Clinical Stress Echocardiography

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Clinical Stress Echocardiography

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Thesis

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CONTENTS

PREFACE

Two-dimensional echocardiography is a commonly used non-invasive method for the assessment of left ventricular function. It provides precise information on both global and segmental myocardial function by displaying endocardial motion and wall thickening.

Dobutamine stress echocardiography (DSE) is currently the leading non-invasive imaging technique for the diagnosis and prognosis of coronary artery disease (CAD), the documentation of myocardial viability and for long-term risk stratification [1]. The term clinical stress echocardiography is starting to be applied as DSE is used in different clinical settings.

Outline of the Thesis

Part 1: Improving Accuracy

Dobutamine stress echocardiography is widely used for the diagnosis of coronary artery disease and the detection of myocardial viability. However assessment of endocardial motion and wall thickening from two-dimensional echocardiography images largely depends on image quality and is both subjective, and qualitative [2]. This may result in interobserver variability. Moreover the sensitivity of DSE for detecting CAD ranges from 81% to 85% with a similar specificity range. These values are less in the presence of single vessel disease [2]. Nevertheless they are similar to single-proton emission tomography (SPECT) and the other non-invasive stress imaging modalities for both the detection of myocardial ischemia and viability [2-7].

Therefore effort should focus either on the development of more sophisticated quantitative techniques or on the improvement of the existing methodology. These should take into account several criteria and should aim at an increase in sensitivity without loss in specificity [8].

Chapter 1 of this thesis is an experimental paper. As part of a muticenter study DSE data from several centres were used to design a coupled-contour and robust fusion technique for an objective assessment of myocardial wall motion abnormalities.

Cardiac ultrasound is a reflection technique. In addition to the fast motion of the heart, respiratory interferences pose additional problems in the analysis [9]. The above mentioned technique takes into account several parameters such as the shape and the motion of both the endocardium and epicardium, providing important information on both excursion and myocardial thickening [8] [9] [10]. Preliminary data have shown maintained sensitivity and increased specificity for the detection of CAD and reduced inter- and intra-observer variability of DSE. It is the first robust automatic coupled-contour myocardial tracking technique that utilizes the thickening of the myocardium during systole.

In Chapter 2 we estimated, in 200 patients, the additional diagnostic value of new or worsening wall motion abnormalities (NWMA) during the recovery phase of DSE after receiving acute

beta-blockade compared to findings at peak and using coronary angiography as reference. One limitation of DSE is the modest sensitivity in patients with single vessel CAD. The assessment of wall motion abnormalities during the recovery phase after acute beta blockade improves the sensitivity of DSE particularly in patients with single vessel CAD. Sensitivity in this subgroup increased significantly from 81% to 99% ($p<0.001$) while specificity was marginally decreased. There was also a prolonged ischemic effect of dobutamine during the recovery phase. So observation and scoring of individual segments at recovery phase, as part of the regular DSE scoring, in patients that receive acute beta-blockade at peak stress, could add to the better assessment of ischemia in CAD patients.

Chapter 3 further evaluates the recovery phase of DSE after acute beta-blocker administration at peak stress, in the setting of myocardial viability estimation and using dual-isotope single photon emission tomography (DISA-SPECT) as reference. We studied 49 consecutive patients with ejection fraction (LVEF) ≤35%. Patients with ≥4 viable segments were considered viable and radionuclide LVEF was performed prior and twelve months after revascularization. It is known that myocardial viability assessment in severely dysfunctional segments by dobutamine echocardiography (DSE) is less sensitive than nuclear scanning. However we demonstrate that the recovery phase of DSE has an increased sensitivity for viability estimation compared to low-high dose DSE. The sensitivity at low-high DSE for viability estimation was 72% (95% CI 68% to 76%) and specificity 74% (95% CI 72% to 76%). When recovery images were also analyzed the sensitivity for viability estimation increased to 85% (95% CI 81% to 89%), while specificity remained unchanged. Moreover multivariate regression analysis showed that, DSE with recovery phase was the only independent predictor of ≥ 5% LVEF improvement after revascularization. Therefore the assessment of myocardial viability by DSE in patients with coronary artery disease has improved sensitivity when scoring of individual segments at recovery phase becomes an integral part of the regular DSE scoring.

Part 2: Prediction of Outcome and Risk Stratification

The safety, accuracy and feasibility of DSE have well been established [1]. Several studies have demonstrated the high predictive value of DSE for long-term cardiac events in a large group of patients [11-13]. However the role of the recovery phase of DSE is underestimated and its value in long term prognosis of patients is yet to be determined.

Moreover the risk stratification in patients undergoing vascular surgery according to their myocardial viability status or the role of DSE according to the entire strata of renal function needs to be clarified.

In Chapter 4 we assess the prognostic value of wall motion abnormalities (WMA) during recovery phase of dobutamine stress echocardiography (DSE) in addition to WMA at peak stress, in 187 consecutive patients for a mean follow up of 36 (± 28) months. Observation and scoring of individual segments at recovery phase, as part of the regular DSE scoring, improve the assessment of myocardial ischemia in CAD patients. The presence of myocardial ischemia (NWMA) during recovery phase was the only independent DSE predictor of late cardiac events

and has an incremental value when added to ischemia at peak. Patients that exhibited ischemic response only in the recovery phase and after acute beta-blockade had a delayed event than those that presented ischemia at peak.

In Chapter 5 we developed, a quantitative prognostic model for HF patients scheduled for surgery using wall motion patterns during dobutamine stress echocardiography (DSE) in 295 consecutive patients with ejection fraction <35%. Cardiac death and myocardial infarction were noted perioperatively and during 5 year follow-up. We demonstrated that DSE provides an accurate risk stratification of HF patients undergoing vascular surgery. Therefore by utilizing DSE we further stratified those patients with resting LV dysfunction, according to their viability profile. Sustained improvement during DSE provided a protective effect in both early perioperative period and long-term cardiac events. On the contrary ischemia proved to be hazardous in both early and long-term follow up periods.

In Chapter 6 we assessed the prognostic value of renal function relative to DSE findings in 2292 patients with known or suspected CAD, that were followed for a mean of 8 years. Ischemia during DSE is an independent predictor of mortality and hard cardiac events among the entire strata of renal function. The degree of renal dysfunction is an additional determinant of survival and hard events among patients with normal DSE as well as those with presence and severity of wall motion abnormalities. The low risk period after a normal DSE is determined by the presence and the severity of renal dysfunction.

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Automated Coupled-Contour and Robust Myocardium Tracking in Stress Echocardiography

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CHAPTER 1

Automated Coupled-Contour and Robust Myocardium Tracking in Stress Echocardiography

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Abstract

Dobutamine stress echocardiography is a commonly used imaging modality for the diagnosis of coronary artery disease and the detection of myocardial viability. The major limitations are that it is operator dependent and that the analysis is subjective and qualitative resulting in interobserver variability. It is also tedious and time consuming. Consequently, several quantitative approaches have been proposed, such as acoustic quantification and color kinesis but none of these has proved to be fully quantitative. In this manuscript we describe the development of a new, quantitative technique based on tracking of both endocardium and epicardium providing information of endocardial excursion and myocardial thickening, a crucial parameter of wall function evaluation. Preliminary data indicate that the method is practical and feasible, but clinical trials are required to prove whether it will improve the sensitivity and specificity of dobutamine stress echocardiography.

Key words: dobutamine stress echocardiography, subjective, quantitative techniques, myocardial thickening.

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Introduction

Two-dimensional echocardiography is a commonly used non-invasive method for the assessment of left ventricular function. It provides precise information on both global and segmental myocardial function by displaying endocardial motion and wall thickening.

Dobutamine stress echocardiography (DSE) is currently the leading non-invasive imaging technique for the diagnosis and prognosis of coronary artery disease (CAD), the documentation of myocardial viability and for long-term risk stratification [1].

However assessment of endocardial motion and wall thickening from two-dimensional echocardiography images largely depends on image quality and is both subjective, and qualitative [2]. This may result in interpretation variability.

Medical Background

Current limitations of Dobutamine Stress Echocardiography

The sensitivity of DSE for detecting CAD ranges from 81% to 85% with a similar specificity range. These values are less in the presence of single vessel disease [2]. Nevertheless they are similar to single-proton emission tomography (SPECT) and the other non-invasive stress imaging modalities for both the detection of myocardial ischemia and viability (table 1) [2-7].

The subjective regional wall motion scoring system in DSE is based on using a five point score (1= normokinesis; 2= mild hypokinesis; 3= moderate or severe hypokinesis; 4= akinesis; and 5= dyskinesis), dividing the left ventricle (LV) in 17 segments according to the recommendations

Table 1: Comparison of sensitivities and specificities of different stress imaging modalities in detecting CAD (table 1A) or myocardial viability (table 1B). Concluding results from meta-analyses [1] [3-7].

Table 1A	Ischemia detection			
	DSE	SPECT	CMR	PET
Sensitivity	80-85%	83-95%	84-91%	93%
Specificity	82%	73%	80%	82%

Table 1B	Viability Estimation			
	DSE	SPECT	CMR	PET
Sensitivity	84%	84%	96%	100%
Specificity	81%	54-69%	86-100%	90%

DSE: dobutamine stress echocardiography
SPECT: single-photon emission computed tomography
CMR: cardiac magnetic resonance
PET: positron emission tomography

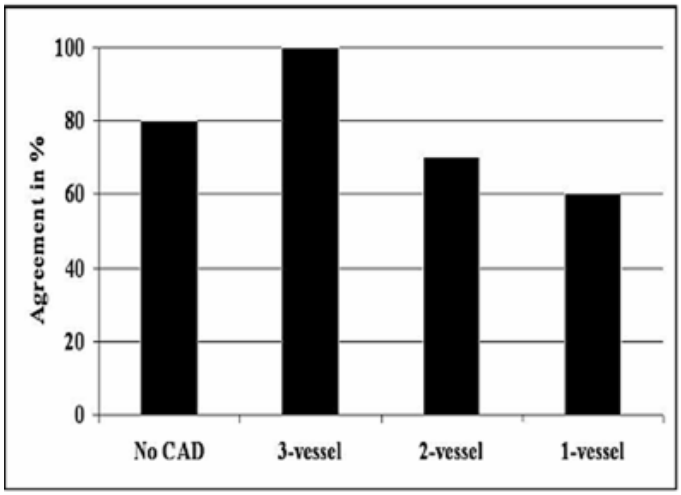

Figure 1: Interinstitutional agreement on stress echocardiography for different degrees of coronary artery disease [10].

of the American Society of Echocardiography [2] [8] [9]. A test is considered positive if new wall motion abnormalities occur (i.e., if wall motion in any segment worsens by 1 grade during testing, with the exception of akinesis becoming dyskinesis) [2] [8] [9].

However currently, DSE is an experience dependent technique subject to a high degree of inter- and intra- observer variability. Signal dropout can be the cause of suboptimal images and even lead to misdiagnosis in some patients. The majority of studies that support its use are mainly derived from expert centres [10] and show the higher agreement for detection of three-vessel disease (figure 1). Limitations occur in the performance of the test in less expert hands, as the results obtained by stress echocardiograms result from subjective interpretation of wall motion[11] (table 2). Furthermore analysis of DSE data is tedious and time consuming.

Quantitative techniques

Quantitative techniques have been developed to provide objective quantitative and reproducible information on global cardiac and regional wall function during stress [1] [2] [11-15].

