up and demonstrate that the benefit of revascularization in patients with substantial myocardial viability may be due, at least in part, to prevention of ongoing LV remodeling.

Study Limitations

Angiographic follow-up was not performed after revascularization. Therefore, graft closure or restenosis may have occurred in some patients, affecting LV remodeling. Moreover, during follow-up, patients received different medications according to the attending physician. The possibility that medications influencing LV remodeling (ACE inhibitors and β-blockers) may have affected the results of the present study cannot be excluded. However, at each study point, medications used were comparable in the 2 groups.

Conclusions

In patients with ischemic cardiomyopathy, substantial myocardial viability prevents ongoing LV remodeling after revascularization and is associated with improvement of symptoms and favorable long-term outcome.

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Chapter 14

Stress and Tissue Doppler Echocardiographic Evidence of Effectiveness of Myoblast Transplantation in Patients with Ischemic Heart Failure

Biagini E, Valgimigli M, Smits PC, Poldermans D,
Schinkel AFL, Onderwater EME, Bountioukos M, Serruys PW

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Abstract

Background. There is experimental evidence that transplanted skeletal myoblasts (SM) into post-infarction myocardial scar improve regional and global left ventricular (LV) function. The aim of this study was to evaluate short- and long-term regional and global LV functional effects of percutaneously transplanted SM in patients with ischemic heart failure.

Methods. Ten patients (mean age 60 ± 10 years, 8 males) with dilated ischemic cardiomyopathy underwent percutaneous injection of autologous myoblasts. Regional and global LV function was evaluated by 2-dimensional echocardiography and tissue Doppler imaging (TDI) at rest and during low-dose dobutamine infusion to assess contractile reserve. After a baseline examination, sequential follow-ups were performed at 1-, 3-, 6-months and 1 year. Repeated measurements were compared using repeated measurements analysis of variance (ANOVA) to evaluate differences across the time.

Results. NYHA functional class decreased from 2.7 ± 0.5 to 1.9 ± 0.5 ($p<0.01$). LV function and volumes at rest remained unchanged while contractile reserve significantly improved during follow-up. At low-dose dobutamine infusion, the peak systolic velocity in the regions of myoblasts injection significantly increased at TDI examination (from 7.7 ± 2.1 to 8.6 ± 1.8 cm/sec, $p=0.02$); LV ejection fraction improved (from 40 ± 9% to 46 ± 8%, $p<0.0001$) and end-systolic volumes decreased (from 56 ± 28 to 50 ± 25 ml/m^2, $p=0.001$) at 1 year.

Conclusions. In patients affected by ischemic heart failure, undergoing percutaneous autologous SM injection, NYHA functional class along with regional and global LV contractile reserve improved during follow-up. The effect was sustained up to 1 year after treatment.

Introduction

The clinical syndrome of heart failure has become the most prevalent cause of mortality, morbidity and hospitalization in industrialized countries over the last decades (1, 2) and the incidence is expected to increase as patients more frequently survive acute myocardial infarction, that represents the aetiology of heart failure in >70% of patients (3). The mechanisms leading to congestive heart failure after acute myocardial infarction are only partially understood (4, 5) and according to the current belief, a progressive decrease in the number of viable myocytes after an acute myocardial infarction could at least partially explain such a transition. Therefore, myocardial infarction and subsequent heart failure can be viewed as a disease of cellular deficiency (6).

Myocardial cell replacement therapy by transplantation of skeletal myoblasts (SM) or bone marrow stem cells into the region of infarcted myocardium has been proposed as an alternative treatment in patients with ischemic cardiomyopathy and severe, drug-refractory heart failure (7-9). Indeed, recent studies have suggested that the transdifferentiation of c-kit-positive bone marrow cells into cardiomyocytes is controversial and the number of cells undergoing this process may be too low to affect cardiac function (10). SM are the only cell types that have been proven to form areas of cellular engraftmenet with histological evidence of viability (development into myotubes and expression of human myosin heavy chain) (11, 12) when injected into the heart. Moreover, they are relatively more resistant to myocardial ischemia compared to cardiomyocytes. Studies in animal models have shown improvement in regional and global LV function late after myoblast transplantation, and initial observations on humans have confirmed this finding (13-18). However, skeletal myotubes fail to overexpress gap-junction proteins such as connexin-43 and N-cadhering both in vitro and in vivo, which makes the electromechanical coupling unlikely to occur (19).

Although cardiac magnetic resonance (MRI) has emerged during the last decade as a gold standard to assess regional and global LV function, its availability may be limited on a large scale study patients. Moreover, the need to implant a cardioverter-defibrillator may further limit the use of MRI in this patient population. Two-dimensional echocardiography with dobutamine infusion is an established technique to quantify regional and global myocardial systolic dysfunction (20). Moreover, the ability to assess even minor change in regional LV function has been recently redefined by the introduction of tissue Doppler imaging (TDI) in the clinical setting (21, 22). Therefore we sought to evaluate the short- and long-term impact of percutaneously transplanted SM in patients with ischemic heart failure as assessed by two-dimensional echocardiography and TDI during dobutamine infusion.

Methods

Patient Population. Patients with a previous myocardial infarction involving the anterior, lateral or inferior walls, depressed LV function (LV ejection fraction [EF] between 20% and 45%), and NYHA class ≥ II despite an optimized medical therapy were included in the study. 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 or LV angiography and no contractile reserve during dobutamine stress echocardiography (DSE). Exclusion criteria for myoblast injections were: target region wall thickness <5 mm by echocardiography, presence of ischemia during dobutamine stress echocardiography, and positive serologic test results for human immunodeficiency virus, hepatitis B or C, or syphilis. Five patients were part of a previously reported (9) monocenter pilot study on safety and feasibility, whereas the remaining 5 have been enrolled in a

multicenters European study (005-006). A TDI substudy was performed only in patients enrolled at the Thoraxcenter, in Rotterdam.

Muscle Biopsy. Biopsy of the quadriceps muscle was done under local anesthesia. All 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 (BioWhittaker, Cambrex Corp., Walkersville, Maryland) for myoblast cell isolation and expansion.

Cell Transplantation. The cell-culturing process was performed as previously described (9). The cell transplantation procedure 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 60° and right anterior oblique 30°) was obtained, an outline of the LV chamber in end diastole was drawn on transparent tabloids that were taped to the fluoroscopy monitors for navigation help and documentation of injection locations. Then a 3D electromechanical NOGA map (23) of the LV was obtained using a 7F NOGASTAR catheter (F-curve) connected to the NOGA console (Biosense-Webster, Waterloo, Belgium).

After mapping the LV, the mapping catheter was exchanged for the injection catheter (Myostar, Biosense-Webster, Waterloo, Belgium). Injections of 0.1 cc each (approximately 15 million cells per injection) were made, using the acquired NOGA map for navigating the tip of the injection catheter along the endomyocardium to the target locations. 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 6- to 8-h intervals.

Two Dimensional Echocardiography. Two-dimensional echocardiography was performed at baseline and 1, 3, 6-months and 1 year of follow-up using a commercially available imaging system equipped with a 1.8 MHz transducer and second harmonic imaging to optimize endocardial border (Hewlett Packard Sonos 5500, Andover, Massachusetts, USA). Short-axis parasternal view and apical 4-, 3-, and 2- chambers views were recorded in a quad-screen format.

Dobutamine Stress Protocol. Before cell transplantation was performed, patients underwent a complete dobutamine stress test targeting the achievement of 85% of maximal age- and gender-predicted heart rate. Dobutamine-atropine stress testing was performed according to a standard protocol as previously reported (24). After obtaining a baseline echocardiogram, dobutamine was administered intravenously at a starting dose of 5-10 μg/kg/min for 5 minutes (low-dose). Incremental dobutamine doses of 10 μg/kg/min were given at 3-minute intervals up to a maximum dose of 40 μg/kg/min. If the test end-point was not reached at a dobutamine dose of 40 μg/kg/min, atropine (up to 2 mg) was given intravenously. Blood pressure, heart rate, and electrocardiography were constantly monitored. Subsequent tests at 1-, 3-, 6-months and 1 year were performed at low-dose dobutamine infusion and were stopped after data acquisition at 10 μg/kg/min dobutamine infusion.

Two-dimensional echocardiographic images were acquired at rest, during dobutamine stress, and recovery. The echocardiograms were recorded in a quad-screen format. Two experienced observers, unaware of the clinical data, scored the echocardiograms using a

standard 16-segment model. In case of disagreement, a consensus decision was achieved by a third observer. 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. For each patient, a wall motion score index (WMSI) was calculated by dividing the sum of scores of visualized segments by the total number of these segments. LV volumes were measured from both resting and low-dose dobutamine stress echocardiography (before and sequentially after myoblast injection). All measurements were performed off line in random order by 2 experienced readers blinded to patient data and time of the studies. LV volumes were measured by the biplane modified Simpson's rule (25). LV volumes were normalized by the body surface area to obtain the end-diastolic volume index and the end-systolic volume index (26). The intraobserver variability was 4±1 ml/m^2 for the end-diastolic volume index and 3±1 ml/m^2 for the end-systolic volume index . The interobserver variability was 5±1 ml/m^2 for the end-diastolic volume index and 4±1 ml/m^2 for the end-systolic volume index.

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 and a sample volume of 4 mm^3. To minimize the variability induced by respiration, (21) the measurement of myocardial velocity was sampled using a six-segment model in 3 apical views (4-chamber, 2-chamber, and long-axis) close to the mitral annulus and during a minimum of 5 consecutive beats. The depth of the sample volume of every region was kept constant during dobutamine stress echocardiography to make sure that LV myocardium was sampled close to the mitral annulus. The electrocardiogram and phonocardiogram were simultaneously recorded with the pulsed-wave TDI velocity profile. Images were both recorded on tape and digitally stored on an Enconcert workstation (Philips, Eindhoven, the Netherlands). 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, in reference to the electrocardiogram and calculated as the mean value of 3 measurements. Cardiac cycles with extrasystolic, postextrasystolic beats, or rhythm disturbance were excluded. Recordings and measurements were performed at baseline and during low-dose (10 μg/kg/min) dobutamine infusion rate. 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 96% and 97%.

Statistical Analysis. Continuous data were expressed as mean value ± SD. The Student's t test was used to analyze continuous data. Proportions for dichotomus data were compared by Chi-square analysis. Repeated measurements were analyzed using repeated measurements analysis of variance (ANOVA) to evaluate differences across the time. For all tests, a two-tailed p value <0.05 was considered statistically significant.

Results

Patients Characteristics. Baseline clinical characteristics and cell-culturing results of the 10 patients (mean age 60 ± 10 years, 80% men) are listed in Table 1. Mean time since the occurrence of previous myocardial infarction and the procedure was 7 years (from 2 to 18 years).

Table 1. Baseline Characteristics (n=10)

Age, (means ± SD)	59 ± 11
Male	8 (80%)
Smoking	1 (10%)
Hypercholesterolemia	3 (30%)
Diabetes mellitus	1 (10%)
Previous AMI (years ago)	7.0 ± 4.7
Previous CABG or PCI	3 (30%)
History of angina	4 (40%)
NYHA class	3.0 ± 0.2
Patent LAD	7 (70%)
Cells at Harvest x 106	297 ± 154
Cells Injected x 106	217 ± 111
Desmin staining	64 ± 27
Cell viability	95 ± 2.8
Potency	81 ± 20

Legend: AMI: acute myocardial infarction; CABG: coronary artery by-pass graft; PCI: percutaneous coronary intervention; LAD: left anterior descending coronary artery.

No procedural complication occurred. A minor elevation of creatine kinase and MB (<2 times upper level) and troponine T (<0.16μg/l) was noted after the procedure in 3 patients.

At 1 year follow-up NYHA functional class decreased from 2.7 ± 0.5 to 1.9 ± 0.5 ($p<0.01$). During a mean follow-up of 29 ± 8 months, 1 patient was readmitted to the hospital due to heart failure symptoms. Two patients out of the 6 with an ICD had appropriate shocks due to major arrhythmias. No patients experienced myocardial infarction.

Resting Contractile Function and Contractile Reserve. The mean LV EF at baseline was 36 ± 8% at rest and 41 ± 9% during low dose dobutamine infusion. In 160 segments evaluated at baseline echocardiography, 23 (14%) were defined having a normal contractile function, while 137 (86%) were defined as dysfunctional, including 29 (18%) mildly hypokinetic, 51 (32%) severely hypokinetic, and 57 (36%) akinetic. Of the 137 dysfunctional segments, 105 (77%) showed contractile reserve during dobutamine infusion (increase in WMSI by one grade or more during low-dose dobutamine infusion). No segments showed myocardial ischemia at peak of stress. The baseline WMSI at rest and during low-dose dobutamine infusion was respectively 6.4 ± 1.9 cm/sec and 7.8 ± 2.5 cm/sec. The hemodynamic response at rest and during dobutamine test at baseline is shown in Table 2. The protocol was completed in all patients without side effects.

Table 2. Dobutamine Stress Echocardiographic Data

Parameters	
Heart rate at rest (beats/min)	68 ± 13
Heart rate at low dose dobutamine (beats/min)	77 ± 12
Heart rate at peak (beats/min)	138 ± 18
Rest systolic blood pressure (mmHg)	123 ± 17
Systolic blood pressure at low dose dobutamine (mmHg)	130 ± 22
Peak systolic blood pressure (mmHg)	144 ± 19
Rest rate pressure product (mmHg/sec)	8153 ± 1439
Peak rate pressure product (mmHg/sec)	19872 ± 5100
Angina during dobutamine stress	1 (10%)
Resting wall motion score index	2.45 ± 0.60
Peak wall motion score index	2.06 ± 0.46

WMSI and TDI Changes during the Follow-up. There were no significant changes of WMSI at rest and low-dose dobutamine infusion at 1 year follow-up (from 6.4 ± 1.9 to 6.4 ± 0.9 cm/sec for resting WMSI, p= 0.33, from 7.8 ± 2.5 to 8.0 ± 1.9 cm/sec for stress WMSI, p=0.51), (Table 3). Similarly, no significant improvement of the global peak systolic velocity determined by TDI at both rest echocardiogram (from 6.5 ± 1.9 to 6.5 ± 1.2 cm/sec, p=0.19) and during low-dose dobutamine infusion (from 7.9 ± 2.4 to 8.2 ± 2.1 cm/sec, p=0.13) was found at 1 year follow-up. Selecting systolic velocity in the regions of myoblasts injections, no significant changes were found at 1 year follow-up in rest measurements, whereas a significant improvement was observed during low-dose dobutamine infusion (from 7.7 ± 2.1 to 8.6 ± 1.8 cm/sec, p=0.02) (Table 3 and Figure 1 and 2).

Table 3. WMSI and TDI Measurements Results

Parameters	Baseline	1 Month	3 Months	6 Months	1 Year	p value
WMSI						
Rest	6.4 ± 1.9	5.2 ± 2.5	6.7 ± 1.6	6.8 ± 1.5	6.4 ± 0.9	0.4
Stress	7.8 ± 2.5	7.3 ± 2.2	8.0 ± 2.4	7.5 ± 1.6	8.0 ± 1.9	0.67
Delta	23.0 ± 16.3	26.8 ± 14.1	17.7 ± 10.7	11.4 ± 11.7	24.7 ± 19.3	0.55
TDI in all regions (cm/sec)						
Rest	6.5 ± 1.9	6.1 ± 1.7	6.7 ± 1.7	6.6 ± 1.3	6.5 ± 1.2	0.19
Stress	7.9 ± 2.4	7.8 ± 2.0	8.1 ± 2.6	8.2 ± 2.3	8.2 ± 2.1	0.13
Delta	23.6 ± 22.3	29.9 ± 21.7	21.5 ± 16.9	23.6 ± 17.0	27.1 ± 25.0	0.90
TDI in the regions of injections (cm/sec)						
Rest	6.2 ± 1.6	6.4 ± 1.6	6.7 ± 1.3	6.6 ± 1.0	6.4 ± 0.7	0.83
Stress	7.7 ± 2.1	8.2 ± 1.8	8.8 ± 2.2	8.7 ± 2.0	8.6 ± 1.8	0.02
Delta	24.7 ± 10.5	29.3 ± 10.5	30.6 ± 13.9	31.8 ± 15.3	39.0 ± 17.3	0.05

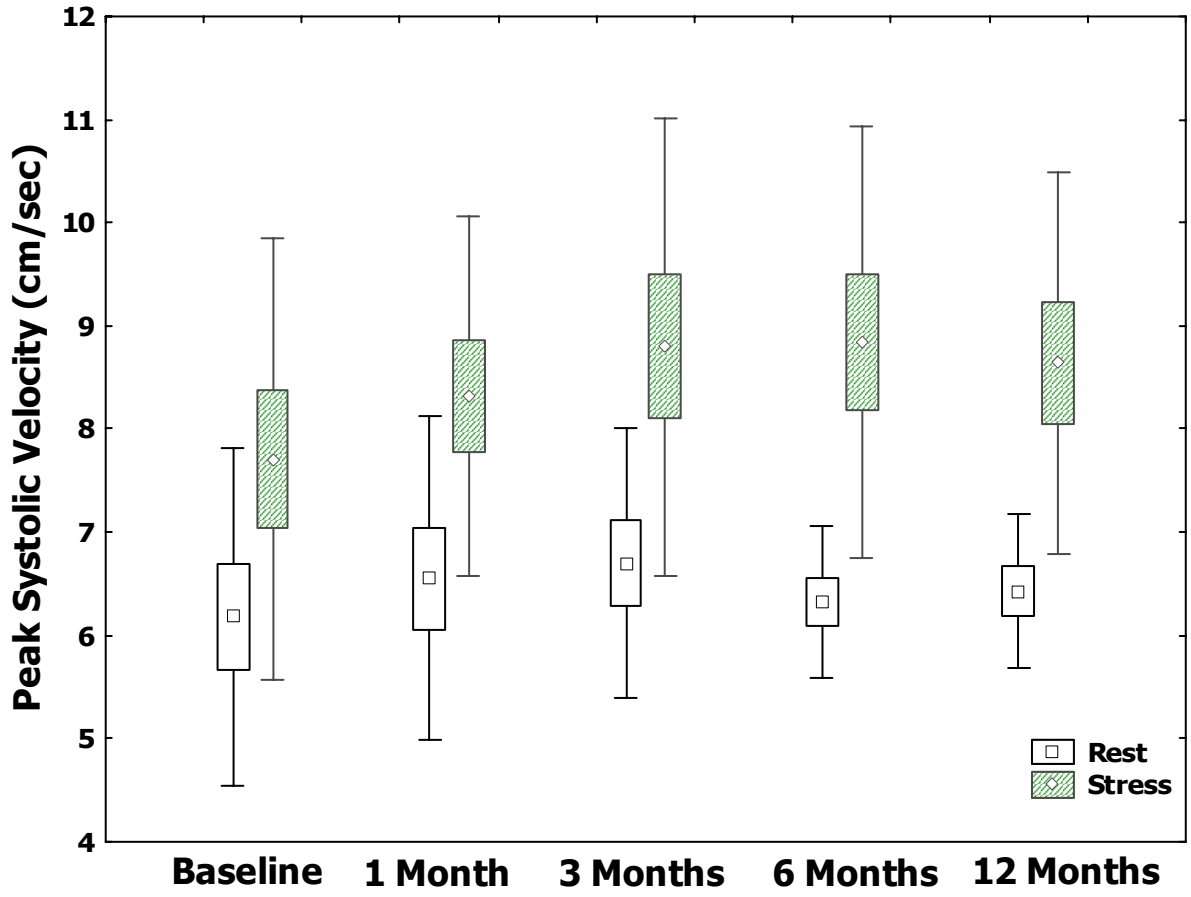

Figure 1. *Changes in peak systolic velocity measured by TDI in the region of myoblast injection during 1 year follow-up. The white and gray boxes indicate resting and low dose dobutamine infusion measurements, respectively.*

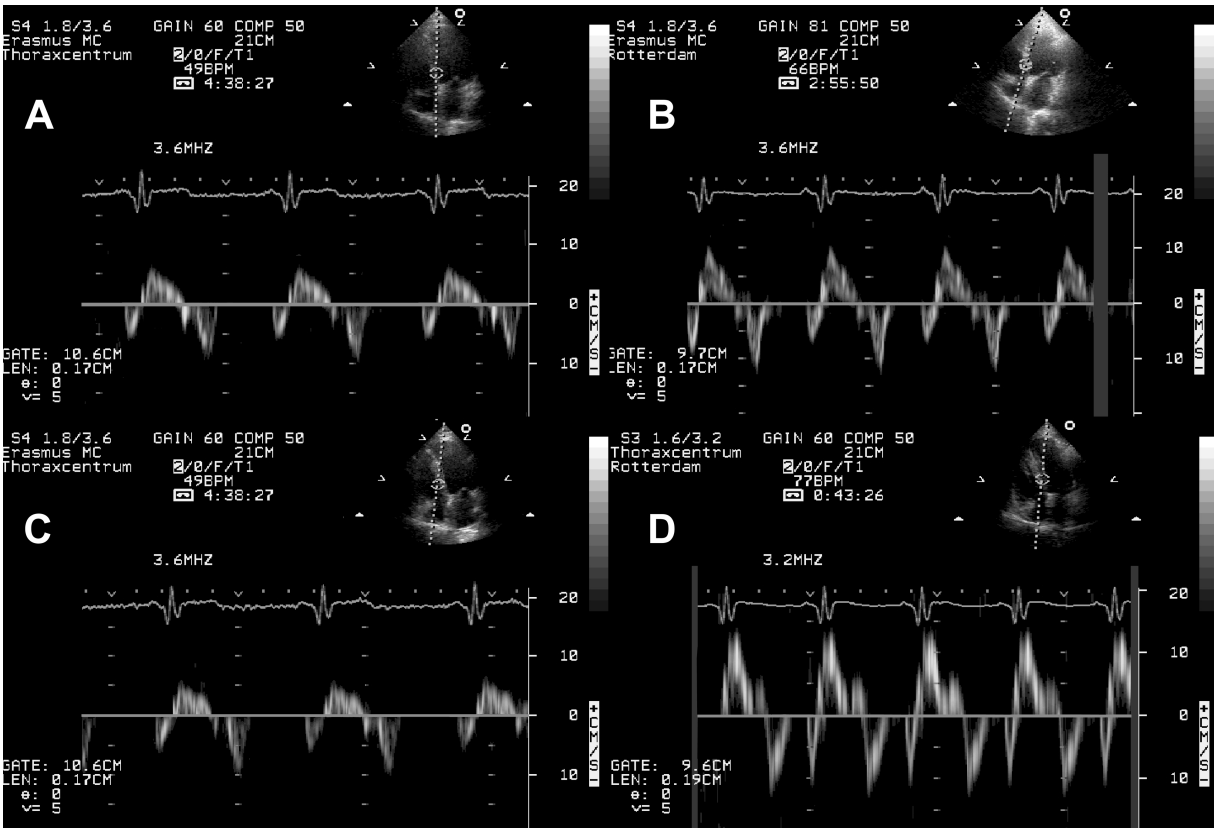

Figure 2. *Peak systolic velocity in the region of myoblast injection measured by TDI at baseline (upper part) and at 1 year of follow-up (lower part) at rest (panel A and B) and during low dose dobutamine stress echocardiography (panel C and D). A significant increase in velocity is shown during low dose dobutamine infusion between baseline and 1 year follow-up.*

Ejection Fraction and Left Ventricular Volumes. No significant improvement in resting LV EF was observed at 1 year follow-up (Table 4 and Figure 3). Similarly, resting end-diastolic and end-systolic volumes index did not significantly change during the follow-up. Conversely, during low-dose dobutamine infusion, a significant improvement in EF was observed (from 40 ± 9% to 46 ± 8%, $p<0.0001$). LV end-diastolic volume index did not significantly change, whereas end-systolic volume index significantly decreased (from 56 ± 28% to 50± 25%, $p=0.001$).