The most important are: (1) image enhancement techniques including second harmonic imaging, endocardial border enhancement by transpulmonary contrast agents (Albunex, Laevo-

Table 2: Stress echocardiography limitations

- Depends on image quality (patient habitus / system requirements)
- Subjective interpretation
- Interobserver variability
- Lower diagnostic accuracy of single vessel CAD
- Follow-up difficult

Table 3 : Criteria for an improved quantitative methodology to stress echocardiography

- Consider the thickening of myocardium
- Tracking both endo- and epi-cardium
- Feasibility/Reproducibility/Reliability of the performance of the algorithm used
- Low inter-observer variability
- Independence from heart rate and translational and rotational motion of heart
- High sensitivity without loss in specificity
- Reference values suitable for most candidates

vist, BY 963) for improving cavity delineation and three-dimensional imaging with or without contrast agents and (2) analytic software improvement, such as automatic contour techniques (acoustic quantification, colour kinesis) and calculation techniques such as tissue Doppler myocardial velocity derived parameters for analysis [1] [12] [15].

They provide better image quality and hence allow a more accurate analysis resulting in less interobserver variability. However none of these methods takes into account the thickening of the myocardium.

Color kinesis requires good to excellent 2D-image quality for tracking of the endocardium, and encodes translational and rotational motion of the heart as endocardial motion. Its accuracy is also affected by tachycardia and arrhythmias including atrial fibrillation and frequent ectopic beats [11] [12].

Endocardial tracking based on tissue Doppler technique is a semi-quantitative technique that can be used for the estimation of global ventricular function but has limitations in the presence of regional wall motion abnormalities mainly because of low temporal resolution [12-14].

Consequently the development of more sophisticated quantitative techniques is needed. These should take into account several criteria and should aim at an increase in sensitivity without loss in specificity [11] (Table 3). Cardiac ultrasound is a reflection technique. In addition to the fast motion of the heart, respiratory interferences pose additional problems in the analysis [17]. A new quantitative technique ideally should take into account several parameters such as the shape and the motion of both the endocardium and epicardium, providing important information on myocardial thickening [11] [15] [17].

Automated coupled-contour and robust myocardium tracking

Coupled-contour and robust fusion for myocardial tracking is a newly developed analytic software that aims to provide automated on-line quantitative data from images obtained in the setting of DSE. It is designed to track both myocardial layers (i.e. epi- and endocardium) and uses both excursion and thickening of the myocardium to detect wall function abnormalities. Early automated contour detection techniques tracked only the endocardium in high-quality images off-line [18].

Preliminary data have shown an at least maintained sensitivity and increased specificity for the detection of CAD. In a few preliminary clinical data standard DSE had a sensitivity of 88% and

specificity 75%. When the automated on-line system was used, sensitivity was greater than 80% (p: non-significant), for 80% specificity ($p > 0.01$). These findings are comparable with the current DSE data, however, potentially there are improvements to be expected as the system is less dependent on the quality of the images obtained. Furthermore, while not a true speckle tracking system, the system uses optical flow, and is capable of measuring rotation [16][19] [21].

Technical considerations for quantitative wall assessment

The new software automatically classifies the myocardial segments as normal or abnormal based on the endocardial excursion and thickening. This process consists of three steps: detection, tracking, and feature extraction and classification [17] [19] (figure 2).

Step1: Detection by Database-Guided Segmentation

The first step is the identification of the endocardium (figure 3). The application is based on learned pattern recognition of several shape models. In general there are several different shape models [17] [19] (figure 4).This is done using a technique called Database-Guided Segmentation [17] [19]. As the name implies, segmentation is guided by a database of cases which attempts to "teach" the system how to detect and segment a border. This is done by first creating a large database of cases which represent the wide variety of patients and diseases types typically tested in coronary artery disease. Each of these cases is then contoured by one or more experts, giving the basis of "learning" to the system. The learning set of the described system is based on data from 345 DSE tests delivered from several centres, scored in Erasmus MC, Rotterdam, The Netherlands. Each segment has a score 1-5 (1=normal, 2=hypokinetic, 3=akinetic, 4=dyskinetic, 5=aneurysmal). From this data-base and domain knowledge of the individual LV contours, a reference set of LV shapes is created. Each reference shape may be the result of averaging shapes of many studies and is referred to as the "learning set". These shapes are subsequently used for matching and recognition of LV contours and shapes during a DSE study [17] [19] [22].

Step 2: Tracking by Robust Information Fusion

The second step of the process is to track the border. This is called Robust Information Fusion [17] [19], and uses learned motion models of the heart to track the endocardium throughout the heart cycle. That is, once the endocardial border is identified in one frame, it needs to be tracked to all of the other frames in the heart. This is done by first recognizing that the specific location of the endocardium as identified by the system has some level of uncertainty (figure 5). These measurement uncertainties stem for the echocardiograms from the acoustic drop-out (where tissue surface is parallel to ultrasound beam) [19-21, 23]. Tracking is performed by obtaining independently from each model a motion estimate and its uncertainty through optical flow [17] [19]. These models are again learned from the database of previous studies, just as detection models were learned for detection.

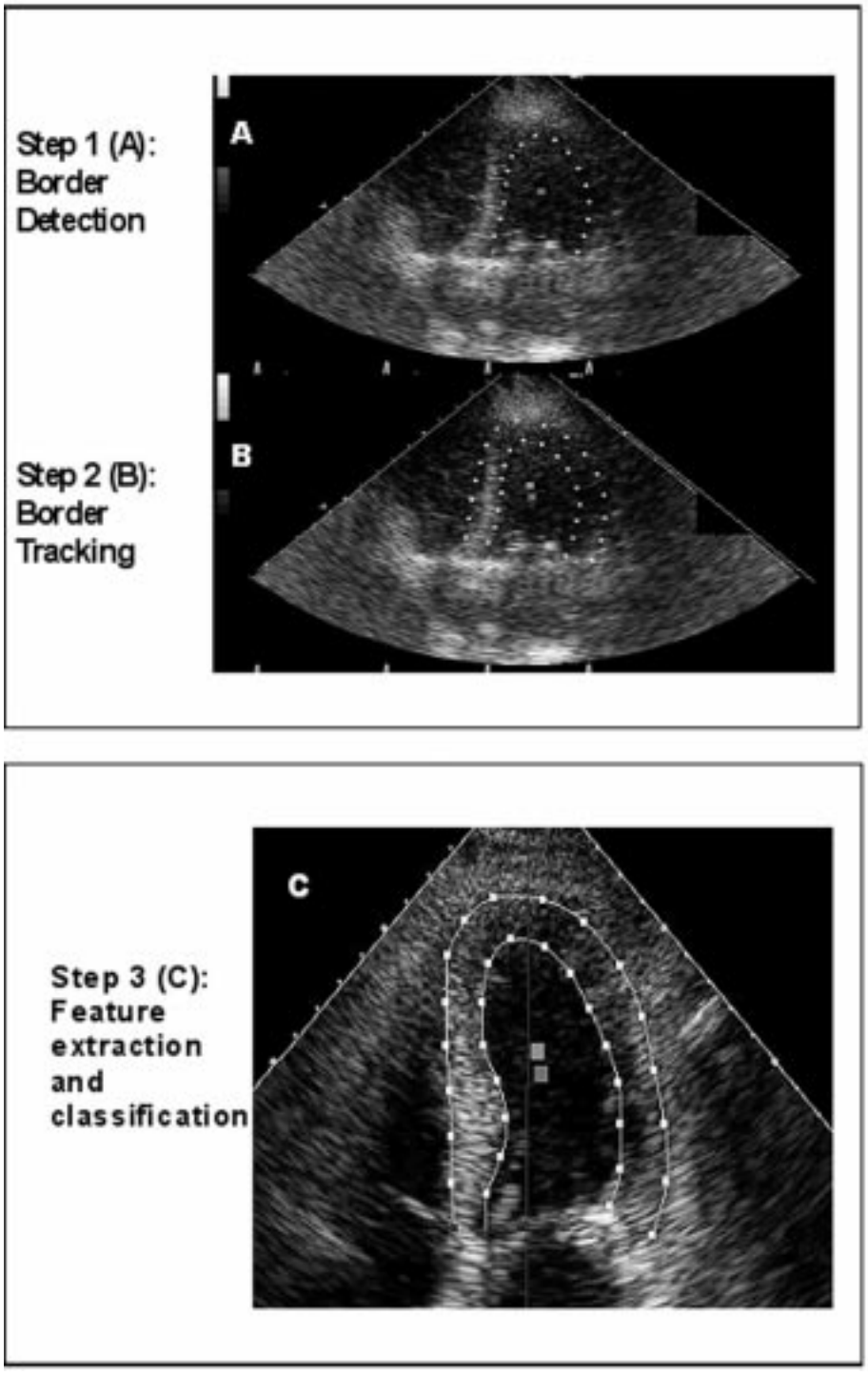

Figure 2: The principle of automatic myocardial wall tracking. A (step 1: Border detection): Dots in the user defined area represent endocardial detection. B (step 2: Border tracking): Dots in the user defined area represent epi- and endocardial tracking. C (step 3: Feature extraction and classification in a different patient than A and B): Dots are interconnected with lines at both the epi-and endocardium to generate contours used for image quantification.

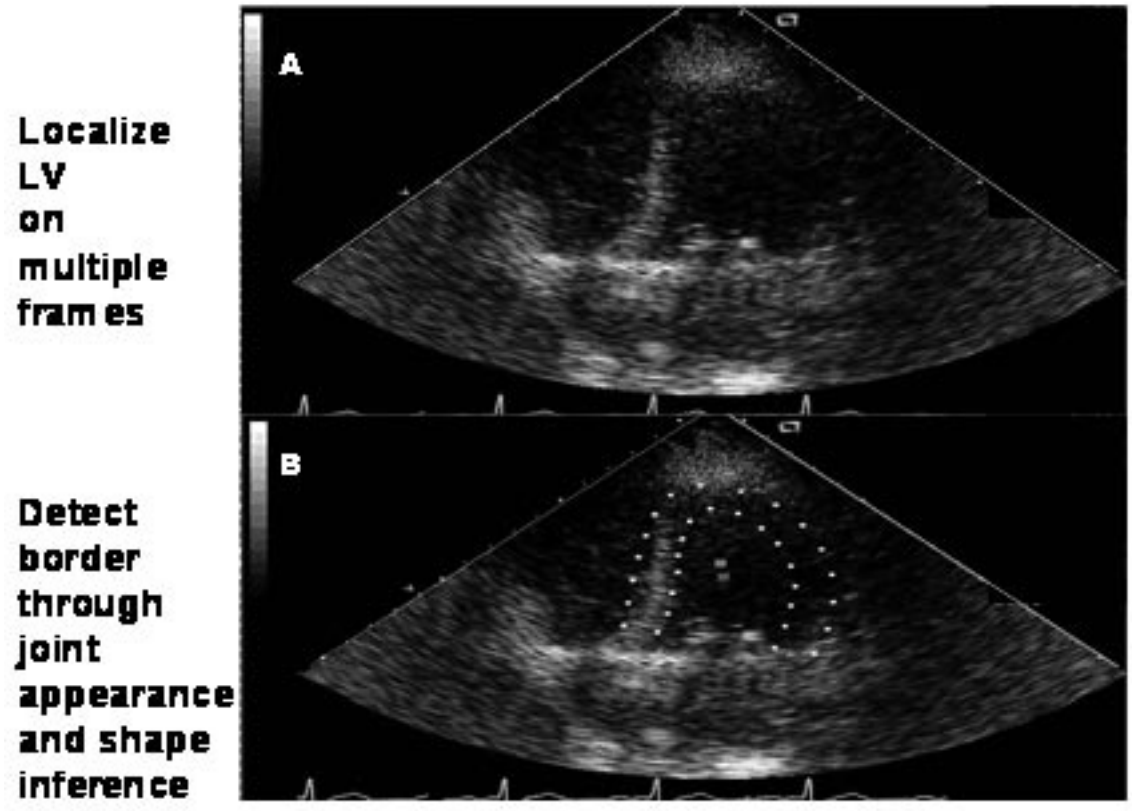

Figure 3: A: The first step is the localization and detection of the endocardium by using multiple LV frames. B: Dots depict the epi- and endocardial border.

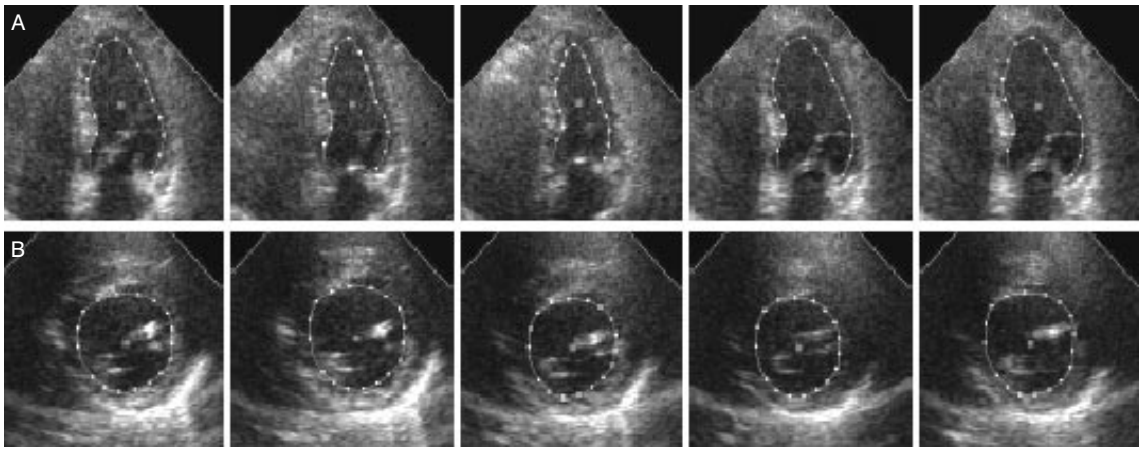

Figure 4: Images of learning sets showing different long-axis (A) and short-axis (B) left ventricular shape models. The whole application is based on pattern recognition using many different shapes of left ventricles learned from patient studies. Each image is an average of several cross-sections obtained from different DSE studies. Dots interconnected by lines represent the endocardium.

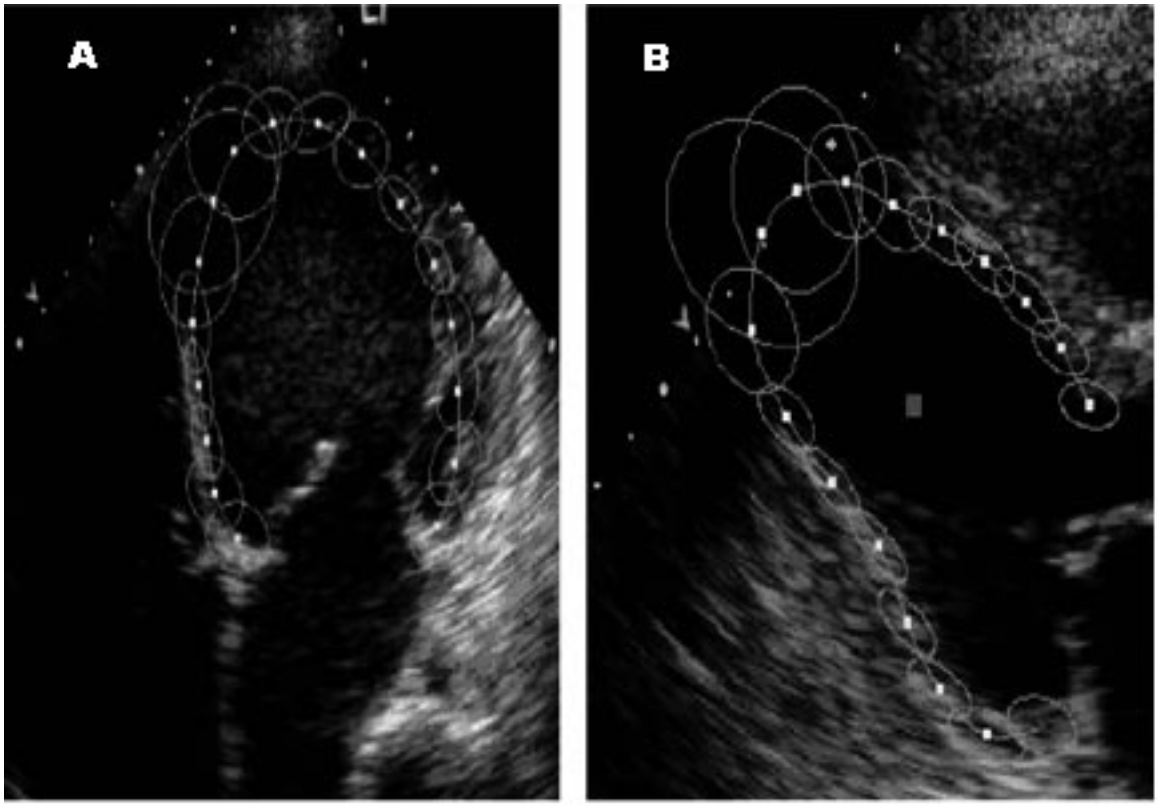

Figure 5: These apical four chamber views are obtained from two different patients undergoing a DSE study. The magnitude of the ellipses shows the uncertainties in motion estimation of the dots representing the endocardium in these examples. The larger the ellipse the bigger the uncertainty. In the panel A the uncertainties are largest in the distal/septal area while in panel B they are largest in the apex. This means that the system cannot accurately recognize the exact location of a certain landmark point in the next frame.

In echocardiographic images the epicardium is often more difficult to identify than endocardium by a software algorithm because of the high-reflecting surrounding structures. So for epicardium tracking, this system utilizes a double contour that can propagate information from the endocardium to guide the localization of the epicardium (or vice versa), and can better follow its location during the cardiac cycle and reduce the chance of crossing [17] [19]. For this purpose it uses the apex, the papillary muscles and the basal end of septum as landmark points that can be automatically assigned [17].This coupled contour approach integrates more spatial information, thus can provide more robust tracking of the endocardium and epicardium (figure 6) and permits accurate border motion tracking [17] [19] [20].

Step 3: Feature extraction and classification

Feature extraction and classification is the third step of the processing of the data. Once the endocardial and epicardial border have been detected and tracked, a coupled-contour is derived, from which the system extracts a few global (involving the whole LV) and local (involving individual segments visible in the image) numerical features for quantitation [17] [19]. These

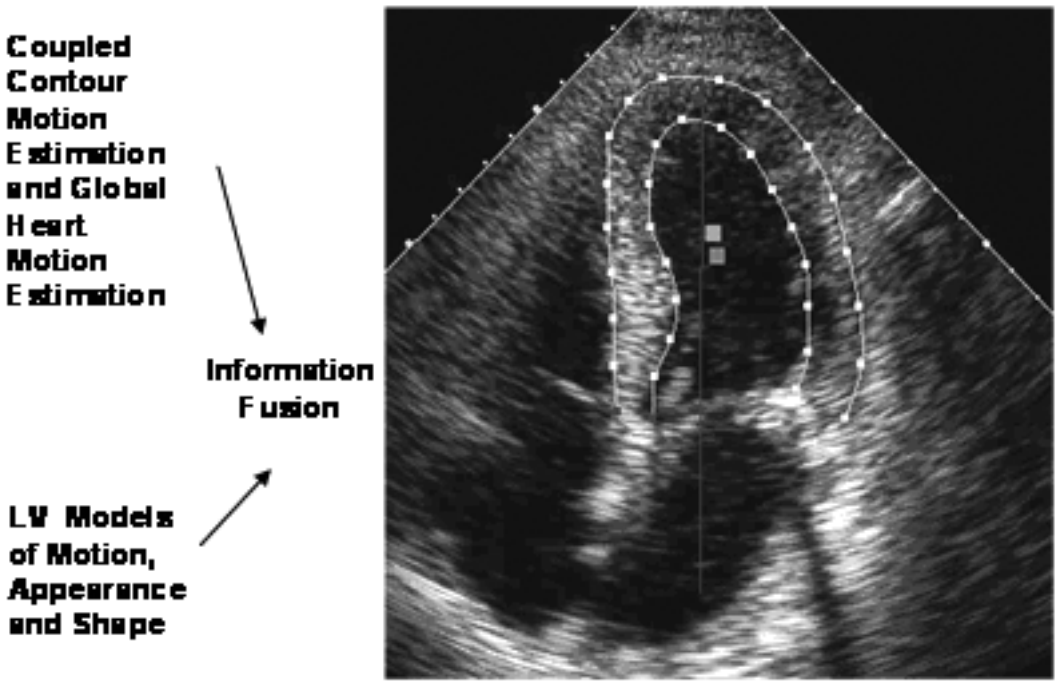

Figure 6: The second step is coupled motion tracking of endo- and epicardial contours. A 4-chamber view is shown as an example. The tracking is done by matching (fusing) the information gained by the learning set of the system's subsequent steps. Then the continuous contour estimation of each subsequent frame follows as shown in figure 5.

features derive from volume changes (segmental volumes by Simpson's rule), velocity, timing, radial strain (thickening) and circumferential strain [17, 19-24] (figure 7).

For each segment of a DSE study, a subset of relevant features is selected for classification. Statistical correlation methods of small number of features are applied for proper feature collection from the DSE study. Using a small number of features not only improves performance time but also results in a more robust and versatile learning set [17] [19]. The collected features are the classifiers and will provide the final automatic quantification.

Figure 7 depicts the diagram of system processing, from data to final quantitative features.