Table 4. LVEF, End-diastolic and End-systolic Index Volumes Results

Parameters	Baseline	1 Month	3 Months	6 Months	1 Year	p value
LV EF (%)						
Rest	36.5 ± 8.2	36.8 ± 8.5	36.3 ± 7.9	34.5 ± 8.9	36.0 ± 7.1	0.12
Stress	40.4 ± 8.8	41.9 ± 8.5	42.7 ± 8.8	45.9 ± 8.5	46.5 ± 8.3	<0.0001
End-diastolic volumes index (ml/m^2)						
Rest	91.2 ± 32.2	91.2 ± 31.3	91.5 ± 31.4	91.1 ± 31.6	91.9 ± 30.9	0.22
Stress	91.6 ± 32.6	91.7 ± 30.6	91.9 ± 33.2	91.5 ± 32.6	91.4 ± 32.3	0.74
End-systolic volumes index (ml/m^2)						
Rest	59.7 ± 28.2	59.4 ± 27.7	59.8 ± 27.5	60.6 ± 28.7	60.3 ± 26.5	0.10
Stress	56.4 ± 27.7	54.9 ± 25.9	54.5 ± 27.2	51.5 ±25.5	50.4 ± 25.0	<0.0001

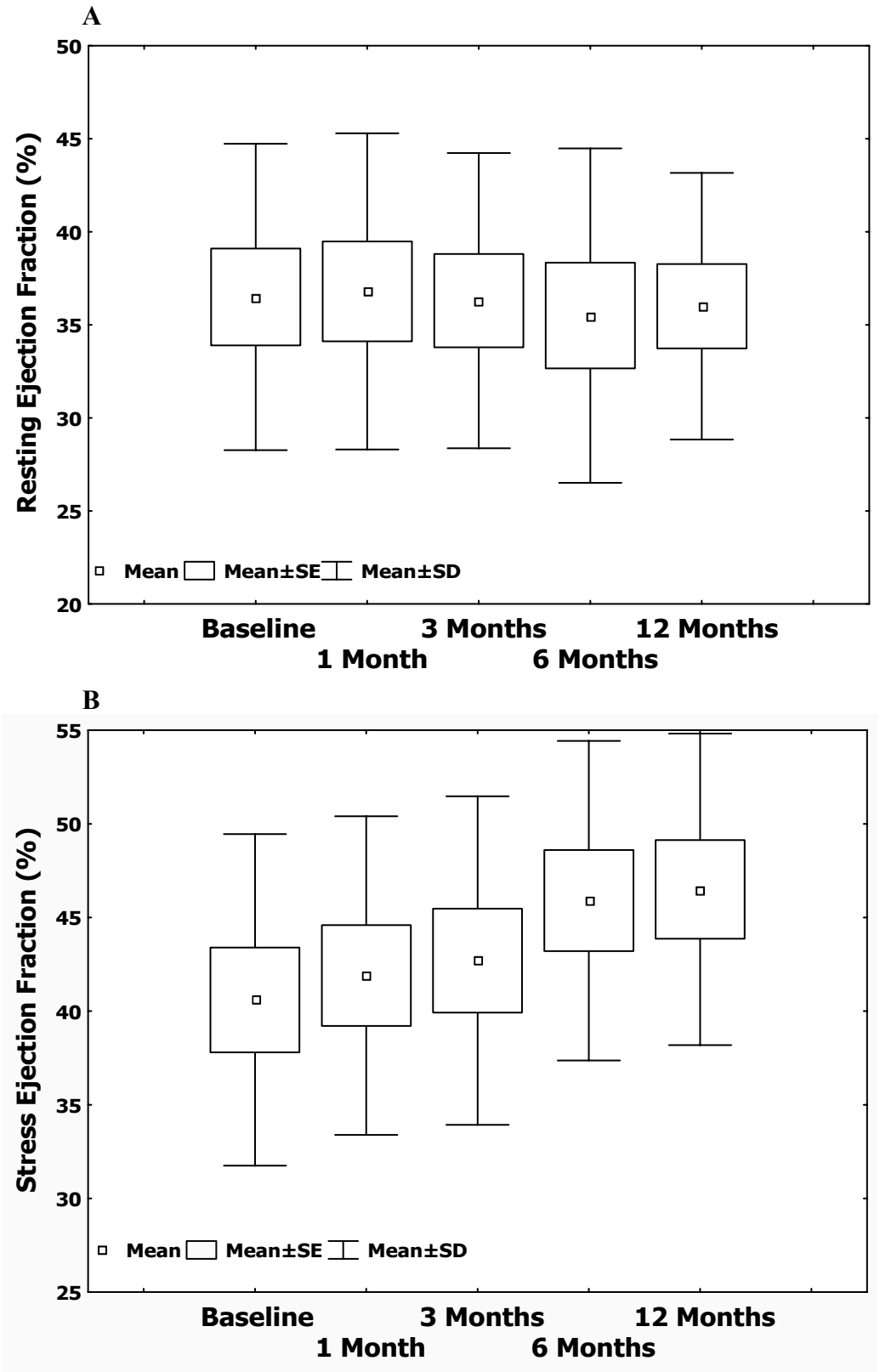

Figure 3. *Changes in LV EF at rest (panel A) and during low dose dobutamine infusion (panel B) during 1 year follow-up.*

Discussion

Transplantation of SM into the region of infarcted myocardium has recently emerged as a promising alternative treatment for severe ischemic LV dysfunction. Our substudy investigation showed an improvement of target wall systolic velocity and of global LV function during low-dose dobutamine infusion, indicating an improvement of contractile reserve. Noteworthy, the observed improvement in LV performance was sustained over time, persisting up to 1 year, underscoring the potential of this novel percutaneous approach in the treatment of end-stage ischaemic LV dysfunction. The wide-available and relatively inexpensive stress two-dimensional echocardiography and TDI appeared as promising tools able to monitor the effect of SM injections in this patient population.

Comparison to Previous Studies. Experimental studies have suggested an improvement on regional and global LV performance after cell transplantation. Ghostine et al. (18), studied global and regional LV function changes by echocardiography and TDI, in a sheep model (n=16) of infarction 4 and 12 months after in-scar injections of autologous SM (n=8) or culture medium (n=8). LV end-diastolic volume increased to a greater extent over time in the control group compared to myoblast group at 4 months, whereas LV EF significantly decreased in the control animals but remained unchanged in the myoblast animals. TDI analysis showed a decrease in the systolic myocardial velocity gradient in the control group but an increase in the myoblast group, with a limit of significance in the difference between the two groups.

Menasché et al (8), studied 10 patients who underwent autologous skeletal myoblast transplantation during bypass surgery in patients with severe ischemic cardiomyopathy. In 8 of the 9 operative survivors LV EF significantly increased after treatment, due to a decrease of end-systolic LV volume, whereas the end-diastolic volume remained unchanged postoperatively. Moreover, 14 out of 22 implanted in-scar segments demonstred new-onset echocardiographic systolic shortening. However, the improvement in regional and global systolic function may reflect the efficacy of myocardial revascularization and can not be related only to the injection of myoblasts.

In a recent pilot study (9), our group reported an initial experience in 5 patients who underwent catheter-based cell transplantation with autologus skeletal myoblasts. A significant improvement in LV EF was observed at three months by angiography but not by nuclear or magnetic resonance imaging assessment. At six months, a trend toward increased LV EF was observed by both angiography and nuclear scan. Similarly, the TDI results showed a trend toward increased contraction velocity at six months follow-up.

Possible Explanation for the Findings. The mechanism whereby an improvement of regional and global function occurs during low-dose dobutamine infusion indicating an improvement of contractile reserve remains unsettled. In animal models an increase in contractility assessed by two-dimensional echocardiography as well as TDI or color kinesis has been shown to be related, at least in part, to the success of the outcome (13, 18). The assumption that the islets of implanted cells could be mechanically recruited by the contraction of the surrounding recipient myocardium, even in absence of gap junctions, may explain an improvement of contractile reserve and systolic function under catecholamine stimulation.

Although the improvement in global LV function during low-dose dobutamine infusion at follow-up could be related to a compensatory phenomenon of the myocardium adjacent to the scar-tissue, the improvement of systolic velocity in the sites of myoblasts injection assessed by TDI can be only explained by an increased systolic contractility of these

regions. Moreover, no patients developed an increase in LV volumes and subsequent LV remodeling during the follow-up. Initial data suggested that in patients with ischemic cardiomyopathy the preservation of ongoing LV remodeling after revascularization have to be considered an important end-point (27), and myocardial viability (assessed by the presence of contractile reserve) represents the most important parameter to determine the direction of LV volumes changes (28).

Limitations

The study population is limited. Further studies, including larger number of patients, are ongoing in the attempt to confirm and possibly extends our current findings. Current echocardiographic measurements were not analyzed by independent core lab.

Clinical Implications and Conclusions

In patients with ischemic heart failure who undergo percutaneous injection of autologous myoblasts, regional and global LV systolic function improves during low-dose dobutamine infusion, indicating an improvement in contractile reserve, at 1 year follow-up.

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Chapter 15

Myocardial Wall Thickness Predicts Recovery of Contractile Function after Primary Coronary Intervention for Acute Myocardial Infarction

Biagini E, Galema TW, Schinkel AFL,
Vletter WB, Roelandt JRTC, ten Cate FJ

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Myocardial Wall Thickness Predicts Recovery of Contractile Function After Primary Coronary Intervention for Acute Myocardial Infarction

Elena Biagini, MD,*† Tjebbe W. Galema, MD,* Arend F. L. Schinkel, MD,* Willem B. Vletter, MSc,* Jos R. T. C. Roelandt, MD,* Folkert J. Ten Cate, MD*

Rotterdam, The Netherlands; and Bologna, Italy

OBJECTIVES We sought to determine whether end-diastolic wall thickness (EDWT) can predict recovery of regional left ventricular contractile function after percutaneous coronary intervention (PCI).

BACKGROUND Regional contractile function does not recover in all patients after PCI for acute myocardial infarction (AMI). Prediction of functional recovery after AMI may help in clinical decision making.

METHODS Forty consecutive patients with AMI were studied with left ventricular contrast echocardiography for accurate wall thickness and function measurement and myocardial perfusion immediately after and two months following PCI.

RESULTS Out of 640 segments, 175 (27%) dysfunctional segments in the infarct territory were analyzed for EDWT, wall function, and perfusion. One hundred and three (59%) dysfunctional segments presented with an EDWT <11 mm and 72 (41%) presented with an EDWT ≥11 mm. Perfusion (partial or complete) was present in 63 segments with an EDWT <11 mm (61%) and 71 segments with an EDWT ≥11 mm (99%) ($p < 0.001$). At two months' follow-up, 66 of 72 segments with an EDWT ≥11 mm (92%) improved, whereas only 35 of 103 of the dysfunctional segments with an EDWT <11 mm (34%) improved ($p < 0.0001$).

CONCLUSIONS Wall thickness is an easy parameter to predict recovery of function after revascularization. Moreover, combining EDWT and perfusion, segments with an EDWT ≥11 mm, and presence of perfusion have the highest chance of recovery; segments with an EDWT <11 mm and perfusion have an intermediate chance of recovery. In segments with an EDWT <11 mm and no perfusion, chances of recovery are very low. (J Am Coll Cardiol 2004;43: 1489–93) © 2004 by the American College of Cardiology Foundation

Early revascularization by percutaneous coronary intervention (PCI) is associated with a good clinical outcome in patients with acute myocardial infarction (AMI) (1). However, in some patients successful PCI does not result in recovery of contractile function in the infarct territory (2). Two-dimensional contrast echocardiography allows assessment of wall function and myocardial perfusion simultaneously. It has been shown in several studies that myocardial contrast echocardiography (MCE) allows researchers to predict recovery of regional contractile function after reperfusion in AMI (3–6). Until now, the end-diastolic wall thickness (EDWT) was not used as a simple parameter to predict functional recovery after PCI. Therefore, myocardial wall thickness was assessed to determine its value as a predictor of recovery of regional contractile function late after PCI. In this study, contrast echocardiography was used for optimal endocardial border delineation (7).

From the *Department of Cardiology, Thoraxcenter, Erasmus Medical Center, Rotterdam, The Netherlands; and the †Institute of Cardiology, S. Orsola, Bologna, Italy.

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METHODS

Study patients. This prospective study comprised 40 consecutive patients without history of hypertension, left ventricular hypertrophy, and primary cardiomyopathy, but with ST-segment elevation AMI and who underwent PCI within 6 h of onset of symptoms. Baseline characteristics of the 40 patients (34 male, mean age 53 ± 13 years) are summarized in Table 1. The diagnosis of AMI was made on the basis of symptoms of myocardial ischemia for ≥30 min and ≥2 mm ST-segment elevation in ≥2 contiguous electrocardiographic leads. The infarct-related artery was identified by the site of the coronary occlusion, and stent implantation was performed. Left ventricular hypertrophy was defined according to recommendations of the American Society of Echocardiography and corrected following the suggestions of Devereux et al. (8). The left ventricular mass index was derived with normal limits defined as ≤125 g/m^2 for men and ≤110 g/m^2 for women (9). The local hospital ethics committee approved the study protocol, and all patients gave informed consent.

Echocardiography and contrast studies. Echocardiography was performed with a Sonos 5500 (Philips, Andover, Massachusetts) using second harmonic mode (1.8-MHz/

Abbreviations and Acronyms

AMI = acute myocardial infarction
EDWT = end-diastolic wall thickness
LVEF = left ventricular ejection fraction
MCE = myocardial contrast echocardiography
PCI = percutaneous coronary intervention

3.6-MHz), within 24 h following revascularization. After recording baseline, myocardial perfusion images were obtained in real time (power modulation) using a low mechanical index (0.1). A slow bolus of 0.75 ml of Sonovue (Bracco, Milan, Italy) was intravenously injected followed by a slow saline flush (5 ml) over 5 s. Imaging was started before contrast injection and "flash" imaging with high mechanical index (1.6) was used at peak contrast intensity for four frames to destroy the microbubbles in the myocardium, to exclude artifacts, and to visualize myocardial contrast replenishment. To obtain maximal image information, the segments related to the infarct territory were placed in the center of the echo sector reducing the problem of artifacts. After the real-time perfusion study, left ventricular opacification images were recorded in all standard parasternal and apical views to improve quantitative assessment of myocardial function (7). Left ventricular ejection fraction (LVEF) was measured using the standard biplane Simpson method. Improvement of LVEF ≥5% was considered significant (10). A follow-up study with MCE to reassess EDWT, function, and perfusion was performed at two months.

EDWT measurement. The EDWT was measured by two experienced observers unaware of the clinical data as previously described (11), using intravenous echo-contrast for better endocardial border detection (7). The EDWT was assessed at the center of each myocardial segment from the leading endocardial edge to the leading epicardial edge as the mean of three measurements. Dysfunctional segments were categorized as segments with an EDWT <11 mm and an EDWT ≥11 mm.

Table 1. Patient Characteristics

Age (yrs, ± SD)	53 ± 13
Men	34 (85%)
Smoking	25 (62%)
Diabetes mellitus	4 (10%)
Hypertension	0
Hypercholesterolemia	6 (15%)
Family history of CAD	13 (32%)
Previous myocardial infarction	5 (12%)
EF (%)	45 ± 6
CK peak (IU)	3,074 ± 2,245 (n < 200 IU)
Site of infarction	
Anterior	22 (55%)
Lateral	16 (40%)
Septal	2 (5%)
Inferior/posterior	19 (47%)
TIMI flow grade 3 after PCI	33 (82%)

CAD = coronary artery disease; CK = creatine kinase; EF = ejection fraction; SD = standard deviation; TIMI = Thrombolysis In Myocardial Infarction.

Analysis of echocardiograms. Regional wall motion and myocardial perfusion were scored using standard parasternal long- and short-axis views and apical two-, three-, and four-chamber views, employing a 16-segment model (12). Only segments related to acute infarct territory were considered for the analysis. Segments were graded as: 1 = normal, 2 = severe hypokinetic, 3 = akinetic, and 4 = dyskinetic. Myocardial contrast perfusion was scored semiquantitatively using a 3-point grading scale: 2 = normal/homogenous opacification, 1 = reduced/patchy opacification, and 0 = no opacification. Segments with a severely hypokinetic, akinetic, or dyskinetic wall motion pattern were considered dysfunctional. Recovery of contractile function was defined as an improvement of segmental wall motion score by ≥1 grade at the follow-up.

Statistical analysis. All continuous data are expressed as mean ± SD; percentages are rounded. Differences between proportions were compared with the chi-square test. The agreement for the measurements of EDWT was assessed from 3 × 3 tables using weighted kappa statistics (13). A value of $p < 0.05$ was considered statistically significant. The EDWT that was related to a high likelihood of improvement of segmental contraction was determined by receiver operating characteristic curve analysis. The optimal cutoff value was the EDWT that yielded the highest sum of sensitivity and specificity.

RESULTS

Mean time from onset of chest pain to PCI was 3.8 ± 1.8 h. Of a total of 640 segments, 175 (27%) dysfunctional segments were located in the infarct-related territory, and EDWT, wall function, and myocardial perfusion were analyzed. A total of 103 (59%) segments had an EDWT <11 mm, and 72 (41%) had an EDWT ≥11 mm. Both intra- and inter-observer agreements for the assessment of EDWT were 0.96 and 0.93, respectively (kappa value). Mean EDWT was 9 ± 1 mm for the group with an EDWT <11 mm, and 12 ± 1 mm for the group with an EDWT ≥11 mm. Real-time perfusion MCE imaging demonstrated that 11 (11%) of the 103 dysfunctional segments with an EDWT <11 mm had normal perfusion, 52 (50%) had partial perfusion, and 40 (39%) had no perfusion. Of the 72 dysfunctional segments with an EDWT ≥11 mm, 33 (46%) had normal perfusion, 38 (53%) had partial perfusion, and 1 had absent perfusion.

Functional outcome. At two months' follow-up, 35 of the 103 (34%) segments with an EDWT <11 mm improved, whereas 66 of the 72 (92%) segments with an EDWT ≥11 mm improved ($p < 0.0001$) (Fig. 1). Sixty-nine of the 72 (96%) segments with an EDWT ≥11 mm became thinner at follow-up (12 ± 1 mm to 9 ± 1.5 mm; $p < 0.05$). Of these 69 segments, 64 (93%) had an EDWT <11 mm at follow-up. Seventy-two of the 103 dysfunctional segments with an EDWT <11 mm (70%) became thinner at follow-up (9 ± 1 mm to 7 ± 1.7 mm; $p < 0.05$). Of the 103

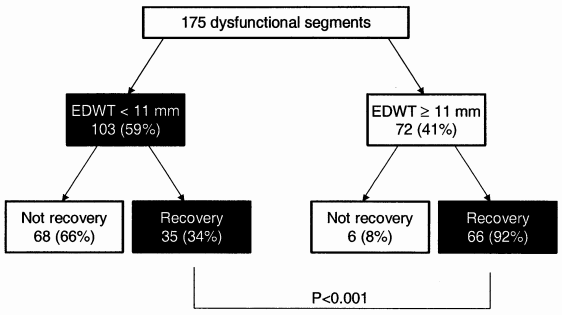

Figure 1. Relation between improvement of left ventricular contractile function and end-diastolic wall thickness (EDWT).

dysfunctional segments with an EDWT <11 mm, 33 (32%) had normal perfusion, 39 (38%) had partial perfusion, and 31 (30%) showed no perfusion at follow-up. In the 72 dysfunctional segments with an EDWT ≥11 mm, myocardial perfusion at follow-up was normal in 49 (68%), partial in 20 (28%), and absent in 3 (4%) segments.

A subanalysis was performed considering only the akinetic segments. Of the 100 akinetic segments, 31 of 33 (94%) with an EDWT ≥11 mm improved at follow-up, whereas only 20 of 67 (30%) segments with an EDWT <11 mm improved ($p < 0.001$).

Nearly all patients (15 of 16 patients, 94%) in which ≥50% of the dysfunctional segments had an EDWT ≥11 mm showed an improved LVEF at follow-up. Conversely, none of the 24 patients in which <50% of the dysfunctional segments had an EDWT ≥11 mm had an improved LVEF at follow-up.

Prediction of recovery by perfusion and wall thickness. To accurately predict functional recovery after revascularization in dysfunctional infarcted areas, information about perfusion and wall thickness should be combined (Table 2). Real-time perfusion MCE imaging demonstrated that perfusion was present in 134 of 175 (77%) dysfunctional segments. In particular, MCE showed that 44 (25%) of the 175 dysfunctional segments had normal perfusion, 90 (51%) had partial perfusion, and 41 (23%) showed no perfusion. However, only 98 (73%) of the adequately reperfused segments recovered at follow-up. Adding EDWT measurements of the adequately reperfused segments, 71 (53%) had

Table 2. Comparison Between EDWT and Myocardial Perfusion as Prognostic Indexes of Recovery of Contractile Function at Two Months' Follow-Up

Category	Number (%) of Segments With Functional Recovery
EDWT ≥11 mm	
P+	66/71 (93)
P−	0/1 (0)
EDWT <11 mm	
P+	32/63 (51)
P−	3/40 (7)

EDWT = end-diastolic wall thickness; P = perfusion (normal or patchy); + = present; − = absent.

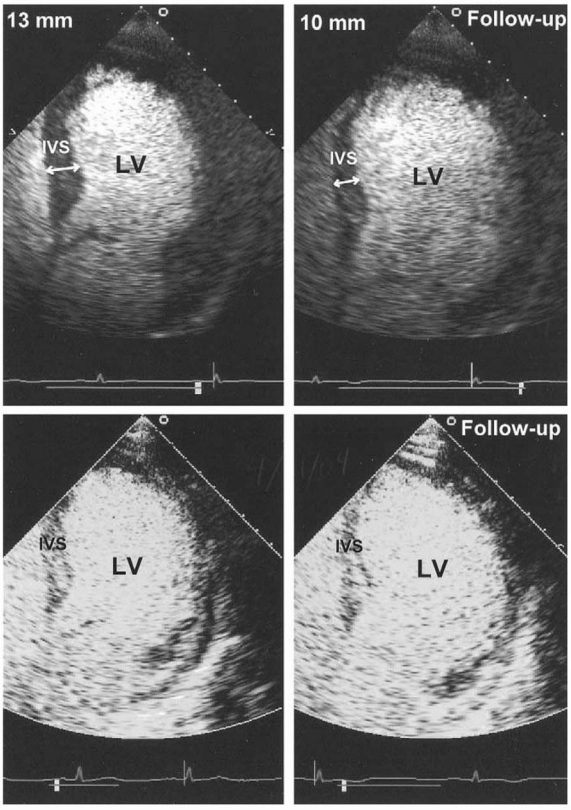

Figure 2. Two-dimensional echocardiograms showing end-diastolic wall thickness **(upper panels)** and perfusion **(lower panels)** in an infarcted region directly after percutaneous coronary intervention **(left panels)**, and after recovery at two months' follow-up **(right panels)**. IVS = interventricular septum; LV = left ventricle.

an EDWT ≥11 mm and 63 (47%) had an EDWT <11 mm. At two months' follow-up, recovery of contractility was present in 66 (93%) of the adequately perfused segments with an EDWT ≥11 mm, whereas only 32 (51%) of the adequately perfused segments with an EDWT <11 mm recovered ($p < 0.001$) (Table 2, Figs. 2 and 3).

DISCUSSION

Restoration of coronary vessel patency does not automatically result in recovery of contractile function in patients undergoing PCI in the setting of AMI. The main finding of the present study is that a relatively simple measurement of EDWT, obtained with two-dimensional echocardiography combined with contrast agent, predicts recovery of regional contractile function after PCI for AMI. Using EDWT alone, dysfunctional segments with an EDWT ≥11 mm showed a high likelihood of recovery of regional contractile function two months after PCI. Moreover, it appears that when at least 50% of the dysfunctional segments show an EDWT ≥11 mm, global recovery may be anticipated. In the present study only 98 (73%) of the adequately reperfused dysfunctional segments had recovery of function at follow-

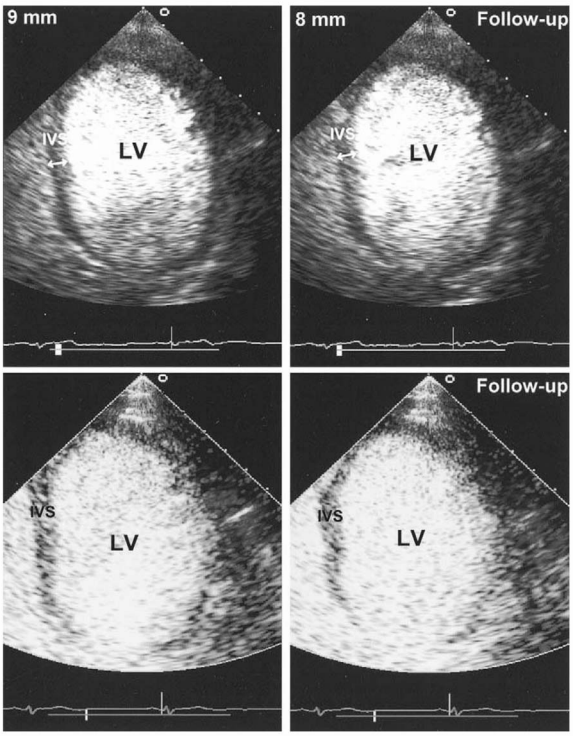

Figure 3. Two-dimensional echocardiograms showing end-diastolic wall thickness **(upper panels)** and perfusion **(lower panels)** in a patient directly after percutaneous coronary intervention **(left panels)** and at two months' follow-up **(right panels)**, in a case where regional function did not recover. IVS = interventricular septum; LV = left ventricle.

up. Combining wall thickness and perfusion, segments with an EDWT ≥11 mm and presence of perfusion have the highest chance of recovery (93%). An intermediate likelihood of recovery was observed in segments with an EDWT <11 mm and presence of perfusion (51%), whereas segments with an EDWT <11 mm and no perfusion nearly never improved. The present results indicate that perfusion data do not provide much additional information for the prediction of recovery of contractile function in segments with an EDWT ≥11 mm, because most of them recover at follow-up. Perfusion data are more relevant for the prediction of functional outcome in segments with an EDWT <11 mm.

Comparison to previous studies. In patients with AMI undergoing PCI, assessment of the amount of myocardial salvage is important for prediction of functional recovery and long-term prognosis. Main et al. (4) demonstrated that MCE compares favorably with low-dose dobutamine echocardiography for the assessment of myocardial viability after an acute anterior infarction. Balcells et al. (5) demonstrated that the extent of microvascular integrity assessed by MCE after PCI correlates with recovery of resting left ventricular function and contractile reserve. Lepper et al. (6) showed that assessment of restoration of myocardial perfusion by MCE after PCI corresponds closely to the evaluation of the microvascular integrity by coronary flow reserve. Moreover, an improvement of myocardial perfusion after revascularization was predictive for subsequent functional recovery. However, EDWT as a predictor of recovery of regional contractile function after PCI has not been specifically addressed.

Possible explanation for the findings. The pathophysiological mechanism underlying the relation between EDWT and long-term recovery of regional contractile function after PCI for AMI is currently not clear. It is conceivable (but speculative) that the high likelihood of recovery in segments with an EDWT ≥11 mm is related to hyperemia and tissue edema in adequately reperfused myocardium. During the early phase of reperfusion, reactive hyperemia may occur (14) followed by myocardial tissue edema within the reperfused myocardium (15). Further studies are needed to elucidate this issue.

Study limitations. A potential limitation of echocardiography to determine myocardial wall thickness is image quality. The use of contrast echocardiography in the present study overcame this limitation because endocardial border detection and EDWT measurements were more accurately assessed, as was shown by Thomson et al. (7). Another limitation is that wall thickness is heterogeneous throughout the left ventricle. The cut-off value of 11 mm, which was described previously (16), is therefore to some extent arbitrary.

Clinical implications and conclusions. The main finding of the present study is that a relatively simple measurement of EDWT, obtained with two-dimensional echocardiography combined with contrast agent, predicts recovery of regional contractile function after PCI for AMI. Dysfunctional segments with an EDWT ≥11 mm had a high likelihood of functional recovery two months after PCI. Moreover, combining wall thickness and perfusion, dysfunctional segments with an EDWT ≥11 mm and presence of perfusion have the highest chance of recovery, segments with an EDWT <11 mm and perfusion have an intermediate chance, whereas segments with an EDWT <11 mm and no perfusion have a very low likelihood of functional recovery at two months' follow-up. Prediction of recovery of contractile function early after AMI could be useful to identify patients who have irreversible left ventricular dysfunction. In these patients, tailored therapy can be started, also considering the possibility of automatic defibrillator implantation (17). Moreover, identification of stunning as the cause of ventricular dysfunction may provide a rationale for the aggressive support of the patients with mechanical methods and perhaps caution against the use of inotropic agents, which may adversely influence the recovery of potentially ischemic segments (18).

Reprint requests and correspondence: Dr. Folkert J. Ten Cate, Erasmus Medical Center, Department of Cardiology, Thoraxcenter, Room Ba302, Dr. Molewaterplein 40, 3015 GD Rotterdam, The Netherlands. E-mail: f.j.tencate@erasmusmc.nl.

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Chapter 16

Comparison between Contrast Echocardiography and Magnetic Resonance Imaging to Predict Improvement of Myocardial Function after Primary Coronary Intervention

Biagini E, van Geuns RJ, Baks T, Boersma E,
Rizzello V, Galema TW, de Feyter PJ, ten Cate FJ

Submitted for publication

Abstract

Background. The relative merits of myocardial contrast echocardiography (MCE) and magnetic resonance imaging (MRI) to predict myocardial function improvement after percutaneous coronary intervention (PCI) have not been evaluated until now.

Methods. Thirty-five consecutive patients with acute myocardial infarction (AMI) were studied after PCI by MCE and MRI using first-pass imaging for evaluation of myocardial perfusion. Delayed-enhancement MRI was included as another methodology to differentiate viable from infarcted tissue. MCE was performed by power modulation and intravenous Sonovue. A 16-segment model of the left ventricle was used to analyze all MCE and MRI images. At 60 days follow-up, a MCE study showed improvement of function in 115 (60%) of 192 dysfunctional segments.

Results. The sensitivity, specificity and accuracy for the prediction of functional improvement were comparable between MCE (87%, 90%, 88%), first-pass MRI (87%, 60%, 79%), and delayed-enhancement MRI (75%, 100%, 82%), all p=NS.

Conclusions. MCE and MRI allow prediction of myocardial function improvement after PCI. MCE has a comparable accuracy and as a bed-side technique may be an alternative tool in the acute phase of AMI.

Introduction

Restoration of coronary blood flow in acute myocardial infarction (AMI) after percutaneous coronary intervention (PCI) is related to an improved clinical outcome (1). However, successful recanalization of the occluded vessel does not always result in recovery of myocardial function, since both microvascular integrity and myocytes may be irreversible damaged after AMI (2). Lack of contractile function after PCI may be caused by reversible (myocardial stunning) or irreversible myocardial damage (necrosis). Distinction between these two pathophysiological entities may help to define individual tailored therapy, justifying the use of mechanical support as well a relative caution with the inotropic therapy in patients with myocardial stunning (3). Myocardial contrast echocardiography (MCE) and contrast-enhanced magnetic resonance imaging (MRI) are both non invasive techniques able to assess myocardial function and perfusion, additionally delayed contrast enhanced MRI is able to asses irreversible cellular damage. Several studies have confirmed the ability of MCE to predict the improvement of myocardial function after reperfusion in AMI (4-12). Recently, it has become clear that contrast-enhanced MRI can be performed in humans early after AMI and allows prediction of functional improvement (13-19). Contrast-enhanced MRI can be performed to evaluate myocardial perfusion during first-pass of the contrast agent or alternatively to detect necrosis using delayed contrast-enhancement 20 minutes after contrast injection. Currently, the relative merits of these non invasive techniques are not clear. The aim of this study was to compare MCE and contrast-enhancement MRI to assess myocardial perfusion/viability and to predict improvement of myocardial function after PCI in AMI.

Methods

Patients and Study Protocol. This prospective study comprised 42 consecutive patients with ST-elevation AMI who underwent PCI within 6 hours of symptom onset. The diagnosis of AMI was made on the basis of symptoms consistent with myocardial ischemia for ≥30 min and ≥2 mm ST-segment elevation in ≥2 contiguous electrocardiographic leads. The infarct related artery was identified by the site of the coronary occlusion during coronary angiography (using CAAS system, Pie Medical, Maastricht, Netherlands) and electrocardiographic criteria. Stent implantation was performed in all patients. The local Hospital Ethics Committee approved the study protocol and all patients gave informed consent. MCE was performed within 48 hours after the coronary intervention and with a time distance not longer than 48 hours from the MRI study, although in the majority of the cases the two techniques were performed on the same day. In 5 patients a MRI study could not be performed due to claustrophobia in 2 patients and to the necessity of an aortic balloon device in 3 patients who presented unstable clinical conditions. Two patients were excluded due to not optimal delay-enhancement images quality. Therefore, the final population consisted of 35 patients. Improvement of resting regional and global contractile function was assessed with a MCE follow-up study at 60 days in all patients, using left ventricular opacification for a better detection of the endocardial border, exactly as in the baseline examinations. The mean difference time between baseline and follow-up was 68 ± 7 days.

Contrast Echocardiography Studies. Echocardiography was performed with a Philips Sonos 5500 system (Andover, Massachusetts, USA) using second harmonic imaging (1.8MHz/3.6MHz), between 24 and 48 hours after revascularization to assess regional and global left ventricular function. After recording the baseline images, myocardial perfusion images were obtained during contrast injection in real-time (power modulation) using a low

mechanical index (MI: 0.1). A slow bolus of 0.75 ml of sulfur hexafluoride (Sonovue, Bracco, Italy) was intravenously injected followed by a slow saline flush (5 ml) over 5 seconds. If left ventricular opacification and myocardial perfusion were not optimal, additional doses of 0.5ml of contrast agent were injected. Real-time power modulation imaging was started before contrast injection and "flash" imaging with high mechanical index (MI: 1.6) was used at peak contrast intensity to destroy the microbubbles in the myocardium in order to exclude artifacts and to visualize myocardial contrast replenishment (15 cycles). After the real time perfusion study, left ventricular opacification images for endocardial border assessment were recorded using a 0.4 mechanical index to improve quantitative assessment of regional and global myocardial function (20). Left ventricular volumes and ejection fraction were measured using the modified biplane Simpson's rule (21). An improvement in left ventricular ejection fraction ≥5% at follow-up was considered clinically significant (22). Images were digitally stored on (Philips, Eindhoven, the Netherlands).

Analysis of Echo Studies. Regional wall motion and myocardial perfusion were scored by two observers who had no knowledge of the clinical, MRI and angiographic data, using standard parasternal long-and short-axis views and apical two-, three and four-chamber views. The left ventricle was divided according to a standard 16-segment model (21). Only segments related to acute infarct territory were considered for the analysis. The myocardial segments were assigned to the coronary arteries as previously described (23). Segments were scored as 1=normal; 2=hypokinetic, 3=akinetic; and 4=dyskinetic. Myocardial contrast perfusion was scored semiquantitatively using a 3-point grade scale: grade 0, no opacification, grade 1, reduced/patchy opacification, and grade 2, normal/homogenous opacification. Segments with a hypokinetic or akinetic wall motion pattern were considered dysfunctional. Recovery of contractile function was defined as an improvement of segmental wall motion score by ≥1 grade at the follow-up. As reported previously (7) in each patient, an MCE score index was derived by averaging the perfusion scores from each dysfunctional segment dividing by the number of dysfunctional segments. A patient was considered to have adequate reperfusion if the MCE score index was ≥1 (7).

Contrast-enhancement MRI Studies. All patients were studied in a supine position, with a 4-channel quadrature body phased array coil placed over the thorax, in a 1.5T whole body MRI system (General Electric, Milwaukee, WI, USA; Signa CV/i, with an amplitude of 40 mTm-1 and a slew rate of 150 Tm-1s-1). For semiquantitative analysis 2-, 3-, 4-chamber and approximately 10 to 12 cine short-axis series (slice thickness 8 mm, gap 2 mm) covering the heart from base to apex where acquired using a breath-hold cardiac triggered steady state free precession sequence (FIESTA) with a TR and TE of 3.5 and 1.3 ms respectively and a flip angle of 45°. Additional imaging parameters were: Field of View of 360 x 270 mm, a matrix of 160x128, the number of shots of 12 resulting in a temporal resolution of 42 ms. After the cine images were acquired, the patients received an intravenous bolus of 0.1 mmol/kg Gadolinium-DTPA (Magnevist, Schering, Berlin , Germany) at a rate of 5 mL/s by means of an infusion pump. A first-pass perfusion scan was acquired simultaneously with the bolus injection for 40 to 50 heartbeats. First-pass perfusion images (early hypo-enhancement) were acquired by using an ECG-gated saturation recovery interleaved gradient echo-planar imaging pulse sequence, covering the heart with 5 to 8 evenly spaced slices every heart beat. Imaging parameters were as follows: TR 6.8 ms, TE 1.2 ms, echo train length 4, image matrix 96x128 interpolated to 256x256 pixels, saturation pulse 90°, flip angle 20°, bandwidth 125 kHz,, spatial resolution 2.8x3.75x8mm. A rectangular field of view of 75% was used. The acquisition window of one image per slice location was approximately (0.75 x 96 x 6.8)/4 = 120 ms. Using the slice selective "notched" prepulse and interleaved acquisitions strategy an

effective TI of approximately 160 ms was achieved (24). Ten to twenty minutes after the injection, delayed-enhancement images (hyper-enhancement) were acquired by using an inversion-recovery prepared gated fast-gradient echo-pulse sequence, similar to that recently described (25). Imaging was performed with the following parameters: TR 7.3 ms, TE 1.6 ms, image matrix 256x192, rectangular field of view of 75%, flip angle 20°, inversion pulse 180°, and inversion time 200 to 250 ms, spatial resolution 1.6x1.6x8mm. The delayed-image prescriptions had the same slice thickness and spacing as the cine short-axis images.

Analysis of MRI. Regional MRI myocardial perfusion and delayed hyper-enhancement imaging were scored using the 2-chamber, 4-chamber and short-axis series using the same 16-segment model as for MCE. Only segments related to acute infarct territory were considered for the analysis. Using first-pass imaging, regional myocardial early hypo-enhancement was graded using a 3-point grade scale: grade 0, severe hypo-enhancement; grade 1, subendocardial hypo-enhancement; grade 2, no hypo-enhancement. Delayed hyper-enhancement imaging on inversion-recovery MRI was scored using a 5-point grading scale assessing the transmural extent of hyper-enhancement: grade I, no hyper-enhancement; grade II, 1%-25% of the wall thickness; grade III, 26%-50%; grade IV, 51%-75%; and grade V, 76%-100% of the wall thickness. MRI images were scored by two observers unaware of clinical, MCE and angiographic data. Similarly to MCE, in each patient an MRI score index regarding both hypo- and hyper-enhancement was derived by averaging the perfusion scores from each dysfunctional segment dividing by the number of dysfunctional segments. A patient was considered to have adequate reperfusion if the hypo-enhancement score index was ≥ 1 and hyper-enhancement score index ≤ 3 (>50% of the wall thickness), and inadequate otherwise.

Statistical Analysis. All continuous data are expressed as mean ± SD. Differences between proportions were compared using the Chi square test. The agreement between MCE and first-pass perfusion imaging for detecting viable segments was assessed by 2 x 2 tables using weighted kappa statistics (26). The individual values of sensitivity, specificity and accuracy of each technique to predict improvement of myocardial function were calculated on the base of an improvement at follow-up of left ventricular ejection fraction ≥5% in both groups of patients with or without an adequate reperfusion. These values were compared using McNemar analysis. Repeated measurements, as left ventricular end-diastolic volume (EDV), end-systolic volume (ESV) and ejection fraction were analyzed using repeated measurements analysis of variance (ANOVA) to evaluate differences across the time. All tests were two-sided. Statistical significance for all tests was stated at the classical tests multiple times. A value of $p < 0.05$ was considered statistically significant.

Results

Patients Characteristic and Perfusion/Enhancement Pattern at Baseline. Baseline characteristics of the 35 patients (30 men, mean age 52±12 years) are summarized in Table 1.

Table 1. Patients Characteristics (n=35)

Age (years)	52 ± 12
Men	30 (86)
Smoking	22 (63)
Diabetes mellitus	3 (1)
Hypertension	12 (34)
Hypercholesterolemia	9 (26)
Family history of coronary artery disease	12 (34)
Left ventricular ejection fraction	42 ± 8
Creatine kinase peak (International units)	3418 ± 2462
Creatine kinase MB peak (International units)	299 ± 237
Anterior infarction	20 (57)
Number of diseased vessels	1.6 ± 0.8

Values are presented as number (%) or mean ± standard deviation. TIMI = thrombolysis in myocardial infarction.

Mean time from symptom onset to first balloon inflation was 4.1±1.8 hours. In 3 out of 35 patients (8%) the infarcted-related coronary artery was suboccluded with a TIMI 3 flow when the angiography was performed. In 241 segments related to the acute infarct territory 72 (30%) were defined hypokinetic and 120 (63%) akinetic according to MCE. Myocardial perfusion in the 192 (80%) dysfunctional segments was evaluated using both MCE and first-pass perfusion MRI, with a good agreement (91%, kappa=0.80). At 60 days follow-up, 115 (60%) out of 192 dysfunctional segments evaluated by MCE showed an improvement of function.

Improvement of Myocardial Function at Follow-up. Perfusion/enhancement patterns detected by real time perfusion MCE, first-pass imaging and delayed-enhanced MRI in the 192 dysfunctional segments are presented in Table 2. At 60 days follow-up 58 (95%), 53 (66%) and 4 (8%) of the segments with normal, partial, and no perfusion detected by MCE exhibited improvement in function respectively. Considering cine MRI with first-pass perfusion imaging (hypo-enhancement), 66 (81%) of segments with no defects, 46 (71%) of segments with a subendocardial defect, and 3 (6%) of segments with a severe hypo-enhancement improved in regional myocardial function. Delayed-enhanced MRI demonstrated that 38 of 39 (97%) segments without hyper-enhancement improved, whereas 31 (96%), 36 (92%), 7 (22%), and 3 (6%) of segments with grade II, III, IV, and V had improved at follow-up.

Table 2. Perfusion/enhancement Patterns Detected by MCE and Contrast-enhancement MRI in Dysfunctional Segments and Improvement of Myocardial Function at Follow-up.

TECHNIQUE	Dysfunctional Segments (N=192)	Recovery at 60 Days Follow-up
MCE		
Normal perfusion	61	58 (95%)
Patchy perfusion	80	53 (66%)
Absence of perfusion	51	4 (8%)
MRI: FIRST-PASS IMAGING (Hypo-enhancement)		
No Defect	81	66 (81%)
Subendocardial defect	65	46 (71%)
Severe hypo-perfusion defect	46	3 (6%)
MRI: DELAYED-ENHANCEMENT IMAGING (Hyper-enhancement)		
0% of the wall thickness	39	38 (97%)
0-25% of the wall thickness	32	31 (96%)
26-50% of the wall thickness	39	36 (92%)
51-75% of the wall thickness	32	7 (22%)
76-100% of the wall thickness	50	3 (6%)

Relation of Adequate Reperfusion Assessed by MCE and Contrast-enhanced MRI to Improvement of Global Myocardial Function. Sensitivity, specificity, predictive value and accuracy for MCE and contrast-enhanced MRI in predicting myocardial function improvement were analyzed on a per patients basis (Table 3). One patient did not show any myocardial dysfunction and was not considered in the analysis. Twenty-one out of 22 patients (95%) with adequate reperfusion by MCE showed an improvement of left ventricular ejection fraction at follow-up. Conversely 3 out of 12 patients (25%) without an adequate reperfusion improved in ejection fraction. On MRI hypo-enhancement evaluation, 21 out of 25 (84%) patients with an adequate reperfusion improved in ejection fraction at follow-up, whereas 3 out of 9 (33%) patients with no adequate reperfusion showed an increasing in ejection fraction ≥5%. Finally, all 18 patients with a hyper-enhancement MRI score index ≤3 showed an increase in ejection fraction, whereas only 6 out of 16 (37%) showed an improvement at follow-up. Sensitivity was comparable between MCE (87%), first-pass perfusion MRI (87%) and hyper-enhancement MRI (75%), p values = 1.0 between MCE and first-pass MRI, 0.1 between MCE and hyper-enhancement MRI, and 0.1 between first-pass and hyper-enhancement MRI (Table 3). Similarly, specificity was not significantly different between MCE (90%), first-pass perfusion MRI (60%) and hyper-enhancement MRI (100%), p values = 0.1 between MCE and first-pass MRI, 1.0 between MCE and hyper-enhancement MRI, and 1.0 between first-pass and hyper-enhancement MRI. No significant differences were present in accuracy between all techniques (MCE: 88%, first-pass perfusion MRI: 79%, delayed-enhancement MRI: 82%, p values = 0.1 between MCE and first-pass MRI, 0.3 between MCE and hyper-enhancement MRI, and 0.7 between first-pass and hyper-enhancement MRI).