Clinical Implications

Coronary artery disease is one of the leading causes for mortality and morbidity. DSE could become the primary test as an everyday clinical tool, if a quantitative technique could substitute the eyeball assessment of regional wall motion abnormalities. The above mentioned technique seems promising as it aims to improve the accuracy and reduce the inter- and intra-observer variability of DSE. It is the first robust automatic coupled-contour myocardial tracking technique that utilizes the thickening of the myocardium during systole. However the system may not accurately recognize the exact location of a certain landmark point in subsequent frames. Moreover the training set of the proposed image processing technique is set by "expert" results which in turn

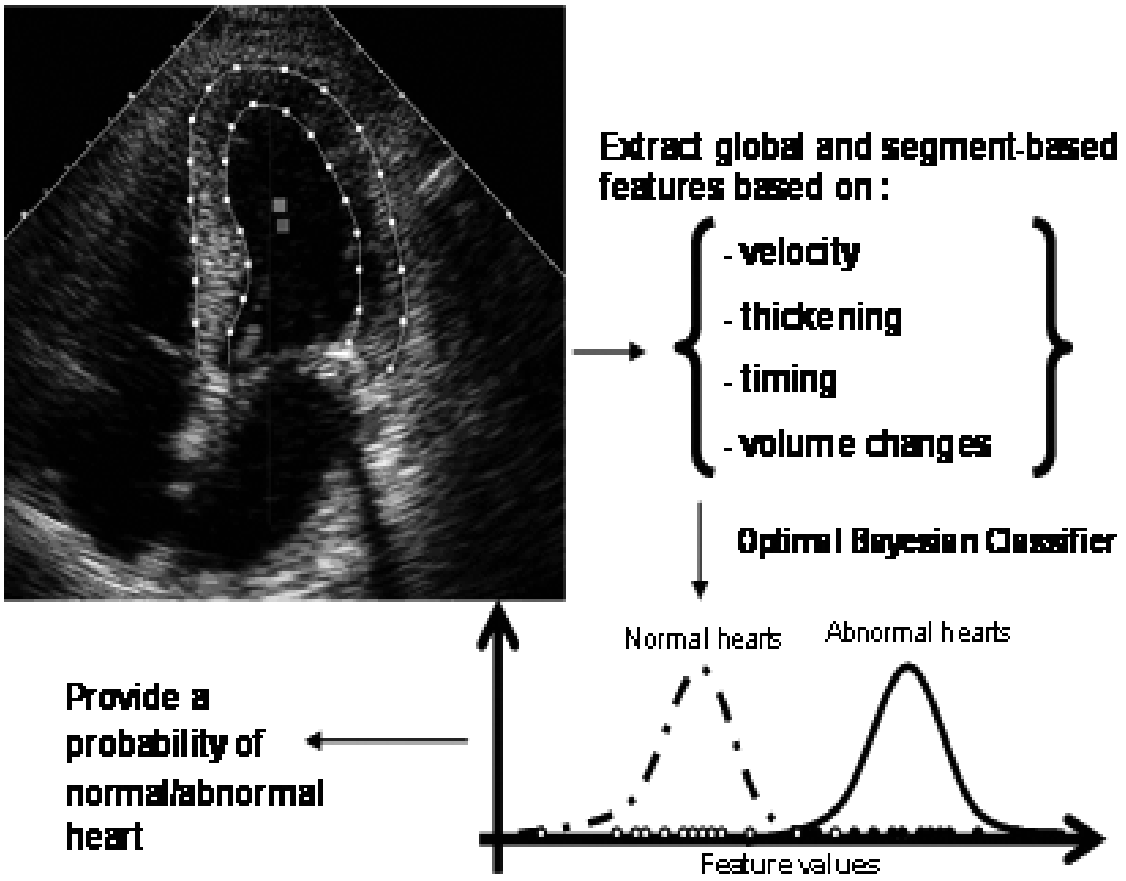

Figure 7: The final step is the feature extraction and classification. Once the endocardial and epicardial borders are detected and their motion is tracked, the system extracts global and segment based numerical features. These are velocity, thickening, timing and volume changes. These numerical features are the classifiers resulting in automatic quantification. Dots and lines in apical four-chamber image represent the coupled-contour of endo- and epicardial border. The graph provides the probability of a normal or abnormal new case (segment) based on numerical feature extraction. The probability curve shifts to the left or to the right according to the number of the features of a new case that match to features previously collected by the learning set of the system and were classified as normal or abnormal using criteria.

are subject to a certain degree of observer variability. These could present possible limitations of the proposed system. It remains to be seen whether this image processing technique will be feasible and will provide an accurate interpretation of wall motion abnormalities.

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Enhanced Sensitivity of Dobutamine Stress Echocardiography by Observing Wall Motion Abnormalities During the Recovery Phase After Acute Beta Blocker Administration

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CHAPTER **2**

Enhanced Sensitivity of Dobutamine Stress Echocardiography by Observing Wall Motion Abnormalities During the Recovery Phase After Acute Beta Blocker Administration

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Abstract

Dobutamine stress echocardiography (DSE) has a modest sensitivity in single vessel coronary artery disease (CAD). Aim of this study was to assess the additional diagnostic value of new or worsening wall motion abnormalities (NWMA) during the recovery phase after acute administration of beta-blockers.

The study population consisted of 200 patients (mean age: 59±11 years; 144 men), who underwent DSE. Images were acquired at rest, low dose, peak dose, and recovery phase. Patients received intravenous metoprolol (1-5 mg/min). The dose was adjusted to achieve a recovery heart rate, within a 10% range of the resting heart rate. Coronary angiography was performed within 2 months.

Inducible new wall motion abnormalities were observed in 168 (84%) patients at peak stress. An additionnal 14 patients (7%) experienced NWMA during the recovery phase. CAD was detected in 182 patients (86 had single vessel CAD). Sensitivity, specificity and accuracy of DSE were 88%, 65%, 73% at peak stress and 97%, 65%, 74% at recovery. Sensitivity was

Running head: Detection of coronary artery disease during recovery phase of stress echocardiography
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particularly higher during recovery than peak stress in patients with single vessel CAD (98% vs. 81%, p<0.001)

The assessment of wall motion abnormalities during the recovery phase after acute beta blockade improves sensitivity of DSE particularly in patients with single vessel CAD.

Text

Introduction:

Dobutamine stress echocardiography (DSE) is a useful non-invasive technique for evaluation of coronary artery disease (CAD). [1,2] One limitation of the DSE is the modest sensitivity in patients with single vessel CAD[1]. Some studies have suggested that wall motion abnormalities may develop in the recovery period after beta-blocker administration[3]. However, it is not yet established whether acute beta-blocker administration improves the accuracy of DSE.

The aim of our study is to estimate the additional diagnostic value of new or worsening wall motion abnormalities (NWMA) during the recovery phase of DSE after receiving acute beta-blockade compared to findings at peak and using coronary angiography as reference.

Methods:

Patients: We prospectively studied 200 consecutive patients with known or suspected CAD with DSE between March 2003 and April 2004. Patients received metoprolol intravenously at peak stress, irrespective of image interpretation at peak stress. Coronary angiography was performed within 2 months. Patient characteristics are presented in Table 1.

Dobutamine stress echocardiography: The DSE protocol was approved by the Hospital Ethical Committee and was performed in accordance with well-established protocols[4,5,6]. Studies were performed using a Philips Sonos 5500 system. Patients underwent a resting two-dimensional echocardiographic examination from the standard apical and parasternal views. Images were recorded on videotape and also digitized for comparison of different stages. Dobutamine was then administered intravenously by infusion pump, starting at 5 mg/kg/min for 3 minutes, followed by 10 mg/kg/min for 5 minutes and increasing by 10 mg/kg/min every 3 minutes to a maximum of 40 mg/kg/min (stage 5), and continued for 6 minutes. The dobutamine infusion was stopped if a target heart rate (85% of a theoretic maximal heart rate (men: (220 – age) x 85%; women: (200 – age) x 85%) was achieved. If the target heart rate was not achieved and patients had no symptoms or signs of ischemia, atropine (starting with 0.25 mg, increased to a maximum of 2.0 mg) was given intravenously at the end of stage 5 while the dobutamine administration was continued. During the test, a 12-lead ECG was recorded every minute. Blood pressure was measured every 3 minutes. Metoprolol was administered (1,0 to 5,0 mg) intravenously according to heart rate response and systolic blood pressure, and after peak stress images were acquired to achieve a recovery phase, defined as heart rate within 10% range of resting heart rate.

The criteria for stopping the test were: (1) achievement of the target heart rate (2) severe and extensive NWMA, (3) horizontal or downsloping ST depression of ≥0.2 mV measured 80 ms

Table 1: Study population characteristics

Patient Characteristics	
Demographics	
Males	144 (72%)
Females	54 (27%)
Age	59±11
Cardiovascular History and cardiac risk factors	
Hypertension	70 (35%)
Heart Failure	44 (22%)
Diabetes Mellitus	32 (16%)
Previous Myocardial Infarction	102 (51%)
Dyslipidemia	102 (51%)
Smoking	50 (25%)
Cardiac Medication	
ACE-inhibitors	90 (45%)
Aspirin	52 (26%)
Statins	44 (22%)
β-blockers	128 (64%)
Nitrates	112 (56%)
Diuretics	44 (22%)
Digoxin	12 (6%)

after the J point, or ST-segment elevation of ≥0.2 mV in the absence of Q waves, (4) symptomatic decline in systolic blood pressure of more than 40 mmHg, or a systolic blood pressure ≤ 90 mmHg, (5) hypertension (blood pressure >240/140 mmHg), (6) the occurrence of sustained cardiac arrhythmias, (7) severe angina pectoris, and (8) intolerable adverse effects considered to be the result of dobutamine or atropine. Two experienced investigators performed off-line assessment of echocardiographic images without knowledge of the patient's clinical and coronary angiography data, but with knowledge of the doses of dobutamine and atropine used. The results of DSE were considered positive if NWMA occurred (i.e., if wall motion in any segment worsened by ≥1 grades during the test, with the exception of akinesis becoming dyskinesis). The extent and location of ischemia were evaluated and a wall-motion score index (total score divided by the number of segments scored) was calculated, at rest, during peak stress, and during the recovery phase. Digital screen format was used to compare images. When there was disagreement between the two assessors, a third investigator viewed the images without knowledge of the previous assessments, and a majority decision was reached.

Coronary angiography: The presence of CAD was established by standard quantitative coronary angiography using the Judkins technique. A luminal diameter stenosis > 70% in a major

Table 2: Results and Hemodynamic data during DSE

DSE results (peak stress)	no CAD		32 (16%)	
	Single-vessel disease		82 (41%)	
	Multi-vessel disease		86 (43%)	
	rest	peak	peak+atropine	Recovery
HR (beats/min)	69±13	107±21	132±13	88±13
SBP (mmHg)	126±22	130±26	129±27	121±23
DBP (mmHg)	71±12	68±14	68±16	68±13
rate-pressure product (mmHg/min)	8694±286	13910 ± 546	17028 ± 351	10648±299

epicardial vessel was considered significant. Multivessel CAD was defined by the presence of significant stenosis of two or three vessels, or more than 50% stenosis of the left main stem.

Statistical analysis: Results are expressed as mean value ± SD. The t-test was used for continuous variable and chi –square test was used for categorical variables. A two-tailed $p<0.05$ was considered significant. Furthermore 2 x 2 tables with weight k statistics were used for comparisons between coronary angiography results and DSE results and for inter-observer agreement. On the basis of Fleiss's classification [7] k values < 0.4, between 0.4 and 0.75, and > 0.75 were considered to indicate poor, fair to good, and excellent agreement respectively. Multivariate logistic regression was used to investigate the predictive value of NWMA in the recovery phase and peak stress of DSE for single vessel disease patients adjusting for age, gender, previous MI, and congestive heart failure.

Sensitivity, specificity, diagnostic accuracy and predictive values were calculated according to standard definitions. At last intra-observer agreement was calculated by Spearman correlation.

Results: CAD was detected in 182 patients, while in 28 no significant abnormalities were detected. Angiographically 86 patients had single vessel CAD and 52 had 2-vessel CAD and 44 The hemodynamic data of DSE are presented in table 2. Rest wall motion abnormalities were observed in 160 patients, while NWMA at peak stress were assessed in 168 patients. During the recovery phase NWMA were assessed in an additional 14 (7%) patients.

Accuracy of DSE for diagnosis of CAD:

At peak stress there were 6 false-positive and 21 false-negative results. In the majority of patients target heart rate was achieved after administration of atropine at peak stress, as 64% of

Table 3: Sensitivity, specificity and accuracy of DSE for detection of CAD, and sensitivities for single and multivessel disease at peak and recovery.