Table 3. Sensitivity, Specificity, Predict Values, and Accuracy of MCE, First-pass Perfusion and Delayed-enhancement MRI to Predict Improvement of Myocardial Function after PCI

	MCE	MRI: First-pass imaging	MRI: Delayed-enhancement
Sensitivity	87 (76-99)	87 (76-98)	75 (60-89)
Specificity	90 (80-100)	60 (34-87)	100
Positive predictive value	95 (88-100)	84 (72-96)	100
Negative predictive value	75 (60-89)	67 (51-83)	62 (49-75)
Accuracy	88 (77-99)	79 (65-92)	82 (69-95)

Values are expressed as percentage (95% confidence interval).

Figure 1 illustrates the relation between MCE and MRI using both first-pass and delayed-enhancement imaging (hypo- and hyper-enhancement pattern) in a patient who underwent PCI of the left anterior descendent coronary artery.

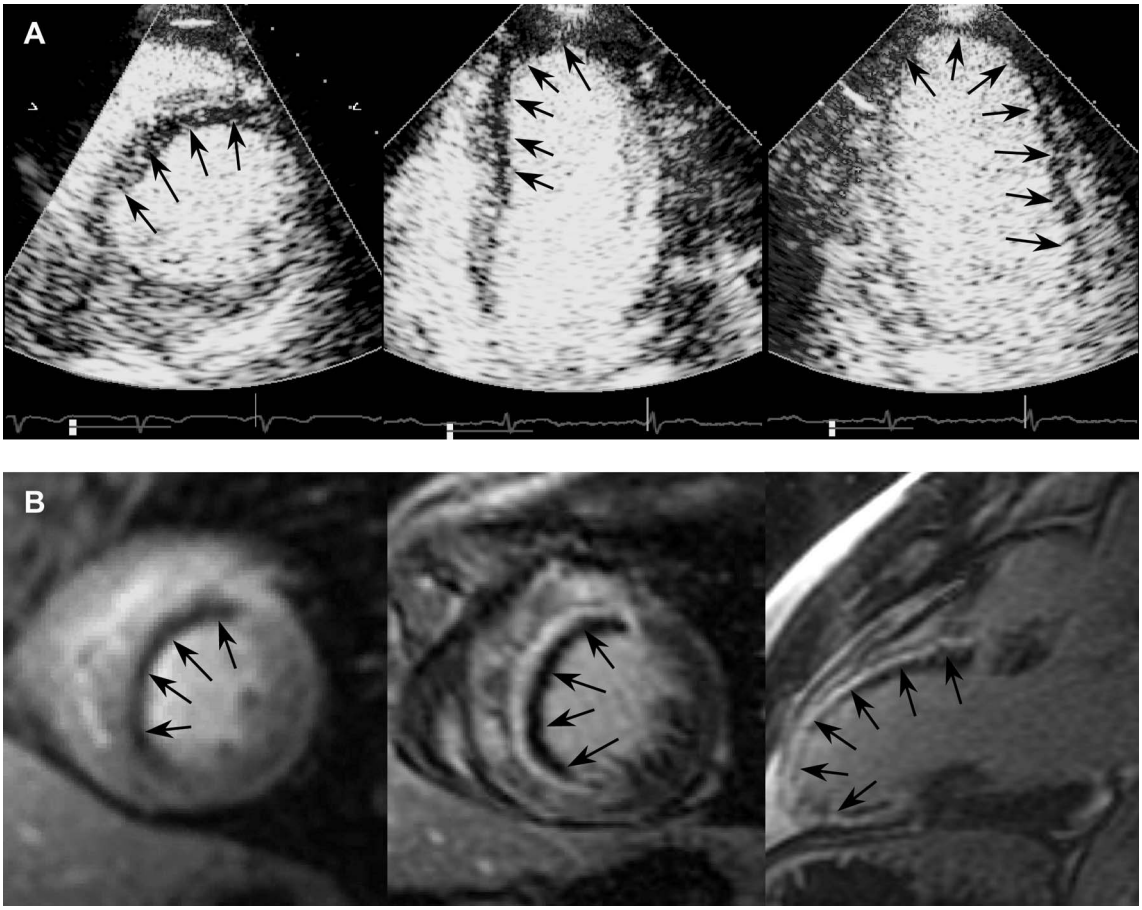

Figure 1. *MCE and MRI images of a patient who underwent PCI of the left anterior descending coronary artery. Panel A: MCE shows a defect of perfusion involving the anterior and posterior septum till the apex in short axis, 4- and 3-chamber views. Panel B: MRI shows a defect of perfusion detected by first-pass imaging (hypo-enhancement) and transmural delayed hyper-enhancement involving the anterior and posterior myocardial septum (short axis images on the left and middle part respectively). Delayed hyper-enhancement involves all the anterior septum till the apex (3-chamber view on the right side).*

To study the time course of left ventricular remodeling after PCI, the EDV was compared to the results of MCE, first pass perfusion and delayed enhancement MRI: Table 4 shows that patients with adequate reperfusion had a small decrease of EDV during follow-up, whereas patients with inadequate reperfusion had adverse LV remodeling with a gradual increment of EDV over time.

Table 4. Changes Over Time of Left Ventricular Volumes and Ejection Fraction (EF) in Patients with Adequate Reperfusion versus Patients with Inadequate Reperfusion Detected by MCE, MRI First-pass Perfusion and MRI Delayed-enhancement respectively

		EDV			ESV			EF		
		Baseline	**Follow-up**	**Delta**	**Baseline**	**Follow-up**	**Delta**	**Baseline**	**Follow-up**	**Delta**
MCE	**Adequate reperfusion**	121 ± 31	118 ± 29	-3 ± 7	66 ± 21	52 ± 17	-13 ± 9	46 ± 7	56 ± 8	10 ± 4
	Inadequate reperfusion	125 ± 38	149 ± 45	24 ± 20	79 ± 25	92 ± 31	13 ± 14	37 ± 4	39 ±6	2 ± 3
	p value			<0.001			<0.001			<0.001
MRI: First-pass imaging	**Adequate reperfusion**	123 ± 31	125 ± 35	1.7 ± 15	70 ± 23	60 ± 29	-9 ± 16	44 ± 8	53 ± 11	9 ± 5
	Inadequate reperfusion	120 ± 39	140 ± 43	20 ± 21	74 ± 24	82 ± 27	8 ± 14	38 ± 3	41 ± 2	3 ± 3
	p value			0.008			0.007			0.003
MRI: Delayed-enhancement	**Adequate reperfusion**	121 ± 34	117 ± 31	-4 ± 6	64 ± 23	49 ± 16	-15 ± 9	48 ± 6	58 ± 4	11 ± 4
	Inadequate reperfusion	124 ± 33	142 ± 41	18 ± 20	78 ± 22	86 ± 29	7 ± 16	37 ± 5	40 ± 7	3 ± 3
	p value			<0.001			<0.001			<0.001

Discussion

In patients who underwent PCI in the setting of AMI, both MCE and contrast-enhanced MRI allow early assessment of microvascular integrity and prediction of improvement of myocardial function. The main finding of the current study is that these modalities provide a comparable sensitivity, specificity and accuracy for the assessment of recovery of contractile function after PCI.

Comparison of MCE with Contrast-enhancement MRI to Predict Improvement of Myocardial Function. Previous studies have showed the efficacy of MCE to assess microvascular flow restoration after revascularization in AMI and the ability of MCE in distinguishing stunned from non-reperfused myocardium (9). Ito and colleagues used MCE to define the "no-reflow" phenomenon after revascularization in AMI (27) and showed how this phenomenon was related to subsequent increased post-infarction complications (28). Bolognese et al. (7), studied 124 patients with AMI who underwent PCI by intracoronary MCE, during a mean follow-up of 46 ± 32 months. Patients who presented microvascular dysfunction by MCE before PCI had a higher mean creatinine kinase, higher baseline wall motion score index and lower baseline left ventricular ejection fraction. At 6 months follow-up, these patients showed left ventricular remodeling (increasing in left ventricular end-systolic and end-diastolic volumes), whereas patients who had an adequate reperfusion showed a decreased end-systolic volumes. Only a slight and not significant improvement of left ventricular ejection fraction characterized patients with inadequate reperfusion, whereas patients who had an adequate reperfusion showed a significant improvement. In our study similar results were found. The grade of myocardial reperfusion was the most important independent predictor of left ventricular dilatation. Moreover, patients with microvascular dysfunction at baseline had a worse outcomes in term of cardiac death and combined events compared to patients with adequate reperfusion. The presence of microvascular dysfunction was the only predictor of both end-points by multivariate Cox analysis. In line with the study of Bolognese et al. (7), baseline differences in volumes and ejection fraction between the two groups could be explained by the occurrence of a smaller infarct size in patients with adequate reperfusion.

Previously, MRI studies showed that an hypo-enhancement pattern detected by first-pass perfusion MRI, representing the no-reflow area after AMI, is associated with a permanent dysfunction at follow-up (13, 29). Wu et al. (13), studied 44 patients after AMI by MRI during a mean follow-up of 16 ± 5 months. Patients with microvascular obstruction showed a greater increasing in left ventricular volumes and scar formation at 6 months compared to patients without obstruction. The present data confirm and extend the previous studies in line with pathological findings which indicate that hypo-enhanced myocardium represents myocardial tissue with microvascular damage and obstruction (no-reflow phenomenon) (30, 31). On the other hand delayed hyper-enhancement in AMI appears to be related to myocardial necrosis considering that gadolinium is a contrast agent able to pass through the microvascular vessels wall and the membrane of damaged cells. Conversely, contrast agents used for MCE remain inside the microvascular circulation allowing to detect exclusively microvascular integrity and therefore myocardial perfusion. Previously, Gerber et al (16) showed that persistent myocardial dysfunction seems to be better correlated with myocardial necrosis assessed by delayed-enhancement MRI than with microvascular damage and obstruction as detected by first-pass MRI. An additional benefit of contrast-enhanced MRI is the higher spatial resolution that allows assessment of the transmural extent of necrosis in the infarct region. In the current manuscript, MRI achieved 100% specificity and was superior to MCE in correctly identifying patients who did not improve in function after

revascularization. Thus, MRI may be advantageous over MCE in identifying patients who may be at increased risk for an adverse outcome and who may need special medical attention. Moreover, data on improvement of regional myocardial function pointed out as predictive accuracy for MCE was high for segments with normal or absent perfusion, but it was limited for segments with a "patchy" perfusion pattern (around 70%). In contrast, the finer scale applied with MRI using delay-enhancement technique, allowed for a better distinction between segments with high or low probability for functional recovery, with a sharp demarcation at the 50% transmural hyper-enhancement level.

Both MCE and MRI can be used to assess recovery of contractile function after PCI, the choice for either MCE or MRI mainly depends on patients characteristics and local availability and expertise. MCE is a rapid real-time bed-side technique that can be easily performed in intensive care units in the acute phase of myocardial infarction, also in unstable patients. Moreover, this technique is less time-consuming compared to contrast-enhanced MRI and is a relatively inexpensive tool. Besides, not all patients can be safely referred to MRI, because of the presence of intra-aortic balloon devices, pacemakers, or claustrophobia. On the other side, MCE is not yet widely applied in clinical routine mainly due to a lack of standardized image acquisition and contrast administration protocols and image interpretation. In contrast, these issues are largely resolved for MRI using delay-enhancement technique. Moreover, MRI may be the preferred modality in patients with a poor acoustic window.

Study limitations

Several limitations of this study need to be addressed. Although a 16-segment model of the left ventricle was used both by MCE and MRI, some misalignment between the different images may have occurred. Due to limited time slots available for MRI these exams were not always performed on the same day. To minimize the influence of time both MRI and MCE were correlated to wall motion scores by the same technique on the same day. Patients with intra-aortic balloon devices or who were clinically instable longer than 48 hours were not included in the study. Although a quantitative analysis of MCE could have been advisable, this technique is not still widely used in daily clinical practise. Although the agreement between wall motion derived by echocardiography and MRI was excellent (kappa 0.88, 93% agreement), a potential bias towards echocardiography can not be completely excluded since it was used to assess improvement of wall motion. Bolus administration of contrast compared to continuous infusion is a potential limitation of this study. However previous studies have shown the effectiveness of the assessment of myocardial perfusion using repeated injections of contrast agents by slow bolus, that represents a practical use in a busy echocardiography laboratory (9). Finally, the use of different contrast agents, infusion protocols or echo-software may give different results so that the described findings should be extrapolated with caution to other scenarios.

Conclusions

This study compares the value of MCE with contrast-enhanced MRI to predict myocardial functional improvement in patients after PCI for AMI. Both techniques allow prediction of myocardial function improvement after PCI. MCE has a comparable accuracy to MRI and as a bed-side technique may be an alternative tool in the acute phase of AMI.

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Chapter 17

Dilated-Hypokinetic Evolution of Hypertrophic Cardiomyopathy: Prevalence, Incidence, Risk Factors and Prognostic Implications in Pediatric and Adult Patients

Biagini E, Coccolo F, Ferlito M, Perugini E, Rocchi G, Bacchi-Reggiani L, Lofiego C, Boriani G, Prandstraller D, Picchio FM, Branzi A, Rapezzi C

J Am Coll Cardiol, in press

Abstract

Background. The aim of this study was to investigate incidence, risk factors and prognosis of dilated-hypokinetic evolution in a large cohort of patients with hypertrophic cardiomyopathy (HCM) followed at a cardiological center serving both the pediatric and adult population.

Methods. 222 consecutive HCM patients (65% men, 19% ≤18 years) were prospectively evaluated for a mean follow-up of 11 ± 9 years.

Results. Diagnosis of dilated-hypokinetic HCM was made in 12 patients at first evaluation, (11 without previous septal myectomy surgery; prevalence= 4.9%) Twelve of the 210 patients with 'classic' HCM at first evaluation underwent dilated-hypokinetic evolution (incidence= 5.3/1000 patient-years). Patients with prevalent/incident dilated-hypokinetic evolution were younger at first evaluation (32 ± 14 vs 41 ± 21 years, p= 0.04), and more often had a family history of HCM (61% vs 26%, p= 0.002) or sudden death (43% vs 19%, p= 0.01) with respect to patients who maintained 'classic' HCM. Moreover, they showed greater interventricular septum (23 ± 3mm vs 19 ± 6mm, p= 0.004) and posterior wall (15 ± 3mm vs 13 ± 4mm, p= 0.006) thickness. Cardiovascular death-free survival was lower among patients with dilated-hypokinetic HCM (p<0.04). Cox proportional hazards regression analysis identified left ventricular wall thickness (HR=1.07, 95%CI 1.01–1.14; p= 0.03) and end-diastolic diameter (HR=1.08, 95%CI 1.04–1.11; p= 0.0001) as independent predictors of cardiovascular death.

Conclusions. Dilated-hypokinetic evolution is rare but not exceptional in HCM. Young age at diagnosis, family history of HCM, and greater wall thickness are incremental risk factors for dilated-hypokinetic HCM, which carries an ominous prognosis.

Introduction

Most patients with hypertrophic cardiomyopathy (HCM) have normal systolic function (in terms of left ventricular ejection fraction [LVEF] and other ejection indices) in the context of impaired diastolic function and reduced left ventricular (LV) end-diastolic volume. However, in a minority of patients HCM evolves in to a phase characterized by systolic dysfunction, LV dilatation and wall thinning, resembling the morphologic and functional features of dilated cardiomyopathy (Figure 1).

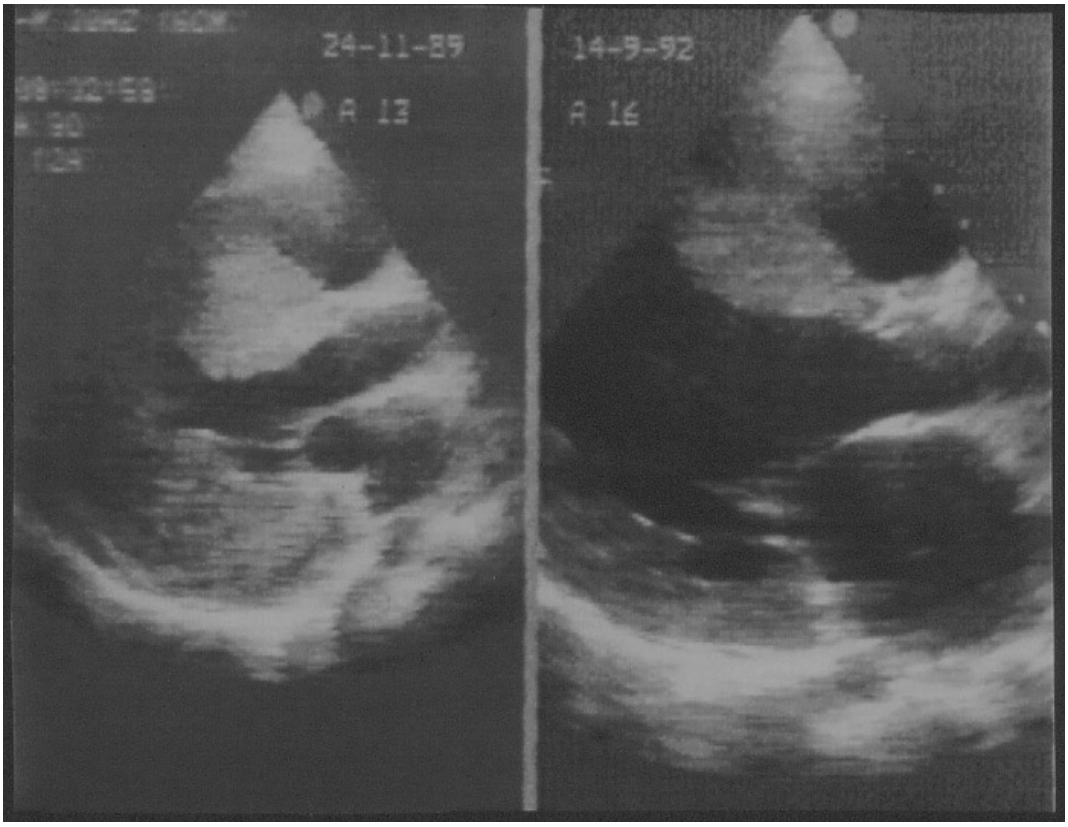

Figure 1. *A representative example of evolution to dilated-hypokinetic HCM in a female pediatric patient.* ***Left****. The basal echocardiogram (at age 13 years) shows HCM with massive LV hypertrophy involving the intraventricular septum and the left posterior wall, accompanied by diminutive LV cavity size.* ***Right****. Three years later (at 16 years), the LV cavity has become enlarged and the walls have thinned in the context of severe heart failure requiring heart transplantation.*

This dilated-hypokinetic evolution of HCM is often designated as 'end-stage', 'burn-out phase' (1-10) or 'progressive disease' (11). This peculiar disease pathway, which had already been clearly described in the 1980s (1, 2, 4-7, 9), has recently attracted renewed scientific interest for at least two reasons. On pathogenetic grounds, it has recently been reported that mutations in sarcomere protein genes can cause either HCM or dilated cardiomyopathy, stimulating two different pathobiological events that remodel the heart (12). Clinically, dilated-hypokinetic evolution is one of the pathophysiological substrates for heart failure in patients with HCM, among whom it is also the single most frequent indication for heart transplantation (3, 13, 14).

The available data on the occurrence of dilated-hypokinetic evolution of HCM mainly regards prevalence (rather than incidence) of adult cases, with very little being known about the pediatric population (15, 16). In the present study, we investigated incidence, risk factors, natural history and prognostic implications of dilated-hypokinetic evolution of HCM in a large population of patients with HCM routinely followed at a cardiological center serving both the pediatric and adult population.

Methods

Eligibility Criteria and Recruitment. The population of this observational study comprised 222 patients with a diagnosis of HCM under observation between 1964 and 2002 in the standard inpatient/outpatient clinics of our cardiologic center in a public teaching hospital open to a large local and regional population. In particular, the study regarded all patients with either a de novo diagnosis of HCM made in our center or an existing diagnosis of HCM who were referred to us for follow-up purposes (all instrumental and clinical findings, including familial analysis with pedigree reconstruction, are routinely stored in an electronic database). The single inclusion criterion was diagnosis of HCM based on 2-dimensional echocardiographic evidence of a non-dilated and hypertrophic LV—defined as wall thickness of ≥15 mm in adults, or the equivalent with respect to body-surface area in children (16)—in the absence of another cardiac or systemic disease that could produce a similar degree of hypertrophy (17). Exclusion criteria were presence of Friedreich's ataxia or Noonan syndrome (based on careful clinical analysis of phenotype); Pompe's disease (clinical and enzymatic evaluation); mitochondrial disease (exclusion of multiorgan involvement, and—in selected patients—histologic evaluation of skeletal muscle biopsy or mitochondrial DNA analysis). In patients evaluated before echocardiography was introduced into our clinical practice (in 1984), the diagnosis of HCM was made by typical electrocardiographic features combined with angiographic findings (17) and was subsequently confirmed by echocardiography (18).

Those patients residing within easy reach of the clinic were regularly followed in our outpatient clinic according to our routine institutional program, comprising two planned clinical checks-up and one echocardiographic examination per year. The remainder of the population (38 patients) was recalled (by mail and then telephone) for an echocardiographic and clinical check up at the end of the study period. Data regarding time and circumstances of death were obtained from relatives and physicians (consulting clinical records and death certificates when necessary). All patients provided written informed consent to anonymous use of their data for research purposes. In line with national and European guidelines, no specific ethical approval was required for this observational study without invasive procedures.

Definitions. Dilated-hypokinetic evolution of HCM was defined as development of hypokinetic and dilated LV, with an end-diastolic cavity dimension measured by M-mode echocardiography exceeding the reference upper 95% confidence limit (95%CI) for body surface area and a LVEF <50% (2, 4, 19). In patients who already presented at our center with a dilated and hypokinetic LV, diagnosis of HCM always included previous echocardiographic documentation of classic HCM. 'Medical treatment at first examination' refers to pharmacological treatment ongoing/started at that time.

Other definitions were those commonly used. Sudden cardiac death was defined as unexpected sudden collapse within 1 hour of onset of symptoms occurring in patients who had previously experienced a relatively stable or uneventful clinical course. Heart failure-

related death was defined as death occurring in the context of cardiac decompensation and progressive disease course ≥1 year before death.

Statistical Analysis. The SPSS statistical package (SPSS Statistical Software Inc., Chicago, IL) was used for all analysis. When not otherwise specified, data are expressed as mean ± 1 standard deviation, or as number of patients (percentage). Prevalence of dilated-hypokinetic HCM was calculated as the ratio between patients with a diagnosis of dilated-hypokinetic HCM at the first evaluation and the total number of study patients. Analysis of incidence was performed among those patients without dilated-hypokinetic HCM at first evaluation. Incidence was calculated as the number of patients who developed dilated-hypokinetic HCM during the follow-up period divided by the total number of person-years of observation accumulated in the study population; patients who underwent myotomy/myectomy or percutaneous transluminal septal myocardial ablation were included in the analysis only up to the time of the procedure. Differences between means were determined using the unpaired or paired Student's t test, as appropriate. Differences between proportions were determined using the chi-square test. To assess the prognostic role of dilated-hypokinetic HCM in terms of risk of cardiovascular death, a multivariate Cox proportional hazards model was fitted to the data (20). The following variables were included: gender, age at first evaluation, family history of sudden-death, NYHA class I–II or III–IV, medical treatment at first evaluation, non-sustained ventricular tachycardia, LV outflow obstruction, maximum LV wall thickness, posterior wall thickness, LV end-diastolic diameter, end-systolic left atrial diameter, and (as a time-dependant covariate) dilated-hypokinetic evolution. Variables were selected in a stepwise forward selection manner with entry and retention set at a significance level of 0.05. Probability of cardiovascular death-free survival was calculated using the Kaplan-Meier method, and survival curves were compared using the log-rank test.

Results

Study Population. The mean age at first evaluation was 40 ± 20 years; 144 (65%) patients were men, 42 (19%) ≤18 years. Baseline clinical and echocardiographic characteristics of the entire population as well as of the two groups of patients with either dilated-hypokinetic or 'classic' HCM at first evaluation are summarized in Table 1. During a mean follow-up of 11 ± 9 years, 29 (13%) patients developed persistent atrial fibrillation, 65 (29%) had heart failure episodes and 20 (9%) experienced syncope. Holter monitoring data were available for 190 (85%) patients; non-sustained ventricular tachycardia were present in 64/190 (34%). A permanent pacemaker or cardioverter-defibrillator were implanted in 10 (4%) and 11 (5%) patients respectively. During the follow-up period, 10 patients (4%) underwent heart transplantation and 50 (23%) died. The cause of death was sudden in 20 (9%) patients, heart failure-related in 13 (6%), stroke-related in 3 (1%) and due to non-cardiac causes in 14 (6%).

Table 1. Baseline Characteristics of the Overall Population, Patients with 'Classic' HCM, and Patients with Dilated-hypokinetic HCM at First Evaluation

	Overall population (n=222)	Dilated-hypokinetic HCM (n=11)*	'Classic' HCM (n=210)	p value†
Male gender	144 (65%)	8 (73%)	135 (64%)	0.8
Family history of HCM	65 (29%)	7 (64%)	58 (28%)	0.03
Family history of sudden death	47 (21%)	4 (36%)	43 (20%)	0.3
Age at diagnosis (yr)	38 ± 18	27 ± 18	39 ± 18	0.05
Age at first evaluation (yr)	40 ± 20	34 ± 16	40 ± 21	0.3
Pediatric age (≤18 yr) at first evaluation	42 (19%)	3 (27%)	37 (18%)	0.6
NYHA class III–IV	22 (10%)	3 (27%)	19 (9%)	0.1
NYHA class (mean)	1.5 ± 0.7	2.1 ± 1.1	1.4 ±1.0	0.1
Syncope	21 (9%)	1 (9%)	19 (9%)	1
Medical treatment at first examination	160 (72%)	9 (82%)	151 (72%)	0.7
Persistent atrial fibrillation	3 (1%)	0 (0%)	3 (1%)	1
Heart failure episodes	12 (5%)	3 (27%)	9 (4%)	0.01
Outflow obstruction	67 (30%)	0 (0%)	68 (32%)	0.05
Maximum LV wall thickness (mm)	19 ± 6	17 ± 6	20 ± 6	0.2
Interventricular septal width (mm)	18 ± 6	16 ± 6	19 ± 6	0.2
Posterior wall thickness (mm)	13 ± 4	14 ± 4	13 ± 4	0.4
LV end-diastolic diameter (mm)	43 ± 11	61 ± 9	41 ± 10	NA
End-systolic left atrial diameter (mm)	43 ± 10	49 ± 8	42 ± 10	0.02
LVEF (%)	67 ± 8	32 ± 10	66 ± 8	NA
Apical HCM	8 (4%)	0 (0%)	68 (32%)	0.05

∗One patient with previous septal myectomy surgery was excluded from this analysis. †The p values refer to comparison between patients with dilated-hypokinetic and patients with 'classic' HCM at first evaluation. NA= not applicable (separation into subgroups was based on these variables)

Prevalence of Dilated-hypokinetic Evolution of HCM. Diagnosis of dilated-hypokinetic HCM was made in 12 patients at the first evaluation. One of these patients, who had entered this phase following septal myectomy surgery, was excluded from the analysis. Therefore, 11 patients were deemed to have dilated-hypokinetic HCM evolution at first evaluation corresponding to a prevalence of 4.9%.

Incidence of Dilated-hypokinetic Evolution of HCM. Twelve of the 211 patients with 'classic' HCM at first evaluation underwent dilated-hypokinetic evolution (their changes in LV cavity dimension, LVEF and maximum wall thickness are individually represented in Figure 2).

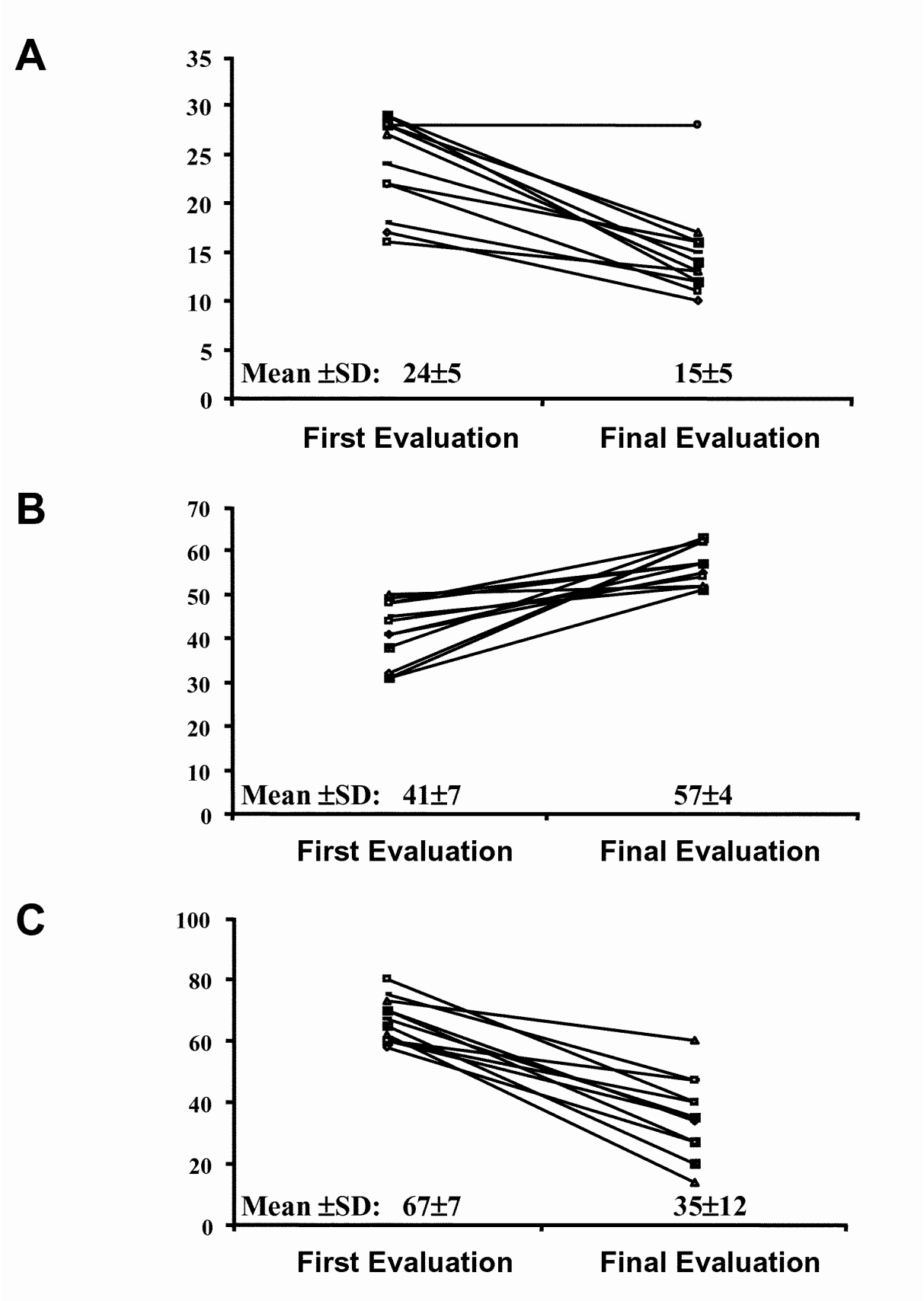

Figure 2. *Changes in LV maximal wall thickness (A), LV end-diastolic diameter (B) and LVEF (C), in the 12 HCM patients who underwent dilated-hypokinetic evolution during the study period.*

Since all 12 of these patients belonged to the subgroup with regular follow-up data from our institutional program, an actuarial incidence curve was constructed (Figure 3). The events (onset) were distributed rather evenly over almost the entire follow-up period (mean 11 ± 9 years, range 4 month to 42 years). The overall incidence of development of dilated-hypokinetic HCM was 5.3 per 1000 patient-years. Of note, a 'restrictive left ventricular filling pattern' was present at echo-Doppler evaluation in 3/12 patients at the time of detection of dilated-hypokinetic evolution.

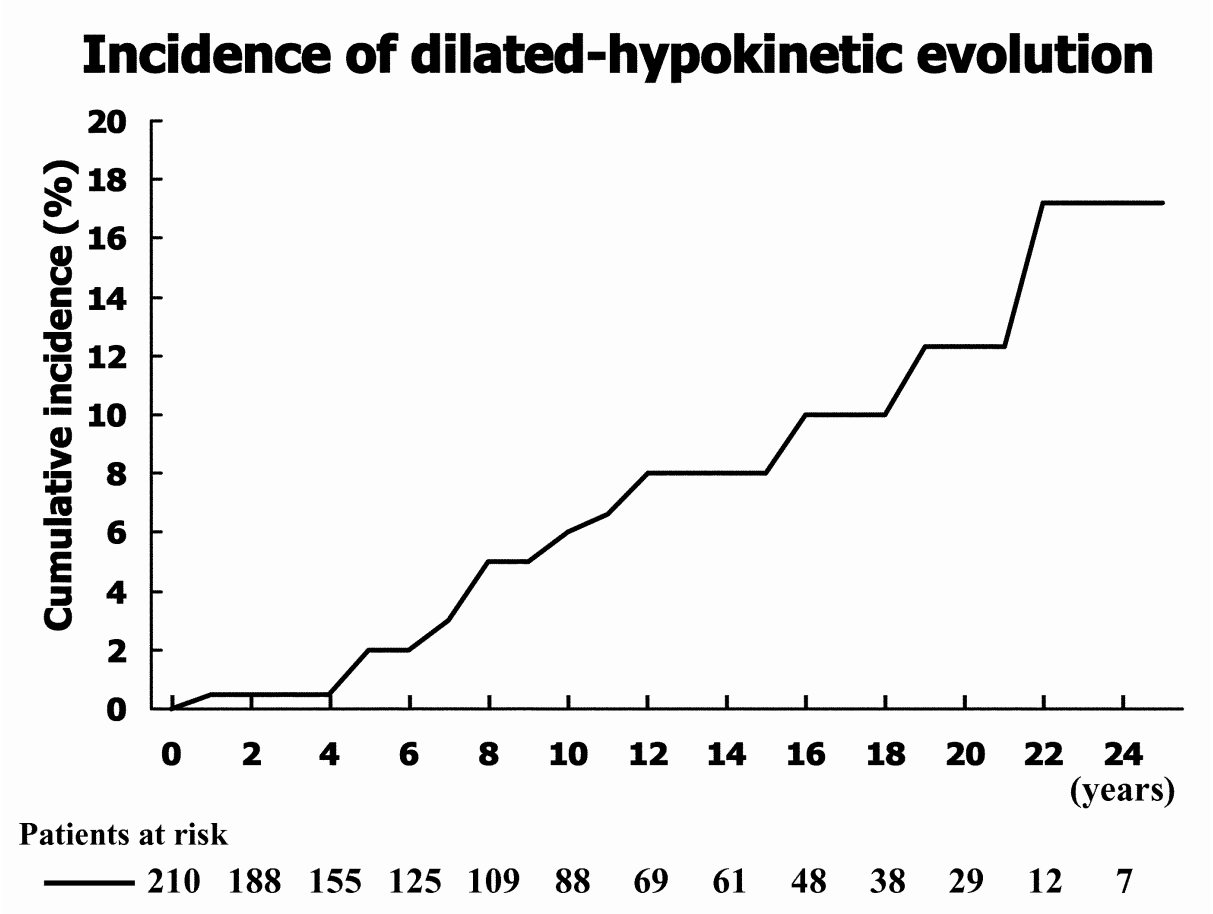

Figure 3. *Actuarial incidence curve of dilated-hypokinetic evolution among 210 patients with 'classic' HCM at first evaluation.*

Characterization of Patients with Dilated-hypokinetic HCM and Prediction of Onset. We first looked at the clinical/morphological profile of patients with prevalent dilated-hypokinetic HCM at baseline (n=11). A comparison between their clinical/morphological characteristics and those of the rest of the population at first evaluation is shown in Table 1.

To look for possible predictors of evolution, we then analyzed the baseline characteristics of patients who had prevalent/incident dilated-hypokinetic HCM (n=23). Table 2 shows a comparison of the baseline characteristics of patients with dilated-hypokinetic HCM and patients who maintained 'classic' HCM (it should be noted that for those patients with prevalent dilated-hypokinetic HCM, measurements were retrieved from prior echocardiographic documentation). At univariate analysis, the two subgroups were similar as

regards gender, symptoms, LV end-diastolic volume and LVEF. On morphologic grounds, patients with dilated-hypokinetic HCM showed greater LV parietal thickness at the posterior as well as interventricular septal level. They also more often had a family history of HCM or a family history of sudden death. They were significantly younger both at the original diagnosis of HCM and at first examination. Due to the small number of patients with dilated-hypokinetic evolution, it was not possible to construct a valid multivariate model.

Of note, the 23 patients with prevalent/incident dilated-hypokinetic evolution belonged to 18 distinct families. Among these 18 nuclei, we could identify 3 pedigrees containing both sudden death in the context of non-dilated HCM and death from heart failure due to end-stage evolution.

Table 2. Baseline Clinical and Echocardiographic Features of Patients with Prevalent/incident Dilated-hypokinetic HCM and Patients who Maintained 'Classic' HCM

	Dilated-hypokinetic HCM (n=23)	**'Classic' HCM (n=198)**	**p value**
Male gender	17 (74%)	126 (64%)	0.5
Family history of HCM	14 (61%)	51 (26%)	0.002
Family history of sudden death	10 (43%)	37 (19%)	0.01
Age at diagnosis (yr)	28 ± 15	39 ± 18	0.03
Age at first evaluation (yr)	32 ± 14	41 ± 21	0.04
Pediatric age (≤18 yr) at first evaluation	9 (39%)	34 (17%)	0.02
NYHA III-IV at first evaluation	0 (0%)	19 (9%)	0.5
NYHA class (mean)	1.5 ± 0.6	1.4 ± 0.7	0.8
Syncope at first evaluation	2 (9%)	18 (9%)	0.99
Medical treatment at first examination	17 (74%)	141 (71%)	1
Outflow obstruction	4 (17%)	67 (30%)	0.2
Maximum LV wall thickness (mm)	24 ± 3	20 ± 6	0.001
Interventricular septal width (mm)	23 ± 3	19 ± 6	0.004
Posterior wall thickness (mm)	15 ± 3	13 ± 4	0.006
LV end-diastolic diameter (mm)	43 ± 4	41 ± 9	0.7
End-systolic left atrial diameter (mm)	45 ± 7	42 ± 10	0.1
LVEF (%)	66 ± 4	66 ± 8	1

Prognostic Implications of Dilated-hypokinetic HCM. Figure 4 shows actuarial cardiovascular death-free survival curves for patients with prevalent or incident dilated-hypokinetic HCM (n=23) and the rest of the study population: patients with dilated-hypokinetic evolution had a poorer cardiovascular death-free survival (p=0.04). In particular, out of the 23 patients with dilated-hypokinetic evolution, 4 died of congestive heart failure and 3 died suddenly.

Cox proportional hazards regression analysis identified LV wall thickness (HR=1.07, 95%CI 1.01–1.14; p=0.03) and LV end-diastolic diameter (HR=1.08, 95%CI 1.04–1.11; p=0.0001) as independent predictors of cardiovascular death; dilated-hypokinetic evolution (considered as a time-dependant covariate) did not appear to affect cardiovascular death-free survival (p=0.51).

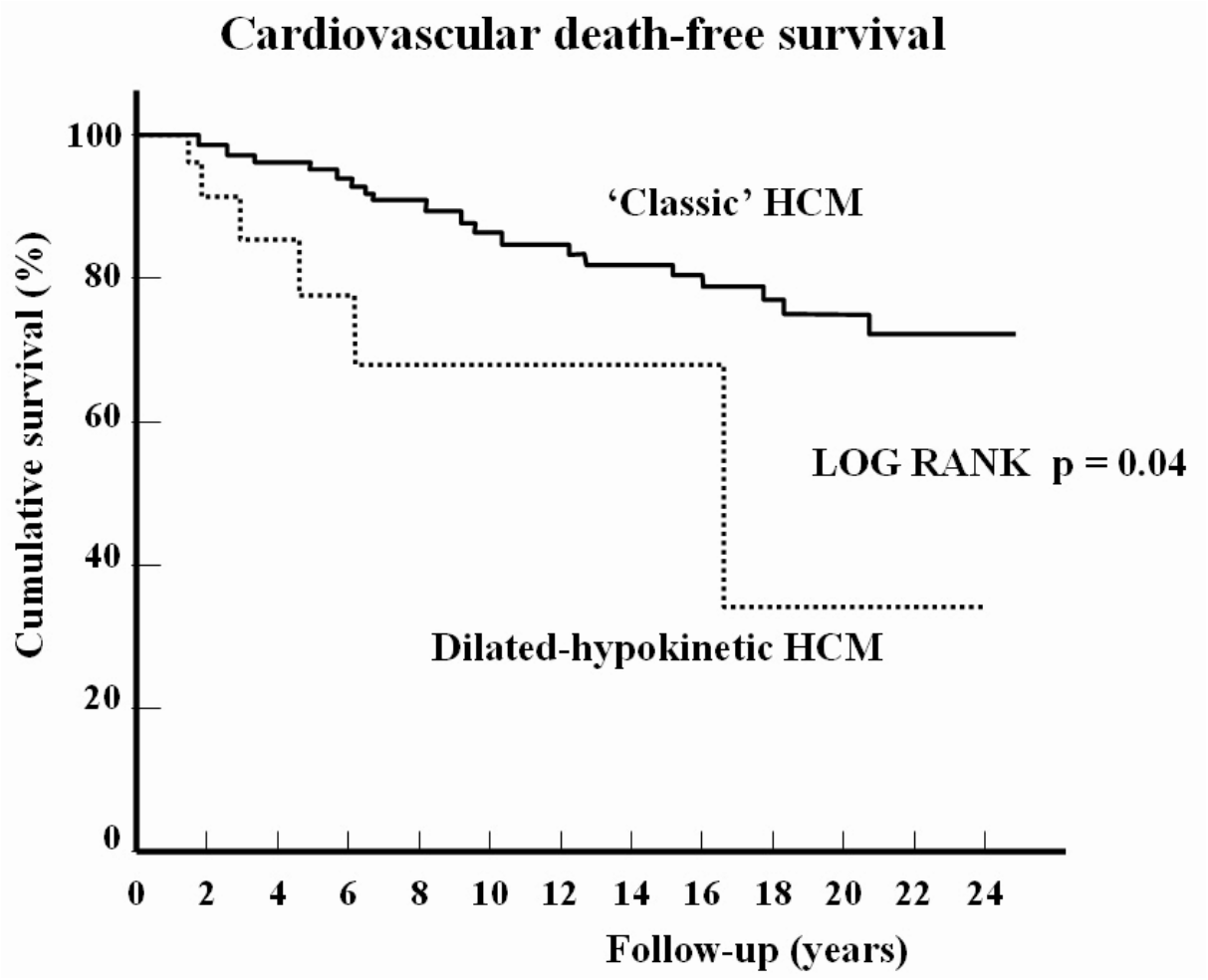

Figure 4. *Kaplan-Meier estimates of cardiovascular death-free survival of patients with and without prevalent/incident dilated-hypokinetic HCM.*

Clinical events observed during follow-up among the subgroups of patients who did and did not develop dilated-hypokinetic HCM during the study period are summarized in Table 3. Overall, patients who developed dilated-hypokinetic HCM more often had persistent atrial fibrillation, episodes of heart failure, ventricular tachycardia (on 24-h Holter monitoring) and heart transplantation. It should be noted, however, that this subgroup had a longer follow-up (14±6 vs 10±7 years, p=0.05). The first signs of LV dilatation and hypokinesis in these 12 'incident' patients became evident within 13 ± 8 years (ranging from 5 to 33 years) after the diagnosis of HCM (mean age of patients 42 ± 17 years). The mean interval from echocardiographic appearance of LV dilatation to development of heart failure (NYHA class III-IV) was 3 ± 2 years (1–7 years). During follow-up, 2 (17%) patients died and 5 (45%) underwent heart transplantation. The mean time between identification of dilated evolution and death or heart transplantation was 5 ± 3 and 5 ± 4 years respectively.