	Sensitivity		Specificity		Accuracy	
	peak	recovery	peak	recovery	peak	recovery
CAD overall (peak 168pts vs recovery 182pts)	88%	97%	65%	65%	73%	74%
Single-vessel disease (peak 82pts vs recovery 92 pts)	81%	98%				
Multivessel disease (peak 86pts vs recovery 90pts)	85%	89%				

them were already on chronic beta-blockade that was not stopped prior to the study. The sensitivity, specificity and accuracy of DSE for detection of CAD, and sensitivities for single and multivessel disease at peak and recovery are summarized in table 3. The sensitivity at peak stress for the detection of CAD was 88% (95% CI 84% to 93%) and specificity 65% (95% CI 59% to 71%). For single-vessel disease the sensitivity at peak stress was 81% (95% CI 75% to 87%) (Figure 1) and for multivessel disease was 85% (95% CI 80% to 90%) (Figure 2). The overall diagnostic accuracy of DSE at peak stress for the detection of CAD was 73% (95% CI 66% to 79%). For detection of single-vessel or multivessel disease the respective percentages were 87% (95% CI 82% to 92%) and 89% (95% CI 85% to 93%).

When recovery images were analyzed the sensitivity for the detection of CAD increased to 97% (95% CI 94% to 99%), while specificity remained unchanged. The increase in sensitivity was especially prominent in patients with single-vessel disease to 98% (95% CI 96% to 100%) (Figure 1). For multivessel disease the sensitivity increased to 89% (95% CI 85% to 94%) (Figure 2).

Patients on chronic beta-blockade did not show any difference in sensitivity compared to the group that did not receive chronically beta-blockers.

Using k-statistics, the detection of agreement between coronary angiography results and DSE results increased from 0.7 at peak stress to 0.85 at the recovery phase, indicating a good agreement of DSE with the angiographic findings in the recovery phase.

Intra-observer and inter-observer variability: We observed good intra-observer agreement (correlation between two measurements of same observer) for rest (r=0.90), low (r=0.93), peak (r=0.88), and recovery images (r=0.88) (all $p<0.001$). Moreover the global inter-observer agreement was 88%.

Response to beta-blockade: After metoprolol injection in 14 patients the diagnosis of CAD changed. In 10 patients NWMA could be detected which had single vessel disease, in 3 patients

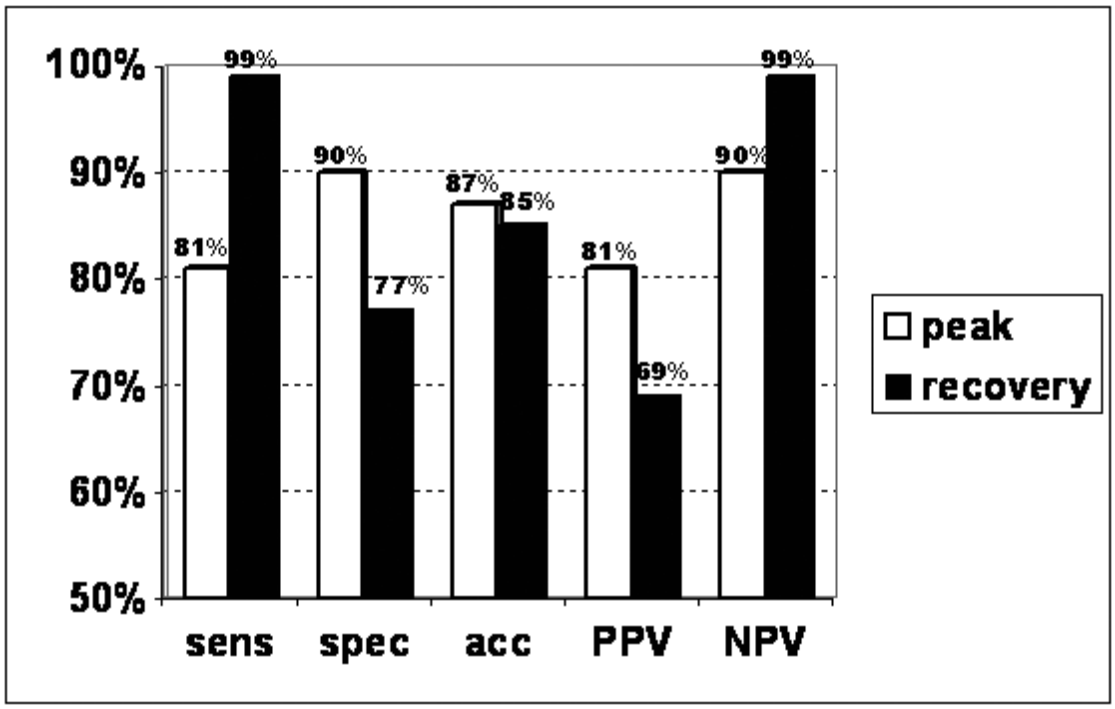

Figure 1: Sensitivity (sens) ($p<0.001$), specificity (spec) ($p=0.05$), diagnostic accuracy (acc) (p:NS), positive predictive value (PPV) (p:NS) and negative predictive value (NPV) ($p<0.01$) for single-vessel disease at peak and recovery.

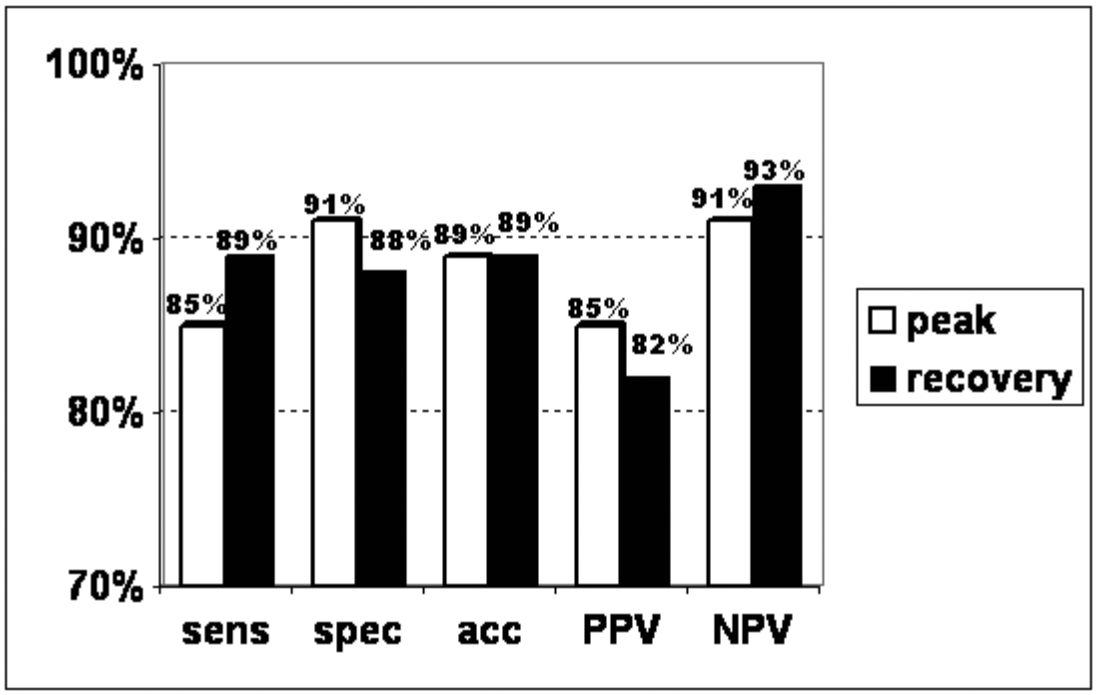

Figure 2: Sensitivity (sens) specificity (spec), diagnostic accuracy (acc) positive predictive value (PPV) and negative predictive value (NPV) for multi-vessel disease at peak and recovery (all p: NS).

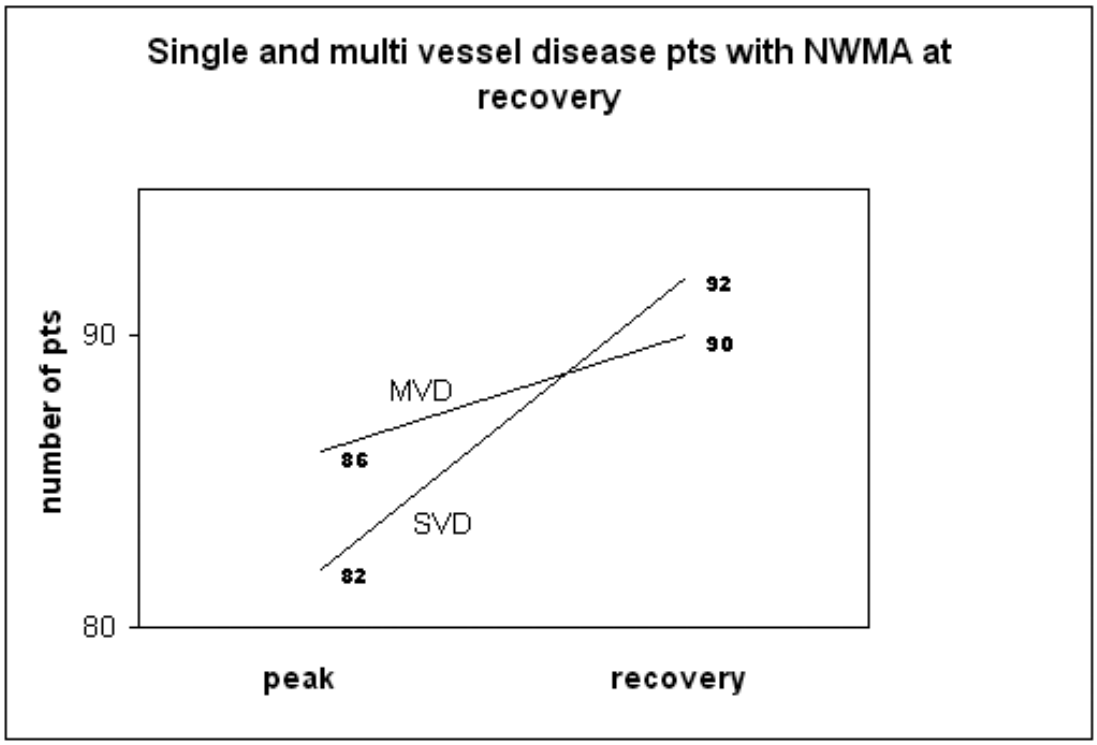

Figure 3: Single- (SVD) and multi- (MVD) vessel disease patients with new wall motion abnormalities at recovery (p<0.001 and p: NS respectively)

the diagnosis was changed from single to multivessel vessel disease and in 1 additional patient the diagnosis changed from normal to multivessel disease (Figure 3). All patients that showed NWMA at peak stress had persisting abnormalities after acute beta-blockade. Multivariate regression analysis showed that, recovery phase results in total and NWMA in the recovery phase were the only independent predictors for single vessel disease patients (odds ratio [OR] 0.14, 95% CI 0.07 to 0.28 and 6.24, 95% CI 2.61 to 14.9 respectively).

Discussion:

Dobutamine stress echocardiography is widely used for the detection of CAD, by observation of NWMA[1]. However the test has a reduced sensitivity for the detection of single vessel disease[1,2]. The sensitivity of DSE for the detection of single vessel disease ranges from 40% to 92% and for multi-vessel disease from 65% to 83% while specificity remains unchanged[8,9,10]. Our study showed that wall motion abnormalities assessment during the recovery phase after acute beta-blockade increased the sensitivity for the detection of single vessel disease significantly from 81% to 99% (p<0.001) while the specificity was marginally decreased. More specifically the decrease in specificity was of borderline statistical significance (p=0.05), a trend that could be regarded as potential limitation of our study; although it could be related to the small number of normal subjects and the high prevalence of disease of the study population. Also in

additional 3 patients the diagnosis was changed from single vessel to multivessel disease and in one from normal to multivessel disease. Moreover during the recovery phase the value of rate-pressure product, as a measure of oxygen consumption rate, was less than its value at peak stress, but more than the value at rest. This indicates a prolonged ischemic effect of dobutamine during the recovery phase.

There is limited knowledge and utilization of regional wall motion abnormalities that continue at recovery phase or even more NWMA that present in the recovery phase of dobutamine stress echocardiography.

Dobutamine exerts its effect by stimulation of β1, β2, and α1-adrenergic receptors[11]. Acute β-blockade interacts with dobutamine β1 and β2 receptors leaving unopposed α1-adrenergic vasoconstriction[12] and therefore leading to reduction of coronary flow reserve[13]. So myocardial ischemia could result from increased vasoconstriction and that could explain the paradoxical enhancement of wall motion abnormalities at the recovery phase.

Another possible explanation of our findings is that at the recovery phase we could better visualize the NWMA that already existed at peak stress but were masked by hyperdymanic contraction of mid- and epicardial layers. This is especially true in single-vessel disease patients in contrast to multivessel disease patients where sensitivity is higher and NWMA are more profound after dobutamine administration. So the sensitivity increase in single vessel disease patients is higher as the baseline sensitivity is less than in multivessel disease.

There is one previous study that showed that the duration of wall motion abnormalities in the recovery phase was correlated to the extent of CAD[14]. Actually this study showed that the persistence of wall motion abnormalities in the recovery phase of dobutamine stress echo was correlated to the severity of CAD, irrespective of the prior administration of beta-blockade infusion to fasten the time to recovery.

In another study it was demonstrated that injection of beta-blockers at the peak dose of DSE might enhance regional wall abnormalities and increase the sensitivity of the combined peak plus metoprolol images especially in single-vessel disease patients[3]. Our results coincide with the above study with even better improvement in sensitivity of the recovery phase assessment only, and not of a combination of peak stress plus recovery phase images as the aforementioned study.

Clinical implications: Although there is a protective effect of beta-blockade in relieving myocardial ischemia[15,16], paradoxically, we observed that a significant percentage of patients developed new wall motion abnormalities during the recovery phase.

In conclusion observation and scoring of individual segments at recovery phase, as part of the regular DSE scoring, in patients that receive acute beta-blockade at peak stress, could add to the better assessment of ischemia in CAD patients.

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Myocardial Viability Estimation During Recovery Phase of Stress Echocardiography After Acute Beta-Blocker Administration

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CHAPTER **3**

Myocardial Viability Estimation During Recovery Phase of Stress Echocardiography After Acute Beta-Blocker Administration

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Abstract

Background: Myocardial viability assessment in severely dysfunctional segments by dobutamine echocardiography (DSE) is less sensitive than nuclear scanning.

Aim: To assess the additional value of recovery phase of DSE after acute beta blocker administration for identifying viable myocardium.

Methods: The study population included 49 consecutive patients with ejection fraction (LVEF)≤35%. All patients underwent DSE evaluation at low-high dose and during recovery phase, and dual-isotope single photon emission tomography (DISA-SPECT) evaluation for viability of severely dysfunctional segments. Patients with ≥4 viable segments were considered viable. Coronary revascularization followed within 3 months in all. Radionuclide LVEF was performed prior and twelve months after revascularization.

Results: Viability with DISA-SPECT was detected in 463 (59%) segments, while 154 (19.7%) segments presented as scar. The number of viable segments increased from 415 (53%) at DSE to 463 (59%) at DSE and recovery and viable patients increased from 43 to 49 respec-

Running head: Viability estimation during recovery phase of stress echocardiography *Word count*: 2797
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tively. LVEF improved ≥5% in 27 patients. Multivariate regression analysis showed that, DSE with recovery phase was the only independent predictor of ≥5% LVEF improvement after revascularization (OR 14.6, CI 1.4-133.7).

Conclusion: In this study we demonstrate that the recovery phase of DSE has an increased sensitivity for viability estimation compared to low-high dose DSE.

Keywords: Dobutamine Stress Echocardiography, recovery phase, viability.

Introduction

Coronary artery disease (CAD) is one of the major causes of left ventricular (LV) dysfunction and is one of the leading causes of mortality and morbidity. So far the predictive value of dobutamine stress echocardiography (DSE) for the recovery of LV function after revascularization is less compared to nuclear scan techniques. As these techniques mainly focus on finding islands of viable tissue, DSE focuses on segmental function of LV; a feature that explains the lower sensitivity of the test compared to other imaging techniques, with a slightly better specificity [1]. The studies published to date on the use and importance of DSE in the evaluation of myocardial viability combine various subgroups of patients. [1][2] A complete test, compared with only low-dose images, is more accurate in predicting LV functional recovery after revascularization. This is ascribed to the ability of full-dose dobutamine to recognize more accurately the biphasic and ischemic response.[1] These ischemic responses may be missed if only a low-dose dobutamine protocol is performed. Furthermore it is shown [3] that recovery phase of DSE in patients receiving acute beta-blockade, after peak images are obtained, is important in identifying further ischemia. It is demonstrated that injection of beta-blockers at the peak dose of DSE might enhance regional wall abnormalities and increase the sensitivity of the combined peak plus metoprolol images [3]. As treatment modalities for LV dysfunction and concomitant heart failure include revascularization we have to clearly identify patients with dysfunctional but viable myocardium. Nevertheless the evaluation of the recovery phase of DSE for viability estimation is not yet studied. The aim of our study is to assess the additional value of viability estimation during the recovery phase of DSE after receiving acute beta-blockade compared to findings at low-high dose DSE and using dual-isotope single photon emission tomography (DISA-SPECT) as reference.

Methods

Patient population

The study population included 49 consecutive patients with known or suspected CAD who were referred at the Thoraxcenter (Rotterdam, the Netherlands) between January 2004 and January 2005. Patients with ejection fraction ≤35% were enrolled. All the patients underwent DSE and DISA-SPECT examination for evaluation of viability. A revascularization procedure followed within 3 months according to the discretion of the referring physician discretion, who was aware of the tests results.

Radionuclide ventriculography was also performed within one month before and twelve months after the revascularization procedure. The local medical ethics committee approved the study protocol. Patients gave an informed consent to undergo the study.

Radionuclide ventriculography

Radionuclide ventriculography was performed at rest with the patient in supine position after administration of 740 MBq of Tc-99m. Images were acquired with a small field-of view gamma camera (Orbiter, Siemens Corp., Erlangen, Germany) oriented in the 45° left anterior oblique position with a 5° to 10° caudal tilt. LV ejection fraction was calculated by standard methods (Odyssey VP, Picker, Cleveland, Ohio).

Dobutamine stress echocardiography

The DSE protocol was approved by the Hospital Ethical Committee and was performed in accordance with well-established protocols.[4][5] Studies were performed using a Sonos 5500 imaging system (Phillips Medical Systems, Eindhoven, The Netherlands). Patients underwent a resting two-dimensional echocardiographic examination from the standard apical and parasternal views. Images were recorded on videotape and also digitized for comparison of different stages. Dobutamine was then administered intravenously by infusion pump, starting at 5 mg/kg/min for 3 minutes, followed by 10 mg/kg/min for 5 minutes and increasing by 10 mg/kg/min every 3 minutes to a maximum of 40 mg/kg/min (stage 5), and continued for 6 minutes. The dobutamine infusion was stopped if a target heart rate (85% of a theoretic maximal heart rate (men: (220 – age) x 85%; women: (200 – age) x 85%) was achieved. If the target heart rate was not achieved and patients had no symptoms or signs of ischemia, atropine (starting with 0.25 mg, increased to a maximum of 2.0 mg) was given intravenously at the end of stage 5 while the dobutamine administration was continued. During the test, a 12-lead ECG was recorded every minute. Blood pressure was measured every 3 minutes. Metoprolol was administered (1,0 to 5,0 mg) intravenously after peak stress images were acquired and according to heart rate response and systolic blood pressure, to achieve a recovery phase, defined as heart rate within 10% range of resting heart rate.

The criteria for stopping the test were: (1) achievement of the target heart rate (2) severe and extensive NWMA, (3) horizontal or downsloping ST depression of ≥0.2 mV measured 80 ms after the J point, or ST-segment elevation of ≥0.2 mV in the absence of Q waves, (4) symptomatic decline in systolic blood pressure of more than 40 mmHg, or a systolic blood pressure ≤ 90 mmHg, (5) hypertension (blood pressure >240/140 mmHg), (6) the occurrence of sustained cardiac arrhythmias, (7) severe angina pectoris, and (8) intolerable adverse effects considered to be the result of dobutamine or atropine. Two experienced investigators performed off-line assessment of echocardiographic images without knowledge of the patient's clinical and coronary angiography data, but with knowledge of the doses of dobutamine and atropine used. Interobserver and intraobserver agreement for analysis of DSE studies were reported previously (92% and 94%, respectively)[6]. Regional function was scored according to a 16 segment, five point scoring model: 1, normal; 2, mildly hypokinetic; 3, severely hypokinetic; 4, akinetic; and 5,

dyskinetic. Wall-motion score index (WMSI) (total score divided by the number of segments scored) was calculated, at rest, low dose, during peak stress, and during the recovery phase.

Myocardial viability was assessed only in severely dysfunctional segments; 4 types of wall motion responses were observed: (1) biphasic pattern: improvement of wall motion at 5, 10, or 20 mg/kg/min dobutamine with worsening at higher dosages; (2) worsening; (3) sustained improvement; and (4) no change. Severely dysfunctional segments exhibiting a biphasic, sustained improvement, or ischemic response were considered viable, whereas segments with unchanged wall motion were considered scarred. The same criteria were applied when recovery phase images were added to the evaluation.

A patient was considered to have viable myocardium in the presence of ≥4 viable segments and as non-viable in the presence of ≥4 viable segments [7]. 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 [7].

Digital screen format was used to compare images. When there was disagreement between the two assessors, a third investigator viewed the images without knowledge of the previous assessments, and a majority decision was reached.

Dual-isotope single photon emission tomography

DISA-SPECT imaging using technetium-99m tetrofosmin (perfusion) and fluorine-18 fluorodeoxyglucose (metabolism) tracers was performed as previously described [8] The left ventricle was divided into 16 segments (6 basal—anterior, anterolateral, inferolateral, inferior, inferoseptal, and anteroseptal), 6 distal, and 4 apical segments, corresponding to echocardiographic segments. Segmental tetrofosmin and FDG uptake were scored by 1 experienced observer (blinded to echo data) using a 4-point grading system (0, normal;1, mildly-moderately reduced; 2, severely reduced;and 4, absent). According to this scoring model, criteria of viability were (1) normal perfusion and FDG uptake, (2) concordantly mildly-moderately reduced perfusion and FDG uptake, or (3) reduced perfusion with preserved or increased FDG uptake (mismatch). Segments with severely reduced or absent perfusion and concordantly reduced (or absent) FDG uptake was considered scar tissue.

Statistics

Results are expressed as mean value SD. The t-test was used for continuous variable and chi –square test was used for categorical variables. A two-tailed $p<0.05$ was considered significant. Kappa statistics were used for agreement between DISA-SPECT and DSE. On the basis of Fleiss's classification [9] k values < 0.4, between 0.4 and 0.75, and > 0.75 were considered to indicate poor, fair to good, and excellent agreement respectively. A McNemar test was applied to study the difference in DSE results with and without recovery phase evaluation, controlled by nuclear testing results.