Table 3. Clinical Events Observed in Patients who Underwent Dilated-hypokinetic Evolution during Follow-up and in Patients who Maintained 'Classic' HCM

	Dilated-hypokinetic evolution (n=12)	'Classic' HCM (n=198)	P value
Persistent atrial fibrillation	5 (42%)	22 (11%)	0.009
Heart failure episodes	10 (83%)	48 (24%)	0.0001
Syncope	2 (17%)	19 (9%)	0.8
Nonsustained/sustained VT on Holter ECG	9/12 (75%)	49/175 (28%)	0.002
Pacemaker	1 (8%)	8 (4%)	1
ICD	2 (17%)	8 (4%)	0.2
Cardiovascular death	2 (17%)	26 (13%)	0.1
-Sudden death	1 (8%)	17 (9%)	1
-Heart failure-related death	1 (8%)	9 (4%)	1
-Stroke-related death	0 (0%)	3 (1%)	1
Non-cardiovascular death	0 (0%)	14 (7%)	0.7
Heart transplantation	5 (42%)	1 (0.5%)	0.0001

VT= ventricular tachycardia; ICD = implanted cardioverter-defibrillator.

Five of 12 (42%) patients who experienced dilated-hypokinetic evolution during follow-up were younger than 19 years of age at first evaluation; in this subgroup, dilated-hypokinetic evolution occurred at 8 ± 4 years (range 5–16) from HCM diagnosis. After LV dilatation occurred, these patients developed heart failure symptoms earlier compared with adult patients (1 ± 0.5 vs 5 ± 3 years, $p<0.05$). Moreover, 4/5 (80%) pediatric patients underwent heart transplantation (at 5 ± 4 years from appearance of dilatation) and 1 (8%) died of heart-failure occurred in 1 patient (at 2 years from dilatation).

Discussion

Dilated-hypokinetic evolution of HCM is responsible for severe heart-failure symptoms and is the single most frequent indication to heart transplantation among HCM patients (3, 13, 14). This study of a large population of HCM patients routinely followed at a single cardiologic center provides valuable data on the incidence of dilated-hypokinetic evolution among both children and adults, as well as on possible clinical and echocardiographic risk factors for development of this peculiar disease pathway.

Prevalence and Incidence of Dilated-hypokinetic HCM. Since the 1980s, dilated-hypokinetic ('end-stage') evolution of HCM has become an established clinical entity, whose recognition is clearly based on the presence of cavity size enlargement and LV systolic dysfunction, commonly accompanied by ventricular wall thinning (1, 2, 4-7, 9). Our definition of dilated-hypokinetic HCM was based on the simultaneous presence of LV cavity dilatation and reduced LVEF, not obligatorily associated with thinned LV walls. It is noteworthy however that LV wall thinning was documented during the study period in all but one patient (Figure 2). Outside heart transplantation centers, prevalence of dilated-hypokinetic HCM has generally been reported ranging from about 5% to 15% (4). However, these figures

were produced without excluding patients who had previously undergone myotomy-myectomy, and are likely to give rise to a somewhat distorted picture (since myectomy can alter left ventricular end-diastolic diameter as routinely measured by M-mode according to the recommendations of the American Society of Echocardiography, whereas percutaneous septal myocardial ablation can induce left ventricular remodeling with increased volumes (21)). After exclusion of such cases, the recorded prevalence of dilated-hypokinetic HCM in our center was 4.9%.

To our knowledge, this is the first time that the incidence of dilated-hypokinetic evolution has been studied in a large population of HCM patients not submitted to surgical/ablative myectomy. The overall incidence recorded was 5.3 per 1000 patient-years, with a rather even distribution of onset over almost the entire follow-up period (Figure 3).

Prediction of Onset of Dilated-hypokinetic Evolution. Increased posterior wall thickness was the most peculiar morphologic trait in patients with (prevalent/incident) dilated-hypokinetic HCM (Table 2). The pathogenetic significance of this morphologic peculiarity is unclear. One attractive hypothesis is that this phenotypic peculiarity might constitute a marker of a distinct genotype (unfortunately, our study did not contemplate systematic genotyping). Alternatively, it is conceivable that a widespread distribution of LV hypertrophy might exacerbate myocardial ischemia—a very common phenomenon in HCM—and eventually lead to global LV dysfunction. HCM characterized on echocardiography by marked thickening of the posterior left ventricular free wall has been previously described to be associated with early (before age 40) onset of severe symptoms, such as dyspnea, syncope, chest pain and palpitations (22). However, no relation between this peculiar morphologic feature of HCM and dilated-hypokinetic evolution has been previously reported.

Natural History and Prognostic Implications of Dilated-hypokinetic Evolution. Despite the younger age at first evaluation of patients who developed dilated-hypokinetic HCM during follow-up, the interval from diagnosis to LV enlargement was rather long. However, once the dilation was established, the evolution towards heart failure and hence transplantation or death was rapid. The vast majority of our patients with dilated-hypokinetic evolution of HCM had severe symptoms (NYHA class IV), were refractory to medical treatment in spite of a depression of LVEF which might be considered only moderate in comparison with heart transplantation candidates with idiopathic dilated cardiomyopathy (Figure 2). A combination of both diastolic and systolic dysfunction could explain this apparent discrepancy.

Pathogenesis of Dilated-hypokinetic Evolution in HCM. The most likely pathogenetic mechanisms of dilated-hypokinetic evolution of HCM have been widely discussed in the literature. Based on histology, importance has been given to small-vessel disease, myocardial disarray or replacement fibrosis (10, 11, 23-26). Recently, gadolinium-enhanced cardiac magnetic resonance has provided in vivo confirmation that interstitial and replacement fibrosis is the most frequent myocardial substrate of this evolutionary pathway (11). The present study was not designed to clarify the pathogenetic mechanism of dilated-hypokinetic HCM. However, analysis of the clinical and morphologic data regarding our prevalent and incident cases can provide some hints regarding the likely pathogenesis. In our two analyses (Tables 1 and 2), dilated-hypokinetic evolution was most often already present in the third decade of life, and about one-third of the cases were actually pediatric; furthermore, age at diagnosis of HCM appeared to be lower in patients with dilated-hypokinetic evolution as compared with the rest of the population. These observations make a strict aging-related mechanism seem rather unlikely. On the other hand, they fit quite well

with the hypothesis that dilated-hypokinetic HCM often has a genetic basis (27-29). In some families, evolution to the dilated-hypokinetic evolution of HCM seems to occur with a particularly high frequency. A number of mutations in genes encoding proteins of the cardiac sarcomere have been reported in HCM patients in the dilated-hypokinetic evolution. It is unlikely that the propensity to develop this clinical course is exclusively due to any specific HCM-causing mutant gene. Interestingly, Seidman et al (12) recently demonstrated that mutations in the same gene (heavy-chain β-myosin) can cause either hypertrophic or dilated cardiomyopathy. The development of left ventricular wall thinning and systolic dysfunction probably represents a more complex phenomenon influenced by modifier genes as well as environmental factors.

Considerations Regarding the Pediatric Population. Our data indicate that HCM patients diagnosed at a pediatric age are a high-risk subgroup not only as regards sudden death but also congestive heart failure. It is known that the morphologic basis for congestive heart failure in newborns with HCM is massive biventricular hypertrophy, frequently associated with right and/or left ventricular obstruction. Our data set reveals that dilated-hypokinetic evolution is another pathophysiologic substrate, apparently affecting older children and adolescents. In the clinical arena, this peculiar disease pathway of 'classic' HCM must be distinguished from other genetically determined entities that share the same phenotype of symmetrical LV hypertrophy and LV systolic dysfunction, and especially cardiomyopathies associated with mitochondrial disease. The latter, however, are generally characterized by multiorgan involvement, which should provide a valuable clue for a differential diagnosis.

Clinical Implications and Conclusions

The evolution toward a dilated-hypokinetic phase is rare but not exceptional in HCM, particularly among young patients with hypertrophy not confined to the interventricular septum, but also involving the posterior wall. Recognition of this risk profile in individual patients should encourage close follow-up, aimed at timely detection and treatment of congestive heart failure. We think that the option of heart transplantation deserves consideration (and discussion with the patient) on the first appearance of heart-failure symptoms, even if these occur before overt deterioration of systolic function.

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Chapter 18

Intracardiac Echocardiography to Guide Percutaneous Transluminal Septal Ablation in Patients with Obstructive Hypertrophic Cardiomyopathy

Biagini E, Valgimigli M, Baks T, van der Lee C,
Ligthart YML, Serruys PW, ten Cate FJ

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Abstract

Background. Intra-procedural myocardial contrast echocardiography using tranthoracic 2-D echocardiography has been shown to be crucial during percutaneous septal myocardial ablation (PTSMA) in patients with obstructive hypertrophic cardiomyopathy (HCM). The role of intracardiac echocardiography in guiding PTSMA has not been previously investigated.

Methods. Intracardiac echocardiography was performed in 18 consecutive patients with obstructive HCM during PTSMA. A magnetic resonance imaging (MRI) was performed four days after the procedure in 12 patients.

Results. The target septal branch was chosen on the basis of the risk-area visualized using intracardiac echocardiography after selective septal intracoronaric injection of an ultrasound contrast agent. Ethanol (2.1 ± 0.7 ml) was subsequently injected. The maximum width of the interventricular septum measured by intracardiac echocardiography was on average 21 ± 4 mm and correlated with MRI measurements (22 ± 4 mm, r = 0.70). During ethanol administration a backscatter signal enhancement of the infarct area (ablated area) was detected. The ablated area on planimetry was 1.8 ± 0.8 cm2 and correlated with the infarct size detected by MRI (22 ± 7 cc, r = 0.80). Resting left ventricular outflow tract gradient was reduced from 74 ± 35 mmHg to 8 ± 16 mmHg ($p<0.0001$) at the end of the procedure.

Conclusions. Intracardiac echocardiography can be used to monitor ethanol administration during PTSMA in patients with obstructive HCM and reasonably predict the extent of the infarct area assessed by MRI.

Introduction

In patients with hypertrophic cardiomyopathy (HCM), resting left ventricular outflow tract (LVOT) obstruction is an important and independent predictor of progression to severe symptoms of heart failure and of death (1-3). Surgical myectomy is the gold standard for treatment of severely symptomatic patients with obstructive HCM who are refractory to medical therapy (4, 5). Percutaneous transluminal septal myocardial ablation (PTSMA) has emerged as less invasive alternative treatment in these patients and results in clinical and hemodynamic improvement (6-8) in patients with obstructive HCM.. Intra-procedural transthoracic myocardial contrast echocardiography has been shown to be crucial during PTSMA for target vessel selection. Furthermore, improvement of clinical and hemodynamic results, and prevention of misplacement of the ethanol-induced necrosis as a source of potentially fatal complications were observed with this approach (7, 9, 10). Intracardiac echocardiography is an invasive tool that has been recently introduced in the clinical setting (11-13). This technique has the ability to provide a precise cardiac anatomy visualization and to guide interventional procedures. The aim of this study was to evaluate the role of intracardiac echocardiography during PTSMA in patients with obstructive HCM.

Methods

Patient Population. Between September 2003 and February 2005, 19 consecutive patients with obstructive HCM underwent PTSMA at the Thoraxcenter, Rotterdam, the Netherlands. The indication for PTSMA was based on a significant LVOT gradient as documented by transthoracic echocardiography and New York Heart Association (NYHA) functional class II to IV despite medical treatment. All subjects demonstrated a dynamic LVOT gradient of at least 50 mmHg at rest or on provocation. All but 1 procedures were performed under intracardiac echocardiography guidance. In 1 patient intracardiac echocardiography was not performed, due to the occurrence of a venous dissection. Twelve patients underwent magnetic resonance imaging (MRI) 4 days on average after the procedure.

Intracardiac Echocardiography Procedure. The AcunavTM –intracardiac probe is a 10F catheter equipped with a linear phased array bifrequency (6-7 MHz) transducer. The catheter has a quadridirectional steerable tip, with a proximal control unit for tip deflection. The insertable length of the catheter is 90cm. Regular 2D echocardiography along with colour Doppler, pulsed and continuous wave Doppler allows comprehensive anatomical and physiological assessment. The probe was interfaced with Sequoia or Cypress platform (Siemens Acuson, Mountainview, California), and the images were digitally recorded. Bilateral femoral arterial and venous accesses were obtained by a modified Seldinger technique. A 11F venous sheath was placed on the left side to introduce the intracardiac echocardiographic probe. A temporary pace-maker lead was positioned in the right ventricle. The tip of the intracardiac echocardiography probe was advanced into the right atrium with the piezo-electric crystal facing the free wall of the right atrium, then was gradually deflected towards the atrial septum and advanced into the right ventricle to obtain a long axis of the left ventricle. Left ventricular outflow tract and mitral valve were evaluated in echocardiographic secta scan, by Doppler mode. The M mode of mitral valve in this plane confirmed the systolic anterior motion and thickness of the interventricular septum. The probe was locked in this position so as to view the entire proximal and mid septum for further imaging during myocardial contrast injection and ablation. Coronary angiography was performed in multiple projections to delineate the septal perforator branches. The supposed target vessel artery was identified and cannulated with a 0.014 inch guide wire. A 2.5x9 mm over the wire balloon

was advanced into the vessel and inflated at 5-6 atm to prevent the flow back into the left anterior descending coronary artery. Subsequently 1 ml of an ultrasound contrast agent (Sonovue, Bracco, Milan, Italy), was injected through the balloon catheter. Hence the myocardial area supplied by the vessel (risk area) could be visualized and any leakage form the septal branch or an anomalous distribution excluded. PTSMA was performed according to standard protocol (14). The images obtained during infusion of ethanol revealed the progressive appearance of a sharply demarcated area with increased echo density in the septum within the contrast area producing a marked shadowing effect (Figure 1). The procedure was completed by obtaining the 2-D and M mode images in long axis. The patients were sent to the coronary care unit for 24 hours. Serial cardiac enzyme samples were obtained at baseline and at 12, 24, 36, 48, 60, and 72 hours.

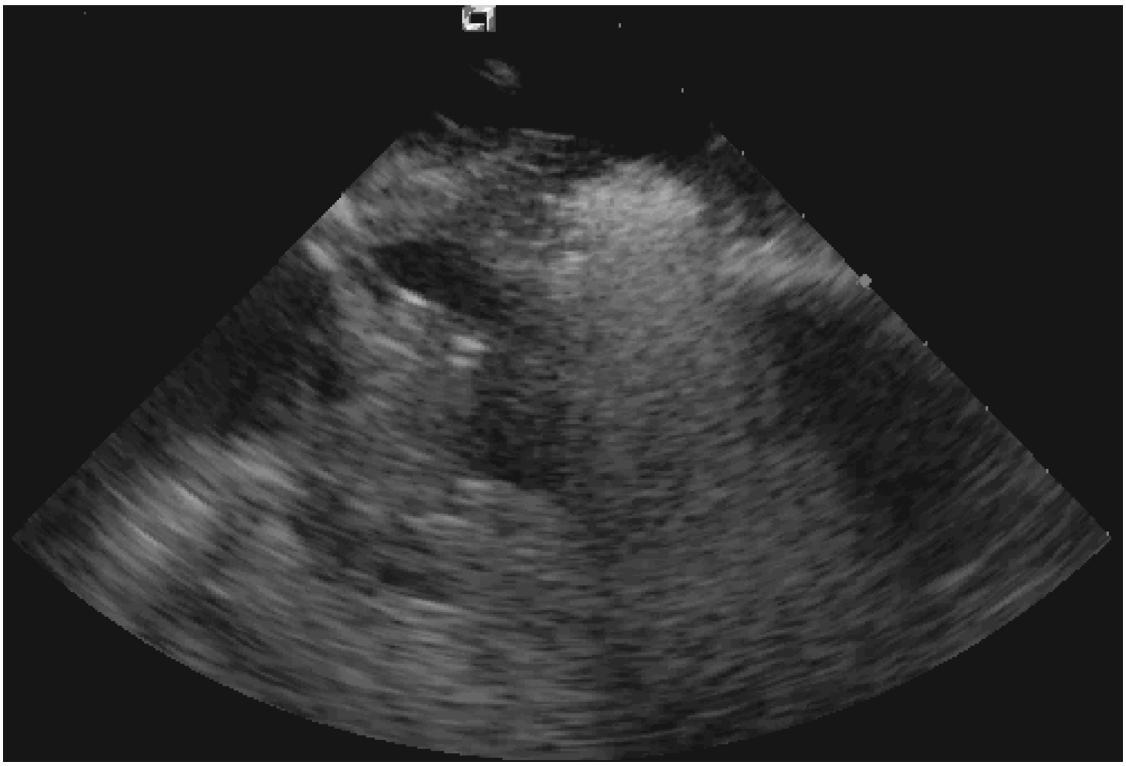

Figure 1. *Image of the ablated area (with ethanol) visualized by intracardiac echocardiography during PTSMA and characterized by marked shadowing effect.*

Measurements. The gradient across the LVOT was continuously monitored with simultaneous pressure recording in the left ventricle and in the ascending aorta, using a pig tail and a guiding catheter respectively. The LVOT gradient was assessed at rest and after premature ventricular beats or post pacing.

Measurements included maximal septal thickness, septal thickness at the site of treatment, mitral regurgitation grade, severity of SAM an LVOT gradient. Septal thickness was measured by intracardiac echocardiography in the long-axis of the ventricle as described above, in an end-diastolic still-frame. Mitral regurgitation severity was assessed by color flow Doppler intracardiac echocardiography echocardiography and graded on a scale from 0 (no regurgitation) to 4 (severe regurgitation). SAM of the anterior leaflet was graded as 0

(absent), 1+ (mild; minimal mitral-septal distance > 10 mm during systole), 2+ (moderate; minimal mitral-septal distance ≤10 mm during systole) or 3 (marked; brief or prolonged contact between the anterior mitral leaflet and septum) (15).
The myocardial hyperechoic area developed during alcohol injection (ablated area) was off-line planimetrized.

MRI Protocol. A clinical 1.5-Tesla MRI scanner with a dedicated cardiac four element phased-array receiver coil was used for imaging (Signa CV/i, GE Medical systems, Milwaukee, Wisconsin). Repeated breath-holds and gating to the electrocardiogram were applied to minimize the influence of cardiac and respiratory motion on data collection. The ce-MRI protocol consisted of cine-MRI and DE-imaging.

Left ventricular volumes and wall dimensions were assessed with cine-MRI using a steady-state free-precession technique (FIESTA) with the following imaging parameters: 6-10 seconds per breath-hold per slice (depending on heart rate), 24 phases per slice location, Field of View: 36 x 36 cm; TR 3.4; TE 1.4; flip angle 45 degrees; matrix 160 x 128, bandwidth 83 kHz, 0.75 NEX.) To cover the entire left ventricle, 9 to 12 consecutive slices of 8 mm were planned in short axis view (gap of 2 mm) perpendicular to the horizontal long axis (4-chamber view) of the left ventricle.

Myocardial distribution of DE was studied 10-20 minutes following intravenous administration of Gadolinium-DTPA (0.1 mmol/kg, Magnevist®, Schering). A 2-dimensional T1-weighted inversion recovery gradient-echo sequence with the following imaging parameters was used; FOV: 40 x 32 cm, slice thickness 8 mm gap 2 mm, TR 7.3, TE 1.6, flip angle 20 degrees, TI 180 - 275 ms, matrix 256 x192, 1 NEX, bandwidth 17.9 kHz. The inversion time was adjusted per patient to null the signal of remote myocardium. Slice locations of the DE-images were copied from the cine images. A myocardial segment was judged as non-assessable if the region of DE could not be differentiated clearly from the healthy myocardium (breathing artefacts, erroneous ECG triggering).

Analysis of MRI. The maximum width of the interventricular septum was measured on cine-images in the LVOT-plane. DE-myocardium was clearly differentiated from remote myocardium (nulled signal) with the use of an inversion recovery pulse sequence. Data from one patient had to be excluded since image quality was impaired. The volume of DE was quantified by manually selecting the enhanced regions from the consecutive 2D slices encompassing the left ventricle with dedicated software (Cine, GE, 3.4.0, USA).

Results

Eighteen patients (mean age 62 ± 13 years; 12 (67%) men) completed the procedure under intracardiac echocardiography guidance. The mean baseline NYHA class was 2.5 ± 0.5. All patients had sinus rhythm at baseline electrocardiography.

The maximum widths of the interventricular septum measured by intracardiac echocardiography ranged from 15 to 30 mm, (mean 21 ± 4 mm). These measurements correlated with MRI measurements of interventricular septum (22 ± 4 mm, r=0.70). Width of interventricular septum measured by intracardiac echocardiography at the level of alcohol injection was on average 20 ± 4 mm. The mean grade of systolic anterior motion judged by M-mode and 2-D intracardiac echocardiography was 2.2 ± 0.9. Moderate mitral insufficiency was present in 3 patients (17%).

Ethanol dose injected during the procedure was on average 2.1 ± 0.7 ml. Resting LVOT gradient was reduced from 74 ± 35 mmHg to 8 ± 16 mmHg ($p<0.0001$) at the end of the procedure LVOT gradient after extrasystolic beats or post pacing was reduced from 130 ± 49 mmHg to 34 ± 33 mmHg ($p<0.0001$). In 1 patient the not extremely proximal localization of the ablated area associated with a low reduction of the resting LVOT gradient (20 mmHg), droved the decision of selecting a second more proximal septal branch. The procedure was successful and the reduction of gradient was higher (50mmHg). Peak of creatinekinase-MB and troponine was 161 ± 58 IU and 2.5 ± 1.1 UI.

The ablated area (with ethanol) on planimetry was on average 1.8 ± 0.8 cm2 and correlated with the infarct size detected by delay-enhancement MRI at four days after the procedure (22 ± 7 cc, r=0.80) (Figure 2, 3, 4, 5). In 1 patient intracardiac echocardiography guidance was not performed due to a venous dissection occurred in the attempt of position the venous long sheat. No complications related to the intracardiac echocardiography guidance occurred in the other patients.

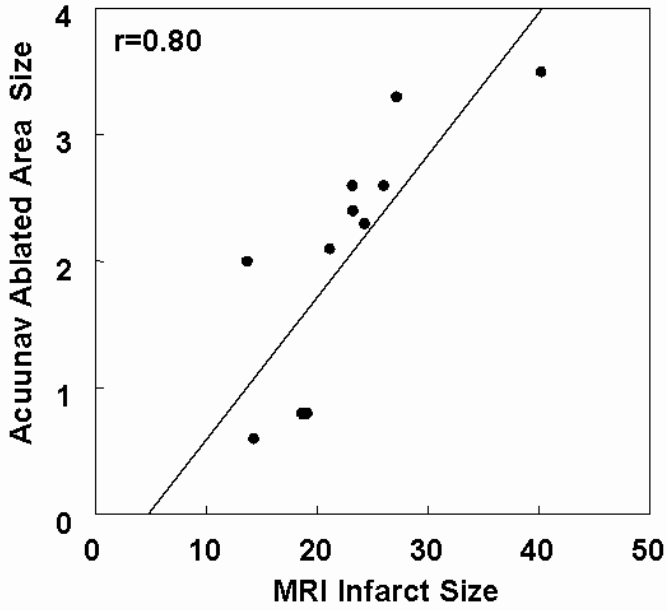

Figure 2. *Relation between the ablated area on planimetry measured by intracardiac echocardiography and the infarct size measured by delay-enhancement MRI.*

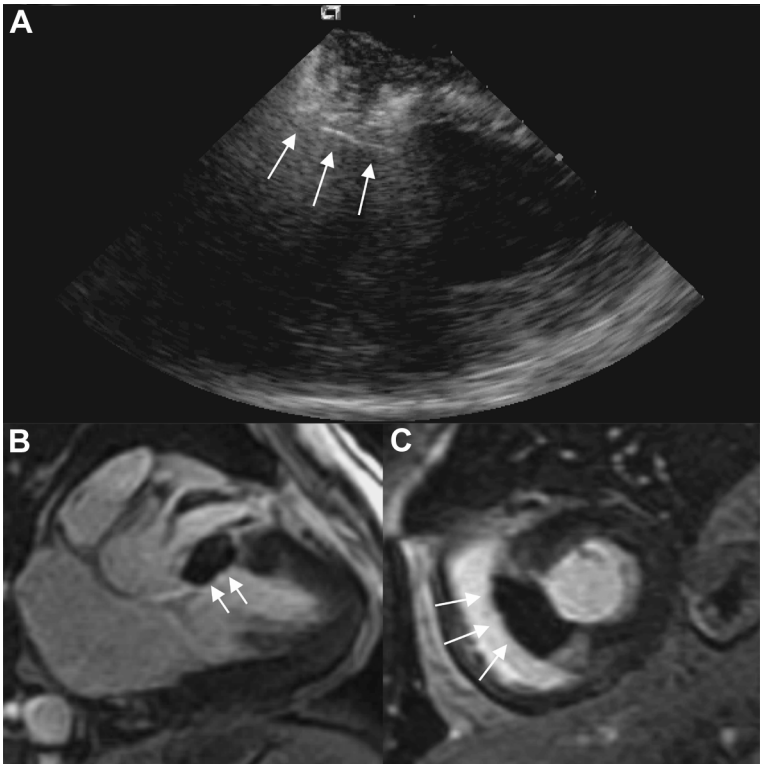

Figure 3. *Extensive ablated area visualized by intracardiac echocardiography during PTSMA (panel A) and corresponding infarct area visualized by delay-enhancement MRI long (panel B) and short axis (panel C).*

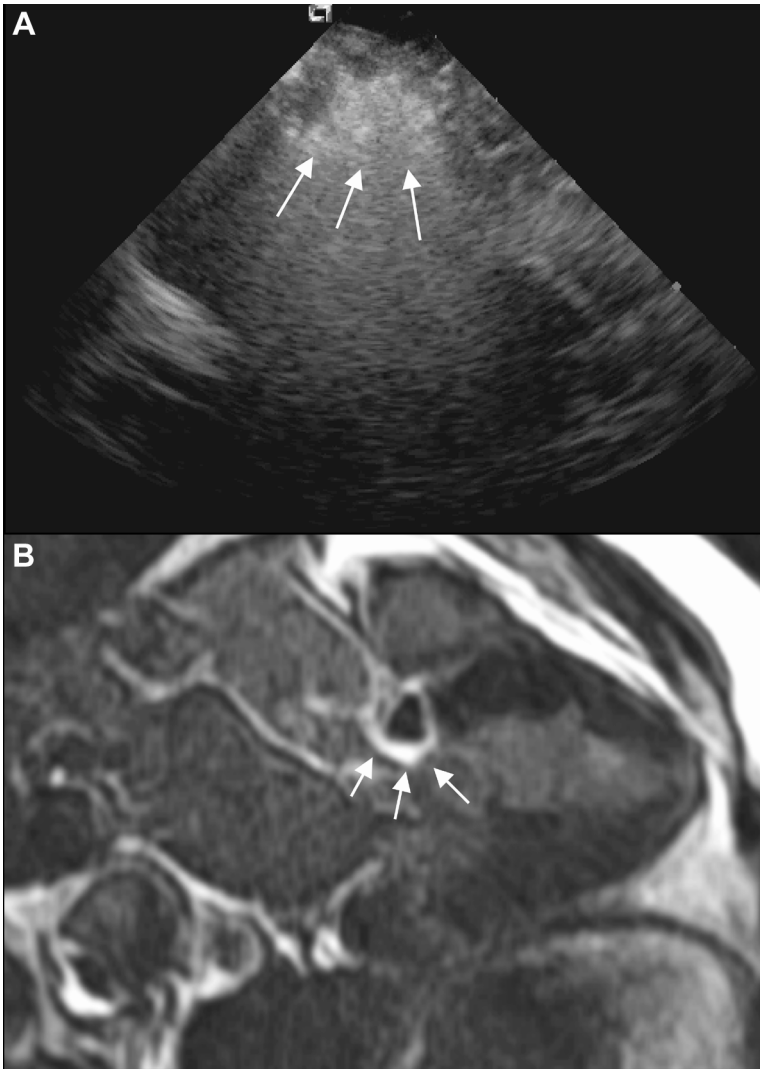

Figure 4. *Triangular shaped ablated area visualized by intracardiac echocardiography during PTSMA (panel A) and corresponding infarct area visualized by MRI long axis (panel B).*

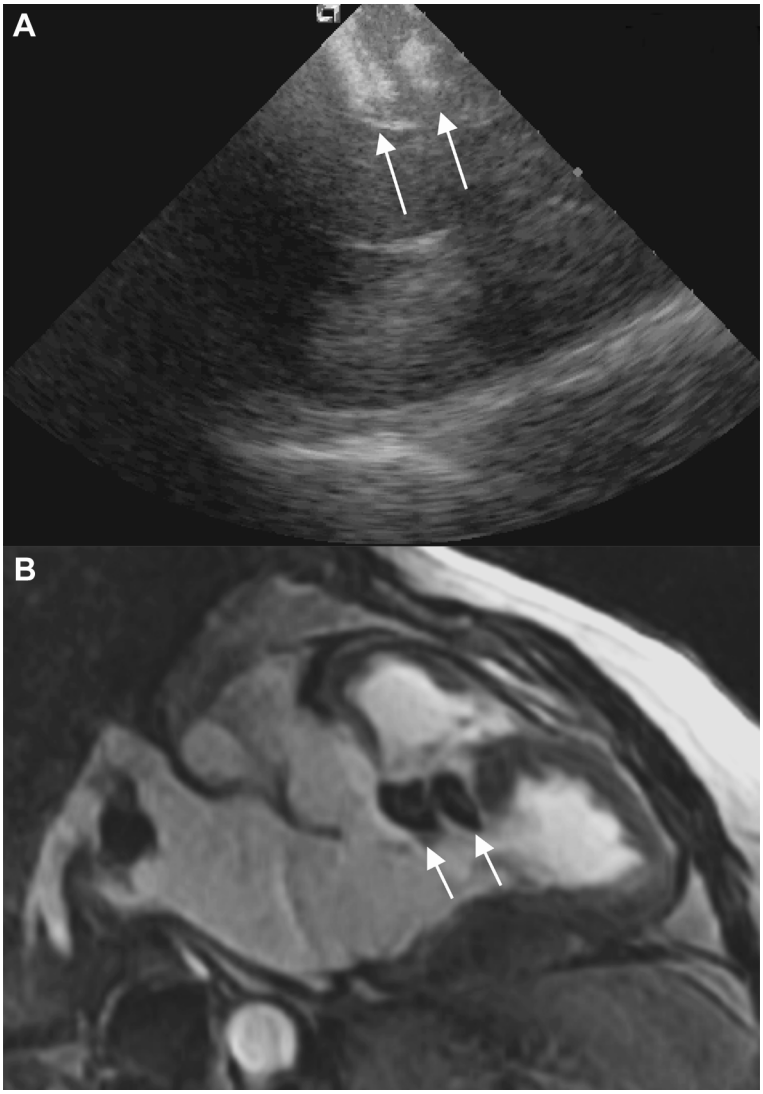

Figure 5. *Ablated area visualized by intracardiac echocardiography and corresponding infarct area visualized by MRI long axis (panel B) in a patients who underwent PTSMA of two septal branches.*

Discussion

Intracardiac echocardiography during PTSMA is a safe imaging technique and can be used to guide ethanol administration during PTSMA in patients with obstructive HCM, particularly in the selection of appropriate septal branch. The planimetric ablated area visualized by intracardiac echocardiography correlates with the infarcted size measured by delay-enhancement MRI at 4 days after the procedure.

Myocardial contrast echocardiography using transthoracic 2-dimensional echocardiography has been shown to be useful in guiding and monitoring PTSMA procedure, with a cumulative impact on the interventional strategy reported in about 15-20%. Moreover, it can be helpful in defining the end of the procedure. An appropriate impregnation of the target region has been reported to represent a possible marker to interrupt the procedure, independently of the hemodynamic result since the remodeling process that lately occurs, plays a role in the reduction of the obstruction (16). A dose of 2.0 ml of ethanol on average has been described to be as safe and efficacious as higher doses (around 4.0 ml) reported during the initial experiences from different centers (16, 17). During an invasive procedure as PTSMA, intracardiac echocardiography could be a complementary tool to transthoracic myocardial contrast echocardiography in guiding the procedure. This technique may be managed in a completely autonomous fashion by the same interventional team and the constant presence of an ehocardiographic machine and/or an additional operator during the entire procedure could be avoided. Moreover, intracardiac echocardiography provides a clear definition of the cardiac structures and a higher resolution of the images compared to the transthoracic approach. It can overcome the major limitations of a 2- D transthoracic imaging approach, including anatomic acoustic barriers (ribs and lungs), obesity, thoracic wall deformity, pulmonary conditions, and the fact that patients are examined in a supine position during PTSMA.

Conclusions

Intracardiac echocardiography can be used to monitor ethanol administration during PTSMA in patients with obstructive HCM, since it provides high quality and continous imaging of the treated segment of the septum during the whole procedure. Moreover, the planimetric ablated area visualized by intracardiac echocardiography can predict the infarcted size measured by delay-enhancement MRI.

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Summary and conclusions

In this thesis multiple echocardiographic approaches and techniques to predict clinical and functional outcome were evaluated.

The value of high-dose dobutamine stress echocardiography for the prediction of long-term cardiac events was evaluated in various clinical settings in patients with known or suspected coronary artery disease. Low-dose dobutamine stress echocardiography and tissue Doppler imaging were used to evaluate myocardial viability and left ventricular remodelling in patients with ischemic cardiomyopathy who underwent myocardial revascularization or percutaneous transplantation of skeletal myoblasts. The value of myocardial contrast echocardiography was studied to predict functional recovery in patients with acute myocardial infarction who underwent primary coronary intervention. Next, resting 2-D echocardiography was used to predict the onset of dilated-hypokinetic evolution and cardiovascular events in patients with hypertrophic cardiomyopathy. Finally, the role of intracardiac echocardiography was investigated for prediction of the infarct area in patients with obstructive hypertrophic cardiomyopathy who underwent percutaneous septal myocardial ablation.

Role of dobutamine stress echocardiography for prediction of cardiac events in patients with known or suspected coronary artery disease.

Dobutamine stress echocardiography has a high accuracy for the detection of coronary artery disease (1). Additionally it provides clinically useful prognostic information, such as resting left ventricular function, myocardial viability, stress-induced ischemia, vascular extent of wall motion abnormalities, and changes of end systolic volume and ejection fraction with stress (Chapter 1). The timing, extent and severity of the stress-induced wall motion abnormalities are important determinants of long-term prognosis. Previous studies have shown the efficay of stress echocardiography in predicting long-term cardiac events in mixed patient groups and the value of this test in selected patient subsets (2-6).

In this thesis specific patient groups were evaluated. The prognostic value of dobutamine stress echocardiography was studied in multiple patient subsets, as described in the Table.

	No. pts	*Males (%)*	*Age*	*End-point*	*Clinical predictors*						*Echocardiographic predictors*		
					Age	Male	Smoking	Hyperten.	HF	Diabetes	Rest WMA	New WMA	Abnormal DSE
General population (Chapter 2)	3381	(67)	61±10	CD/MI	1.03 (1.02-1.04)				1.7 (1.3-2.1)	1.4 (1.1-1.8)	1.06* (1.04-1.09)	1.04* (1.02-1.07)	
Females (Chapter 3)	1172	/	61±12	All mortality	1.10 (1.06-1.14)		2.3 (1.4-3.1)	1.7 (1.1-2.6)	2.7 (1.5-4.7)		1.7 (1.1-1.8)	1.5 (1.1-2.7)	
Elderly (Chapter 4)	1434	(67)	72±3	All mortality	1.06 (1.05-1.08)	1.5 (1.2-1.8)	1.3 (1.1-1.6)	1.2 (1.1-1.4)		1.4 (1.1-1.8)	1.06* (1.06-1.09)	1.3 (1.1-1.6)	
Myocardial ischemia (Chapter 6)	931	(72)	61±12	CD	1.06 (1.04-1.08)	1.8 (1.2-2.7)	1.5 (1.1-2.0)				/	2.1 (1.1-4.1)	
Angina without ischemia (Chapter 7)	2117	(54)	61±13	CD/MI	1.03 (1.02-1.04)	1.6 (1.1-2.2)	1.5 (1.1-2.9)			1.8 (1.2-2.8)	2.6 (1.8-3.8)	/	
High pre-test probability (Chapter 8)	329	(63)	64±10	CD	1.06 (1.03-1.10)	3.2 (1.5-6.7)		1.9 (1.1-3.6)			1.9 (1.1-3.7)	2.5 (1.3-4.8)	
Right bundle branch block (Chapter 10)	163	(80)	64±11	CD/MI	1.04 (1.01-2.08)				2.3 (1.1-5.1)				3.0 (1.2-7.4)
Pacemaker (Chapter 11)	136	(69)	64±12	CD			2.9 (1.2-7.4)			3.1 (1.1-9.6)		4.1 (1.2-14.9)	
Left anterior hemiblock (Chapter 12)	1187	(57)	63±12	CD	1.05 (1.03-1.08)		2.0 (1.3-3.1)		1.8 (1.1-3.3)	1.4 (1.1-2.4)	/	1.8 (1.1-2.9)	

Legend: CD: cardiac death; MI: myocardial infarction; HF: heart failure; WMA: wall motion abnormalities; DSE: dobutamine stress echocardiography.
* per segment.

Clinical predictors of cardiac events:
- As demonstrated in the Table, *age* was an important independent predictor of adverse events. Age had a homogeneous predictive power in the different settings of the population, in particular in females (Chapter 3). However, in patients with a permanent pacemaker (Chapter 11) it was not predictive f cardiac events, probably due to the relatively small size of the study population.
- *Male gender* was another important and constant independent predictor of cardiac events in different patient subsets. In the general population (Chapter 2) male gender was an independent predictor of hard cardiac events (cardiac death and myocardial infarction) in patients with a normal test. Conversely, the outcome of patients with abnormal dobutamine stress echocardiography was related to the severity of left ventricular dysfunction and ischemia on dobutamine stress echocardiography, but not to gender (after adjusting for the other variables). These data indicate that women with abnormal DSE should be treated as aggressively as men considering the clinical and echocardiographic risk profiles since the risk imposed by these parameters was not gender related. In patients with permanent pacemaker (Chapter 11) male gender was not a significant predictor of cardiac events, probably due to the relatively small size of the study population.
- *Smoking* was, in most of the studies in this thesis, an independent predictor of cardiac events, together with the other important risk factors such as s*ystemic hypertension, history of heart failure and diabetes mellitus*.

Echocardiographic predictors of cardiac events:
- *Resting wall motion abnormalities* were in the majority of the described studies, an important independent variable for prediction of clinical outcome. However, resting wall motion abnormalities were not predictive of cardiac events in: 1) patients with myocardial ischemia (where probably this last echocardiographic variable resulted much stronger than resting left ventricular function), 2) in patients with permanent pacemaker (probably due to the small number of patients), and 3) in patients with suspected coronary artery disease where the significance of left anterior hemiblock was investigated (since patients with history of previous myocardial infarction, cardiac pacemaker, pathological Q wave, and complete left or right bundle branch block on baseline electrocardiogram were excluded).
- *New wall motion abnormalities or myocardial ischemia* was the strongest independent predictor of cardiac events substantially in all patient subsets (see Table). In patients with right bundle branch block an abnormal stress echocardiogram was significantly associated with cardiac events.

In the elderly, the presence and the extent of myocardial ischemia during dobutamine stress echocardiography provided incremental information over clinical and resting echocardiographic data to predict all cause of mortality (Chapter 4). However, in not all patients stress echocardiography can be performed due to patient characteristics as a poor acoustic window. This thesis showed that in the elderly, myocardial perfusion imaging using Tc-tetrofosmin SPECT provides incrmental prognostic information on total mortality, cardiac death, and hard cardiac events.

In patients with a left bundle branch block, the diagnosis of coronary artery disease and the prognostic stratification is challenging because of the pre-existent repolarization abnormalities. To elucidate this clinical issue, a meta-analysis (Chapter 9) of the published data on exercise electrocardiography, myocardial perfusion imaging and stress echocardiography for the detection of coronary artery disease and the prediction of cardiac events in patients with a left bundle branch block was performed. Analysis of pooled data showed that the relative risk of cardiac death or myocardial infarction in patients with an

abnormal stress echocardiography and myocardial perfusion imaging was elevated >7-fold but did not differ by imaging modality (p=0.9).

In conclusion, dobutamine stress echocardiography had an incremental prognostic value in various patient subsets, as well as in patients with resting electrocardiographic abnormalities.

In all studies described in this thesis, myocardial ischemia on stress echocardiography was predictive of future cardiac events. This may seem somewhat strange, because, nowadays, with good medical therapy and recent developments in revascularization procedures, one may expect that patients who received a complete treatment have the same prognosis as patients with a normal stress echocardiography. Several factors may cause this apparent discrepancy. First, dobutamine stress echocardiography is a relative new technique, introduced at the Thoraxcenter in 1990, with a systematic and consistent organization. Substantial clinical progress in the treatment of coronary artery disease has occurred during the long follow-up period with possible impact on interpretation of results of this test. Recent trials have demonstrated the benefit of a complete medical therapy with aspirin, beta-blockers, ACE-inhibitors, spironolacton and statins in patients with documented coronary artery disease. The prescription rate of beta-blockers, calcium antagonist, ace-inhibitors and statins in the population studied in this thesis, was relatively low, even in those with myocardial ischemia. Second, not all the patients with myocardial ischemia on dobutamine stress echocardiography underwent coronary revascularization. There may have been good clinical reasons for this; in some patients, coronary anatomy, high age and comorbidities may have limited the possibility of myocardial revascularization. The decision to perform coronary angiography was made on clinical grounds by the treating cardiologist. In general, it seems that dobutamine stress echocardiography was not always used for clinical decision making. Probably the extent of induced ischemia also could be the cause of an inadequate optimization of medical therapy or the detainment from myocardial revascularization. Third, as stated in Chapter 6, it seems that in some patients, symptoms of angina instead of signs of ischemia on dobutamine stress echocardiography were the reason to prescribe betablockers or calcium antagonists and to perform myocardial revascularization. Nevertheless, survival curves for patients with normal and abnormal dobutamine stress echocardiography continued to diverge during the entire follow-up, indicating that the prognostic value of dobutamine stress echocardiography was maintained during follow-up. Last, the natural progression of underlying coronary artery disease may be a cause of the adverse prognosis of patients with ischemia on dobutamine stress echocardiography, even if these patients recieve a complete therapy/coronary revascularization.

Recent advances in technology, such as second harmonic imaging or the use of contrast agents may have resulted in changes in sensitivity and specificity of dobutamine stress echocardiography. Echocardiographic machines equipped with second harmonic imaging were introduced in 1998 in our center, whereas the use of contrast agents for visualization of left ventricular endocardial border was introduced in 1999. These technical changes could have contributed to an improvement in sensitivity and specificity of dobutamine stress echocardiography in predicting cardiac events. Moreover, other new modalities, such as automatic border detection, could further improve the accuracy in detection myocardial ischemia during stress echocardiography, since it is well known that this technique is operator-dependent and high competence and experience are necessary. Despite these limitations, dobutamine stress echocardiography provides unique information (not provided by other non-invasive tests), that may be important for clinical decision making,

From the content of this thesis can be derived that the proper selection of management strategies in patients with suspected or known coronary artery disease should be based on an accurate estimation of the risk of adverse events. Recognition of patients at high risk of cardiac events is an essential step in guiding the use of invasive procedures and selecting patients who are most likely to benefit and thus avoiding the risk and cost of interventions in low risk patients. Dobutamine stress echocardiography is an effective tool for risk stratification in these patients. Patients with normal stress echocardiogram had a low cardiac event rate (1-2%) and can be exempted for invasive procedures. Negative tests confer a high negative predictive value for cardiac events irrespective of clinical risk. Patients with extensive abnormalities in multi-vascular distribution are at a high risk of death and myocardial infarction. In these patients, coronary angiography and subsequent myocardial revascularization may be justified, with additional consideration of symptomatic status, functional capacity and resting left ventricular function.

Myocardial viability detected by low dose dobutamine infusion and tissue Doppler imaging.

The role of myocardial viability in patients with dilated ischemic cardiomyopathy was evaluated by low dose dobutamine stress echocardiography in patients who underwent to different treatments.

In patients who underwent myocardial revascularization (Chapter 13), the relation between viable myocardium and ongoing or reversed remodeling was evaluated. Substantial myocardial viability prevented ongoing left ventricular remodeling after revascularization and was associated with improvement of symptoms and favorable long-term prognosis.

In patients who underwent percutaneous transplantation of skeletal myoblasts (Chapter 14), resting left ventricular function and myocardial viability were evaluated by resting and low dose dobutamine echocardiography and by tissue Doppler imaging examination. During low-dose dobutamine infusion, the peak systolic velocity in the regions of myoblasts injection significantly increased at tissue Doppler imaging examination; left ventricular ejection fraction improved and end-systolic volumes decreased at 1 year. Thus, in these patients, regional and global left ventricular contractile reserve showed a sustained improvement, up to 1 year after treatment.

Myocardial contrast echocardiography.