Multivariate logistic regression was used to investigate the predictive value of viability in DSE+recovery phase, versus low-high DSE, for global left ventricular improvement after revascularization, adjusting for age, gender, previous MI, and congestive heart failure [10].

Table 1: Study population characteristics

Characteristics in 49 patients	
Demographics	
Males	
35 (72%)	
Females	14 (28%)
Age	59±11
Cardiovascular History and cardiac risk factors	
Hypertension	17 (35%)
Heart Failure	11 (22%)
Diabetes Mellitus	8 (16%)
Previous Myocardial Infarction	25 (51%)
Dyslipidemia	25 (51%)
Smoking	12 (25%)
Previous PCI	27 (55%)
Cardiac Medication	
ACE-inhibitors	22 (45%)
Aspirin	13 (26%)
Statins	11 (22%)
β-blockers	31 (64%)
Nitrates	27 (56%)
Diuretics	11 (22%)
Digoxin	3 (6%)

Sensitivity, specificity, diagnostic accuracy and predictive values were calculated according to standard definitions.

Results

The patients' clinical characteristics are presented in Table 1. The patients' medications were not discontinued during the study. All patients were submitted for revascularization; 40 underwent percutaneous transluminal coronary angioplasty and 9 coronary artery by-pass grafting. In total 27 patients showed a ≥5% increase in left ventricular ejection fraction 12 months after revascularization.

Patient Characteristics and Hemodynamic response

During DSE the heart rate increased significantly from rest to peak stress. Test end point was target heart rate and was reached in 94% of patients. Atropine was added at peak stress in 31 patients as the majority was on chronic beta-blockade that was not stopped prior to the study.

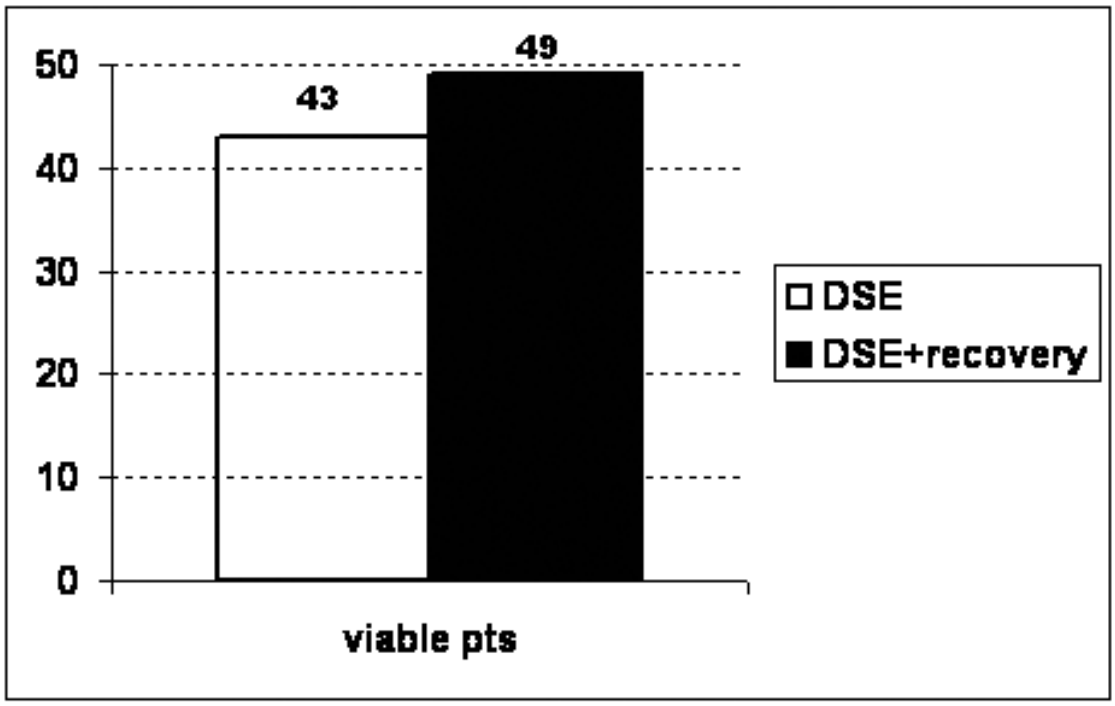

Figure: Patients with viability at DSE versus DSE + recovery ($p<0.03$ after controlling for DISA-SPECT results).

The mean maximal dobutamine dose was 38 ± 8 mcg/kg/min. All patients received metoprolol (1,0 to 5,0 mg) intravenously after peak stress images were acquired and according to heart rate response and systolic blood pressure. Side effects included hemodynamically stable sustained ventricular tachycardia (>10 complexes) in 1 (2%) patients, non-sustained ventricular tachycardia (<10 complexes) in 2 (3%) patients, atrial fibrillation in 2 (3%) patients and severe hypotension (decrease of systolic blood pressure >40mmHg) in 1 (2%) patients. No myocardial infarction or ventricular fibrillation was recorded during or attributed to DSE.

The rate pressure product values at rest, low, peak and recovery were 8694 ± 286, 13910 ± 546, 17028 ± 351 and 10648 ± 299 respectively. WMSI at rest was 2.05 ± 0.91, at low dose 1.83± 0.79, at peak dose 1.90 ± 0.83 and at recovery phase 2.15 ± 0.94.

The number of viable segments increased from 415 (53%) at DSE to 463 (59%) at DSE + recovery. 295 segments developed an ischemic response at peak and another 48 only during recovery phase.

During DSE 43 patients had ≥4 viable segments. During the recovery phase another 6 patients were considered as viable (Figure). These were patients that changed from non-viable i.e. unchanged response to dobutamine at peak, to ischemic indicating a prolonged ischemic effect of dobutamine during the recovery phase, after acute beta-blocker injection. Only 3 of these patients had a ≥5% increase in left ventricular ejection fraction 12 months after revascularization.

Table 2: Sensitivity, specificity, accuracy, positive predictive value and negative predictive value for viability evaluation at DSE and DSE+recovery.

	DSE	DSE+recovery	p
Sensitivity	72%	85%	0.001
Specificity	74%	78%	ns*
Accuracy	73%	82%	0.01
Positive Predicitve Value	80%	85%	ns*
Negative Predicitive Value	65%	78%	0.001

ns* = non-significant

DISA-SPECT and Radionuclide ventriculography

Viability was detected in 463 (59%) segments, while 154 (19.7%) segments presented as scar. The rest of the segments had normal or mildly reduced function and metabolism. Mean left ventricular ejection fraction as assessed by radionuclide ventriculography was 28% ±7% prior to revascularization and 37% ± 6% post revascularization.

DSE in viability estimation

Table 2 shows the respective changes of sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) for the detection of viability at DSE and DSE+recovery and by using DISA-SPECT as reference. The sensitivity at low-high DSE for viability estimation was 72% (95% CI 68% to 76%) and specificity 74% (95% CI 72% to 76%). When recovery images were also analyzed the sensitivity for viability estimation increased to 85% (95% CI 81% to 89%), while specificity remained unchanged.

Patients on chronic beta-blockade did not show any difference in sensitivity compared to the group that did not receive chronically beta-blockers.

Using k-statistics, the detection of agreement between DISA-SPECT results and DSE results increased from 0.55 at low-high DSE to 0.68 at DSE + recovery, indicating a good agreement of DSE with the nuclear findings when recovery phase was also scored.

Multivariate regression analysis showed that, DSE+recovery phase results in total were the only independent predictors of improved left ventricular function (ejection fraction improvement ≥5%) after revascularization (p=0.04, odds ratio [OR] 14.65, 95% CI 1.34 to 133.7). Furthermore the number of scarred segments as shown by DISA-SPECT, was the only independent

predictor of deterioration of left ventricular function after revascularization, in multivariate analysis (p=0.03, OR 0.78, 95% CI 0.62 to 0.98).

Discussion

Dobutamine stress echocardiography is widely used for viability detection in patients with CAD [11-14]. However the sensitivity of the test is less than in other imaging techniques, with a slightly better specificity [11-14]. In this study we demonstrated that the sensitivity increased from 72% to 85% ($p<0.001$) when recovery phase was also scored and more importantly it was not accompanied by a decrease in specificity. Furthermore the negative predictive value of the test was also significantly improved (Table 2).

Previously, Tsoukas et al.[15] have studied the presence of myocardial ischaemia during the recovery phase of DSE. Their results have shown that patients with extended coronary artery disease have more prolonged ischaemia. Furthermore, Mathias et al.[3] have demonstrated that injection of beta-blockers at the peak dose of DSE might enhance regional wall abnormalities and increase the sensitivity of the recovery images for detecting ischemia. We similarly found an enhanced sensitivity in our study. Moreover as no myocardial infarction or ventricular fibrillation was recorded during or attributed to DSE we could support that the use of acute beta-blockade during DSE is safe. Concerning viability, a study by Zaglavara et.al.[16] has suggested that beta blocker withdrawal is not necessary before DSE studies as far as a completed DSE protocol is performed. This is required as some viability can be detected at higher doses than the traditional low dose stages. Our protocol also included recovery phase evaluation as part of standard DSE.

In our study during the recovery phase the status in 6 patients changed from “non-viable” at peak i.e. unchanged response to dobutamine, to “viable” i.e. ischemic (p=0.03) (Figure), indicating a prolonged ischemic effect of dobutamine during the recovery phase, after acute beta-blocker injection. This is also indicated by the value of rate-pressure product during the recovery phase, as a measure of oxygen consumption rate, which was less than its value at peak stress, but more than the value at rest. Dobutamine stimulates β1, β2, and α1-adrenergic receptors[17]. Acute β-blockade interacts with dobutamine β1 and β2 receptors leaving unopposed α1-adrenergic vasoconstriction [18] and therefore leading to reduction of coronary flow reserve[19]. This means that increased vasoconstriction can cause myocardial ischemia and that could also explain the paradoxical enhancement of ischemic response at the recovery phase.

Our findings have also demonstrated that viability estimation by the combination of low, peak, and recovery phase scoring was the only independent predictor of improved left ventricular function after revascularization. Indeed this finding was similar to that of a previous study that has shown that DSE is both sensitive and specific in predicting improved myocardial function after revascularization [16]. Furthermore Afridi et.al [20] demonstrated that myocardial viability was the only multivariable predictor of good outcome after revascularization.

We have also found a good correlation between the two imaging techniques for detecting myocardial viability when recovery phase was also scored, and irrespectively of resting left ventricular ejection fraction; a finding that is in concordance with previous studies. [1,14,16,20-22]

To our knowledge this is the first study demonstrating the additional value of the recovery

phase of DSE in the estimation of viability in patients with CAD. An increased sensitivity of the test, as we found, could add to the clinical usage of DSE in this respect.

Possible limitations of our study could include the fact that the study population consisted of patients with chronic ischemic LV dysfunction. Findings may not apply to patients with acute or recent myocardial infarction. Another limitation could be the subjectivity of DSE interpretation. This potential limitation may be reduced by the introduction of automatic quantitative scoring systems. A third limitation was the large number of scarred nonviable segments. Limitations also include that the specificity of the reference method could be expected to be low and that there was not a follow-up echo 12 months after revascularization. Global left ventricular function improvement as estimated by radionuclide ventriculography was selected for evaluation post revascularization over the actual recovery on a segmental level as it is an acceptable and important clinical surrogate which is easily understood by most general physicians.