In patients with acute myocardial infarction, myocardial contrast echocardiography may be useful to assess dysfunctional myocardium after primary percutaneous revascularization and distinguish reversible (myocardial stunning) from irreversible myocardial damage (no-reflow phenomenon). Moreover, several studies demonstrate that myocardial contrast echocardiography can predict the recovery of regional function after primary percutaneous coronary intervention.

In chapter 15 the additional value of end-diastolic myocardial wall thickness was evaluated together with myocardial contrast echocardiography to predict recovery of regional left ventricular function after primary coronary intervention. A relatively simple measurement of end-diastolic myocardial wall thickness, obtained with 2-D echocardiography combined with contrast agent, predicted recovery of regional contractile function. Using end-diastolic myocardial wall thickness alone, dysfunctional segments with an end-diastolic myocardial

wall thickness ≥11 mm showed a high likelihood of recovery of regional contractile function two months after primary coronary intervention. Moreover, it appeared that when at least 50% of the dysfunctional segments showed an EDWT ≥11 mm, global recovery may be anticipated.

The relative merits of myocardial contrast echocardiography and magnetic resonance imaging to predict myocardial function improvement after percutaneous coronary intervention was evaluated in Chapter 16. The sensitivity, specificity and accuracy for the prediction of functional improvement were comparable between myocardial contrast echocardiography, first-pass magnetic resonance imaging, and delayed-enhancement magnetic resonance imaging. Thus, myocardial contrast echocardiography, as bed-side technique, may be an alternative tool in the acute phase of myocardial infarction.

Predictive echocardiography in hypertrophic cardiomyopathy.

The incidence, risk factors and prognosis of dilated-hypokinetic evolution in 222 consecutive patients with hypertrophic cardiomyopathy was evaluated over 11 years in Chapter 17. Patients with prevalent/incident dilated-hypokinetic hypertrophic cardiomyopathy were younger at first evaluation, more often had a family history of hypertrophic cardiomyopathy or sudden death, and showed greater myocardial wall thickness compared with patients who maintained 'classic' hypertrophic cardiomyopathy. Cox proportional hazards regression analysis identified left ventricular wall thickness and end-diastolic diameter both measured by 2-D echocardiography as independent predictors of cardiovascular death.

In patients with obstructive hypertrophic cardiomyopathy who underwent percutaneous septal myocardial ablation, the role of intracardiac echocardiography was evaluated in Chapter 18. This imaging modality was useful in the selection of the appropriate septal branch and in guiding ethanol administration. The planimetric ablated area (with ethanol) visualized by intracardiac echocardiography correlated with the infarct size measured by delay-enhancement magnetic resonance imaging at 4 days after the procedure.

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2 Pingitore A, Picano E, Varga A, Gigli G, Cortigiani L, Previtali M, Minardi G, Colosso MQ, Lowenstein J, Mathias W, Jr., Landi P. Prognostic value of pharmacological stress echocardiography in patients with known or suspected coronary artery disease: a prospective, large-scale, multicenter, head-to-head comparison between dipyridamole and dobutamine test. Echo-Persantine International Cooperative (EPIC) and Echo-Dobutamine International Cooperative (EDIC) Study Groups. J Am Coll Cardiol. 1999;34:1769-77.

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Samenvatting en conclusies

In dit proefschrift werden verschillende echocardiografische benaderingen geëvalueerd om klinisch en functioneel herstel te voorspellen. Eerst werd de prognostische waarde van dobutamine stress echocardiografie geëvalueerd in verschillende klinische situaties bij patiënten met (mogelijk) coronair lijden. Vervolgens werd tissue Doppler imaging, gedurende dobutamine stress echocardiografie uitgevoerd om het korte en lange termijn effect op regionale en globale linker ventrikel functie te evalueren van coronaire revascularizatie en percutaan getransplanteerde skelet myoblasten bij patiënten met ischemisch hartfalen. Verder werd de waarde van myocardiale contrast echocardiografie voor het voorspellen van herstel van functie bij patiënten met een acuut myocard infarct bestudeerd. Vervolgens werd het nut van 2-D echocardiografie onderzocht om het beloop van patiënten met een hypertrofische obstructieve cardiomyopathie te voorspellen. Tenslotte werd de rol van intracardiale echocardiografie bij het uitvoeren van percutane septale myocard ablatie bij patiënten met obstructieve hypertrofische cardiomyopathie onderzocht.

De rol van dobutamine stress echocardiografie voor het voorspellen van cardiale events bij patiënten met (mogelijk) coronair lijden.

Dobutamine stress echocardiografie is een nuttige techniek voor risico stratificatie bij patiënten met (mogelijk) coronair lijden (1). Deze test verschaft klinisch bruikbare prognostische informatie over linker ventrikel functie, myocard vitaliteit, stress geïnduceerde ischemie, uitgebreidheid van myocardischemie, en veranderingen van eindsystolisch volume en ejectie fractie met stress (Hoofdstuk 1). Eerdere studies hebben aangetoond dat stress echocardiografie nuttig is voor het voorspellen van cardiale events op lange termijn (2-6). In dit proefschrift werd de prognostische waarde van deze test in verschillende klinische situaties onderzocht.

	Aantal pat.	*Man (%)*	*Leeftijd*	*Eind-punt*	*Klinische voorspellers*						*Echocardiographic predictors*		
					Leeftijd	Man	Roken	Hypertensie.	HF	Diabetes	Rest WMA	New WMA	Abnormal DSE
Algemene populatie (Hoofdstuk 2)	3381	(67)	61±10	CD/MI	1.03 (1.02-1.04)				1.7 (1.3-2.1)	1.4 (1.1-1.8)	1.06* (1.04-1.09)	1.04* (1.02-1.07)	
Vrouwen (Hoofdstuk 3)	1172	/	61±12	Alle mortaliteit	1.10 (1.06-1.14)		2.3 (1.4-3.1)	1.7 (1.1-2.6)	2.7 (1.5-4.7)		1.7 (1.1-1.8)	1.5 (1.1-2.7)	
Ouderen (Hoofdstuk 4)	1434	(67)	72±3	Alle mortaliteit	1.06 (1.05-1.08)	1.5 (1.2-1.8)	1.3 (1.1-1.6)	1.2 (1.1-1.4)		1.4 (1.1-1.8)	1.06* (1.06-1.09)	1.3 (1.1-1.6)	
Myocardischemie (Hoofdstuk 6)	931	(72)	61±12	CD	1.06 (1.04-1.08)	1.8 (1.2-2.7)	1.5 (1.1-2.0)				/	2.1 (1.1-4.1)	
Angina zonder ischemie (Hoofdstuk 7)	2117	(54)	61±13	CD/MI	1.03 (1.02-1.04)	1.6 (1.1-2.2)	1.5 (1.1-2.9)			1.8 (1.2-2.8)	2.6 (1.8-3.8)	/	
Hoge vooraf kans (Hoofdstuk 8)	329	(63)	64±10	CD	1.06 (1.03-1.10)	3.2 (1.5-6.7)		1.9 (1.1-3.6)			1.9 (1.1-3.7)	2.5 (1.3-4.8)	
Rechter bundeltak block (Hoofdstuk 10)	163	(80)	64±11	CD/MI	1.04 (1.01-2.08)				2.3 (1.1-5.1)				3.0 (1.2-7.4)
Pacemaker (Hoofdstuk 11)	136	(69)	64±12	CD			2.9 (1.2-7.4)			3.1 (1.1-9.6)		4.1 (1.2-14.9)	
Linker anterior hemiblock (Hoofdstuk 12)	1187	(57)	63±12	CD	1.05 (1.03-1.08)		2.0 (1.3-3.1)		1.8 (1.1-3.3)	1.4 (1.1-2.4)	/	1.8 (1.1-2.9)	

Legenda: CD: cardiale dood; MI: myocard infarct; HF: hart falen; WMA: wandbewegingsstoornissen; DSE: dobutamine stress echocardiografie.

- per segment.

Klinische voorspellers van cardiale events:
- Zoals wordt getoond in de Tabel, was *leeftijd* een belangrijke voorspeller van cardiale events. Leeftijd had een homogene voorspellende kracht in verschillende groepen, vooral bij vrouwen (Hoofdstuk 3). Echter bij patiënten met een permanente pacemaker (Hoofdstuk 11) was leeftijd geen voorspeller van cardiale events, waarschijnlijk door de relatief kleine studie groep.
- *Mannelijk geslacht* was een andere belangrijke en constante onafhankelijke voorspeller van cardiale events bij verschillende patiënt groepen. In de algemene populatie (Hoofdstuk 2) was mannelijk geslacht een onafhankelijke voorspeller van harde cardiale events (cardiale sterfte en myocard infarct) bij patiënten met een normale test. De prognose van patiënten met een abnormale dobutamine stress echocardiografie was echter gerelateerd aan de Ernst van de linker ventrikel dysfunctie en ischemie volgens dobutamine stress echocardiografie, maar niet gerelateerd aan het geslacht (na correctie van andere factoren). Deze gegevens tonen aan dat vrouwen met een abnormale DSE net zo voortvarend behandeld moeten worden als mannen, omdat het risico op cardiale events niet geslacht gerelateerd was. Bij patiënten met een permanente pacemaker (Hoofdstuk 11) was mannelijk geslacht geen significante voorspeller van cardiale events, waarschijnlijk door de relatief kleine studie groep.
- *Roken* was, in de meeste studies in dit proefschrift, een onafhankelijke voorspeller van cardiale events, samen met andere belangrijke risicofactoren zoals *hypertensie, hartfalen en diabetes mellitus*.

Echocardiografische voorspellers van cardiale events:
- *Wandbewegingsstoornissen in rust* waren in de meeste studies een belangrijke onafhankelijke variabele om de prognose te voorspellen. Echter, wandbewegingsstoornissen in rust waren geen voorspeller van cardiale events bij: 1) patiënten met myocard ischemie (waar deze laatste variabele waarschijnlijk een veel sterkere voorspeller is dan linker ventrikel functie in rust), 2) patiënten met een permanente pacemaker (waarschijnlijk door de relatief kleine studie groep), en 3) bij patiënten met (mogelijk) coronairlijden, waar de invloed van een linker anterior hemiblock werd onderzocht.
- *Nieuwe wandbewegingsstoornissen of myocard ischemie* was de sterkste onafhankelijke voorspeller van cardiale events in vrijwel alle patiënt groepen (zie Tabel), ook bij patiënten met een rechter bundeltak block en ouderen (Hoofdstuk 4). Bij ouderen bij wie een echo niet goed mogelijk is kan ook een myocard perfusie scan met Tc-tetrofosmin SPECT worden verricht om cardiale events te voorspellen.

Bij patiënten met een linker bundeltak block kan de diagnose van coronairlijden en het inschatten van de prognose een uitdaging vormen, door de aanwezigheid van preëxistente repolarizatie stoornissen. Om dit klinische vraagstuk te verhelderen werd een meta-analyse verricht (Hoofdstuk 9) van de gepubliceerde data betreffende inspanningselektrocardiografie, myocard perfusie scintigrafie en stress echocardiografie voor het vaststellen van coronair lijden en het voorspellen van cardiale events bij patiënten met een linker bundeltak block. Analyse van verzamelde gegevens toonde dat het risico op cardiale sterfte of een myocard infarct > 7 keer verhoogd was bij patiënten met een abnormale stress echo of myocard perfusie onderzoek, dit verschilde niet voor beide afbeeldende onderzoeken (p=0.9).

In conclusie heeft dobutamine stress echocardiografie een toegevoegde prognostische waarde bij verschillende patiënt groepen, ook bij patiënten met preëxistente afwijkingen op het electrocardiogram in rust.

In alle studies beschreven in dit proefschrift, was myocard ischemie bij stress echocardiografie voorspellende voor toekomstige cardiale events. Dit kan wellicht vreemd lijken, omdat, tegenwoordig, met een goede behandeling met medicijnen en recente

ontwikkelingen op het gebied van coronaire revascularizatie, men misschien verwacht dat patiënten die een complete behandeling krijgen dezelfde prognose hebben als patiënten met een normale stress echo. Verschillende factoren kunnen deze schijnbare discrepantie veroorzaken. Ten eerste is dobutamine stress echocardiografie een betrekkelijk nieuwe techniek, geïntroduceerd in het Thoraxcentrum in 1990, met een systematische en consistente organisatie. Substantiële klinische vooruitgang in de behandeling van coronair lijden heeft er plaats gevonden gedurende de lange termijn follow-up, met een mogelijke invloed op de interpretatie van de resultaten van de onderzoeken. Recente trials hebben het voordeel van een volledige behandeling met medicijnen zoals aspirine, beta-blockers, ACE-remmers, spironolacton en statines bij patiënten met coronair lijden. De populatie bestudeerd in dit proefschrift kreeg betrekkelijk weinig beta-blockers, calcium antagonisten, ace-remmers en statines voorgeschreven, zelfs bij patiënten met myocard ischemie. Ten tweede, ondergingen niet alle patiënten met myocard ischemie bij dobutamine stress echocardiografie coronaire revascularizatie. Er kunnen hiervoor goede klinische redenen geweest zijn; bij sommige patiënten kan de coronaire anatomie, hoge leeftijd en co-morbiditeit de mogelijkheden tot coronaire revascularizatie beperkt hebben. De beslissing om coronair angiografie te doen was gebaseerd op klinische gronden, door de behandelend cardioloog. In het algemeen lijkt het dat dobutamine stress echocardiografie niet altijd gebruikt werd om tot een klinische afweging te komen. Ten derde, zoals beschreven in hoofdstuk 6, lijkt het dat bij sommige patiënten symptomen van angina pectoris in plaats van tekenen van ischemie op dobutamine stress echocardiografie de reden waren om beta blockers of calcium antagonisten voor te schrijven en revascularizatie te verrichten. Desalniettemin, liepen de overlevingscurven van patiënten met een normale en abnormale dobutamine stress echo uit elkaar gedurende de gehele follow-up, dit geeft aan dat de prognostische waarde van dobutamine stress echocardiografie behouden bleef gedurende de follow-up. Tenslotte kan het natuurlijk beloop van de onderliggende coronair4 hartziekte een reden zijn voor de slechtere prognose van patiënten met ischemie bij dobutamine stress echocardiografie, zelfs als deze patiënten een volledige behandeling met medicijnen/ coronaire revascularizatie ondergingen.

Recente ontwikkelingen in technologie, zoals second harmonic imaging of het gebruik van contrast middelen kan geresulteerd hebben in veranderingen van sensitiviteit en specificiteit van dobutamine stress echocardiografie. Echocardiografie apparatuur met second harmonic imaging werden geïntroduceerd in 1998 in ons centrum, terwijl het gebruik van contrast voor het visualiseren van de linker ventrikel endocardiale grens werd geïntroduceerd in 1999. Deze technische ontwikkelingen kunnen hebben bijgedragen aan de verbetering van sensitiviteit en specificiteit van dobutamine stress echocardiografie voor het voorspellen van cardiale events. Bovendien kunnen andere technieken zoals automatische endocardiale grens detectie de precisie van stress echocardiografie verder verbeteren, omdat het bekend is dat deze techniek afhankelijk is van degene die de test uitvoert en dat een hoge vakbekwaamheid en ervaring nodig zijn. Ondanks deze beperkingen, verschaft dobutamine stress echocardiografie unieke informatie die belangrijk kan zijn bij het nemen van klinische beslissingen.

Uit de inhoud van dit proefschrift kan afgeleid worden dat het kiezen van de juiste behandeling bij patiënten met (mogelijk) coronair lijden gebaseerd zou moeten zijn op een nauwkeurige schatting van het risico op cardiale events. Het herkennen van hoogrisico patiënten is een essentiële stap in het nemen van beslissingen omtrent het gebruik van invasieve procedures en het selecteren van patiënten die naar alle waarschijnlijk baat zullen hebben bij deze procedures, en zo risico's en kosten te mijden bij patiënten met een laag risico. Dobutamine stress echocardiografie is een effectieve test voor risico stratificatie bij

deze patiënten. Patiënten met een normale stress echocardiogram hadden een lage cardiale event rate (1-2%) en hoeven geen invasieve procedures te ondergaan. Een negatieve test heft een hoge negatief voorspellende waarde voor cardiale events. Patiënten met uitgebreide afwijkingen in het gebied van meerdere coronairen hebben een hoog risico voor sterfte en myocard infarct. Bij deze patiënten kan een coronair angiografie en revascularizatie gerechtvaardigd zijn, na evalueren van symptomen, functionele capaciteit en linker ventrikel functie in rust.

Myocard vitaliteit gedetecteerd met lage dosis dobutamine infusie en tissue Doppler imaging.

De rol van myocardvitaliteit bij het proces van linker ventrikel remodeling na revascularizatie werd geëvalueerd bij een grote groep patiënten met ischemische cardiomyopathy in Hoofdstuk 13. Het aantal vitale segmenten was de enige voorspeller voor linker ventrikel remodeling. De kans op remodeling nam af als het aantal vitale segmenten steeg. Bij patiënten met ischemische cardiomyopathie, voorkomt de aanwezigheid van een substantiële hoeveelheid dysfunctioneel maar vitaal myocardweefsel het proces van linker ventrikel remodeling na revascularizatie en is tevens geassocieerd met een verbetering van hartfalen symptomen en een betere prognose.

In Hoofdstuk 14 wordt het korte en lange termijn effect op regionale en globale linker ventrikel functie van percutaan ge transplanteerde skelet myoblasten bij patiënten met ischemisch hartfalen geëvalueerd met 2-dimensionale echocardiografie en tissue Doppler imaging. Gedurende lage dosis dobutamine infusie nam de maximale systolische snelheid in de regio's waar myoblasten waren geïnjecteerd significant toe gemeten met tissue Doppler imaging; de linker ventrikel ejectie fractie verbeterde en de eind-systolische volumes namen af na 1 jaar. Dus bij deze patiënten verbeterde de regionale en globale linker ventrikel contractiele reserve gedurende de follow-up. Het effect was ook nog na een jaar follow-up detecteerbaar.

Myocardiale contrast echocardiografie.

Bij patiënten met een acuut myocard infarct is het gebruik van myocardiale contrast echocardiografie nuttig om een onderscheid te maken tussen reversibele myocard dysfunctie (myocardial stunning) en irreversibele myocardiale beschadiging (no-reflow fenomeen). In Hoofdstuk 15 werd de toegevoegde waarde van het meten van de eind-diastolische myocardiale wanddikte bepaald om herstel van regionale contractiliteit van de linker ventrikel te voorspellen na primaire coronaire revascularizatie. Segmenten met een eind-diastolische wanddikte ≥11mm met een intacte perfusie hebben de grootste kans op herstel, segmenten met een eind-diastolische wanddikte <11mm en intacte perfusie hebben een gemiddelde kans op herstel. Segmenten met een eind-diastolische wanddikte <11mm zonder perfusie hebben een lage kans op herstel.

De waarde van myocardiale contrast echocardiografie and magnetische resonantie onderzoek om verbetering van myocardfunctie te voorspellen na een percutane coronaire interventie werd geëvalueerd in Hoofdstuk 16. De sensitiviteit, specificiteit and accuratesse voor het voorspellen van verbetering van functie was vergelijkbaar voor myocardiale contrast echocardiografie, first-pass magnetische resonantie onderzoek en delayed-enhancement magnetische resonantie onderzoek. Dus myocardiale contrast echocardiografie en magnetische resonantie onderzoek kunnen nuttig zijn bij het voorspellen van verbetering van

myocard functie na primaire percutane interventies. Myocardiale contrast echocardiografie heeft een vergelijkbare accuratesse als magnetische resonantie onderzoek en kan een alternatief zijn voor deze techniek omdat het aan het ziekbed verricht kan worden in de acute fase na een myocard infarct.

Voorspellende echocardiografie bij hypertrofische cardiomyopathie.

De incidentie, risico factoren en prognose van gedilateerde-hypokinetische evolutie werd onderzocht bij 222 opeenvolgende patiënten met hypertrofische cardiomyopathie gedurende een follow-up van 11 jaar (Hoofdstuk 17). Patiënten met gedilateerde-hypokinetische hypertrofische cardiomyopathie waren gemiddeld jonger, hadden vaker een positieve familie anamnese voor hypertrofische cardiomyopathie of plotselinge sterfgevallen, en hadden een grotere myocardiale wanddikte dan patiënten met een "klassieke" hypertrofische cardiomyopathie. Cox proportional hazards regression analyse toonde dat de linker ventrikel wanddikte en de einddiastolische diameter (beiden gemeten met 2-D echocardiografie), beiden onafhankelijke voorspellers waren van cardiovasculaire sterfte.

De rol van intracardiale echocardiografie gedurende percutane septale myocard ablatie bij patiënten met obstructieve hypertrofische cardiomyopathie werd geëvalueerd in Hoofdstuk 18. Deze onderzoekstechniek is veilig en nuttig om ethanol toediening te leiden, vooral om de juiste septale tak te selecteren. Het ablatie gebied (met ethanol) dat gevisualiseerd werd met intracardiale echocardiografie correleerde goed met metingen van het infarct gebied vastgesteld met delay-enhancement magnetische resonantie onderzoek, 4 dagen na de procedure.

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Curriculum Vitae

Elena Biagini

Date of birth: 10 September 1973
Place of birth: Cesena, Italy

Education and Professional Experience

1992	High school Diploma at Liceo Classico "Vincenzo Monti" in Cesena, Italy.
1992-1998	Graduated from the School of Medicine and Surgery from the University of Bologna, Italy, *Summa cum laude*. Title of the thesis: "Infective endocarditis in hypertrophic cardiomyopathy: prevalence, incidence, and indications for antibiotic prophylaxis". (Circulation. 1999;99:2132-2137).
1998	Clinical Fellow at the Royal Brompton Hospital in London, United Kingdom (Prof. Poole Wilson).
	General practitioner.
1999-2003	School of Specialization in Cardiology, University of Bologna, Italy. Master's degree in Cardiology, *Summa cum laude*.
2003-2005	Research Fellow at the Thoraxcenter, Department of Cardiology, Erasmus MC, Rotterdam, The Netherlands.

Since January 2004 Doctorate candidate in "Pathophysiology of Heart Failure" at the University of Bologna, Italy.

Awards:

Italian Society of Cardiology 2002 (SIC, Rome): Finalist in Young Investigators' awards

European Society of Cardiology 2004 (ESC, Munich): Finalist in Young Investigators' awards in Clinical Science

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Imaging to Predict Improvement of Myocardial Function after Coronary Intervention. Submitted.

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ABSTRACTS

1. Prognosis of patients having silent versus symptomatic myocardial ischaemia during dobutamine stress echocardiography. **Biagini E**, Rizzello V, Elhendy A, Schinkel AFL, Bax JJ, Bountioukos M, van Domburg RT, Poldermans D. *ESC* 2003.

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