In conclusion the assessment of myocardial viability by DSE in patients with coronary artery disease has improved sensitivity when scoring of individual segments at recovery phase becomes an integral part of the regular DSE scoring.

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The Long Prognostic Value of Wall Motion Abnormalities During the Recovery Phase of Dobutamine Stress Echocardiography After Receiving Acute Beta-Blockade

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CHAPTER **4**

The Long Prognostic Value of Wall Motion Abnormalities During the Recovery Phase of Dobutamine Stress Echocardiography After Receiving Acute Beta-Blockade

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Abstract

Objective: To assess the prognostic value of wall motion abnormalities (WMA) during recovery phase of dobutamine stress echocardiography (DSE) in addition to WMA at peak stress.

Methods: WMA were assessed at peak and during recovery phase of DSE in 187 consecutive patients, who were followed for occurrence of cardiac events.

Results: During follow up (mean 36 months±28), 19 patients (10%) died from cardiac causes, 34 (18%) patients suffered non-fatal myocardial infarction and 77 (41%) patients underwent late revascularization. Univariable predictors of cardiac events by Cox regression analysis were age (hazard ratio HR1.01 confidence interval CI1.00-1.03), dyslipidaemia (HR1.41 CI1.02-1.95), rest WMA (HR1.37, CI 1.14-1.64), new WMA (HR1.18 CI 0.95-1.45) at peak and new WMA (HR1.33, CI 1.11-1.59) at recovery phase of DSE. The best multivariable model to predict cardiac events included new WMA (HR5.34 CI 1.71-16.59) at recovery phase of DSE, after controlling for clinical and peak DSE data.

Keywords: Dobutamine Stress Echocardiography, ischemia, risk stratification

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Running head: Significance of ischemia during recovery phase of stress echocardiography

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Conclusions: Myocardial ischemia at recovery phase of DSE is an independent predictor of cardiac events and has an incremental value when added to ischemia at peak.

Introduction:

Dobutamine Stress Echocardiography (DSE) is one of the leading non-invasive imaging techniques for detection of coronary artery disease (CAD), viability estimation and for prognosis and risk stratification in the setting of CAD and prior to non-cardiac surgery[1]. Its safety accuracy and feasibility have well been established[2]. Several studies have demonstrated the high predictive value of DSE for long-term cardiac events in a large group of patients[3]. However the role of the recovery phase of DSE is underestimated and its value in long term prognosis of patients is yet to be determined. The aim of our study is to assess the additional prognostic value of reversible wall motion abnormalities (myocardial ischemia) of the recovery phase of DSE, compared to ischemia at peak stress, for long-term cardiac events.

Methods:

Patient population

The study population included 200 consecutive patients who were referred to DSE for the evaluation of suspected or known CAD at the Thoraxcenter (Rotterdam, the Netherlands) between March 2001 and March 2003, who were unable to perform an adequate exercise test and underwent coronary angiography within 3 months of DSE. Thirteen patients underwent early coronary revascularization, in the first 60 days after DSE, and were excluded from the analysis as the decision for the revascularization might be influenced by the results of DSE. Therefore the final analysis included 187 patients. Diabetes mellitus was defined as fasting plasma glucose level of ≥126 mg/dl on at least two occasions and/or requirement for insulin or oral hypoglycaemic agents, according to the criteria by the American Diabetes Association[4,5]. Hypercholesterolemia was defined as total cholesterol of 200 mg/dl or use of a cholesterol-lowering agent. Hypertension was defined as systolic blood pressure of 140 mmHg, diastolic blood pressure of 90 mmHg, or use of antihypertensive medication. Heart failure was defined according to the New York Heart Association classification. The local medical ethics committee approved the study protocol. Patients gave an informed consent to undergo the study.

Dobutamine stress echocardiography

The DSE protocol was approved by the local medical ethics committee and was performed in accordance with well-established protocols[6-8]. Studies were performed using a Sonos 5500 imaging system (Phillips Medical Systems, Eindhoven, The Netherlands). Patients underwent a resting two-dimensional echocardiographic examination from the standard apical and parasternal views. Images were recorded on videotape and also digitized for comparison of different stages. Dobutamine was then administered intravenously by infusion pump, starting at 5 mg/kg/min for 3 minutes, followed by 10 mg/kg/min for 5 minutes and increasing by 10 mg/kg/min every

3 minutes to a maximum of 40 mg/kg/min (stage 5), and continued for 6 minutes. The dobutamine infusion was stopped if a target heart rate (85% of a theoretic maximal heart rate (men: (220 – age) x 85%; women: (200 – age) x 85%) was achieved. If the target heart rate was not achieved and patients had no symptoms or signs of ischemia, atropine (starting with 0.25 mg, increased to a maximum of 2.0 mg) was given intravenously at the end of stage 5 while the dobutamine administration was continued. During the test, a 12-lead ECG was recorded every minute. Blood pressure was measured at the end of every dobutamine infusion stage. Metoprolol was administered (1,0 to 5,0 mg) intravenously according to heart rate response and systolic blood pressure, and after peak stress images were acquired, to achieve a recovery phase, defined as heart rate within 10% range of resting heart rate.

The criteria for stopping the test were: (1) achievement of the target heart rate (2) severe and extensive NWMA, (3) horizontal or downsloping ST depression of ≥0.2 mV measured 80 ms after the J point, or ST-segment elevation of ≥0.2 mV in the absence of Q waves, (4) symptomatic decline in systolic blood pressure of more than 40 mmHg, or a systolic blood pressure ≤90 mmHg, (5) hypertension (blood pressure >240/140 mmHg), (6) the occurrence of sustained cardiac arrhythmias, (7) severe angina pectoris, and (8) intolerable adverse effects considered to be the result of dobutamine or atropine. Two experienced investigators performed off-line assessment of echocardiographic images without knowledge of the patient's clinical and coronary angiography data, but with knowledge of the doses of dobutamine and atropine used. Regional function was scored according to a 16 segment, five point scoring model: 1, normal; 2, mildly hypokinetic; 3, severely hypokinetic; 4, akinetic; and 5, dyskinetic. The results of DSE were considered positive if NWMA occurred (i.e., if wall motion in any segment worsened by ≥1 grades during the test, with the exception of akinesis becoming dyskinesis). The extent and location of ischemia were evaluated and a wall-motion score index (WMSI) (total score divided by the number of segments scored) was calculated, at rest, during peak stress, and during the recovery phase. Digital screen format was used to compare images. When there was disagreement between the two assessors, a third investigator viewed the images without knowledge of the previous assessments, and a majority decision was reached.

Coronary angiography

The presence of CAD was established by standard quantitative coronary angiography using the Judkins technique. A luminal diameter stenosis > 70% in a major epicardial vessel was considered significant. Multivessel CAD was defined by the presence of significant stenosis of two or three vessels, or more than 50% stenosis of the left main stem. The operators were blind to DSE results.

Long term follow up

Follow-up data were obtained in 2006 for the period between 2001 and 2003. The mean period of follow-up was 36 ± 28 months after DSE. Physicians who were unaware of patients' stress test results assessed events. There was a formal centralized adjudication process. The present status was determined by contacting the patient's general physician and/or review of the

hospital records. The date of the last interview or review was used to calculate the follow-up time. Evaluated end points were cardiac death, myocardial infarction, and late coronary revascularization. Cardiac death was defined by clinical data of acute myocardial infarction and/or significant cardiac arrhythmias and/or refractory congestive heart failure, together with ECG and autopsy studies when available. Elevations of cardiac isoenzyme levels and development of new ECG changes defined a nonfatal myocardial infarction. Revascularization by coronary angioplasty or bypass surgery 6 months after the original DSE was considered to reflect new or progressive symptoms. In patients with more than one cardiac event, the worst event was chosen: documented cardiac death (worst), nonfatal infarction (less worst), and coronary revascularization (least worst).

Statistical analysis:

Characteristics were summarized as percentages for categorical variables and as mean standard deviation for continuous variables. Univariate and multivariate analysis of clinical and echocardiographic variables with the end points were assessed using the Cox proportional hazards model. All clinical variables and representative DSE variables were considered in the model, regardless of their univariate significance. Variables were selected in a stepwise forward selection manner with entry and retention set at a significance level of 0.05. The incremental value of the recovery phase of DSE over the clinical variables in the prediction of events was assessed by adding various echocardiographic data to clinical and stress test parameters. More specifically, three modelling steps were used: 1) clinical variables alone, 2) clinical, rest, and stress echocardiographic variables and 3) clinical, rest, and stress and recovery echocardiographic variables were compared via their log likelihood ratio chi-square statistics. The fitted model included age only for the purpose of adjustment; all other models were based on the variables selected in the stepwise algorithm, which were replaced by dichotomous versions to facilitate ease of clinical use. The risk of a variable was expressed as a hazard ratio (HR) with a corresponding 95% confidence interval (CI). The probability of cardiac event-free survival was calculated by the Kaplan-Meier method and the resulting curves were compared by the log rank test[9,10]. All analyses were performed using SPSS-11.0 statistical software (SPSS Inc., Chicago, Illinois).

Results:

Patient Characteristics and Hemodynamic response

Patients' clinical characteristics are presented in Table 1. The patients' medication was altered accordingly to DSE results and clinical symptoms during the study. During DSE the heart rate increased significantly from rest to peak stress. Test end point was target heart rate and was reached in 94% of patients. Atropine was added at peak stress in 120 patients as the majority was on chronic beta-blockade. The mean maximal dobutamine dose was 38 ± 8 mcg/kg/min. Side effects included hemodynamically stable sustained ventricular tachycardia (>10 complexes)

Table 1: Study population characteristics

Characteristics in 187 patients	
Demographics	
Males	136 (73%)
Females	51 (27%)
Age	59±11
Cardiovascular History and cardiac risk factors	
Hypertension	65 (35%)
Heart Failure	41 (22%)
Diabetes Mellitus	34 (18%)
Previous Myocardial Infarction	99 (53%)
Dyslipidemia	95 (51%)
Smoking	47 (25%)
Previous PCI	103 (55%)
Cardiac Medication at baseline	
ACE-inhibitors	84 (45%)
Aspirin	49 (26%)
Statins	41 (22%)
β-blockers	120 (64%)
Nitrates	105 (56%)
Diuretics	41 (22%)
Digoxin	11 (6%)

in 2 (1%) patients , non-sustained ventricular tachycardia (<10 complexes) in 6 (3%) patients, atrial fibrillation in 4 (2%) patients and severe hypotension (decrease of systolic blood pressure >40mmHg) in 2 (1%) patients. No myocardial infarction or ventricular fibrillation was recorded or attributed to DSE.

Echocardiographic and Angiographic data

Rest wall motion abnormalities were observed in 123 (66%) patients. New WMA were present in 176 (94%) patients in total, 131 (70%) had new WMA at both peak and recovery phase, while 45 (24%) patients had new WMA only in the recovery phase after acute beta-blockade. During peak stress new WMA were present in 58 single-vessel disease and in 73 multi-vessel disease patients while during the recovery phase in 88 single- and 88 multi-vessel disease patients respectively. Furthermore all patients that showed ischemia at peak stress had persisting abnormalities after acute beta-blockade. Thirty single-vessel disease patients exhib-

Table 2: Predictors of late cardiac events (cardiac death, MI, late revascularization)

	Univariable predictors			Multivariable predictors		
	HR	95% CI	p Value	HR	95% CI	p Value
Diabetes	1.23	0.81 to 1.85	NS	2.23	1.10 to 4.49	0.024
HTN	1.06	0.75 to 1.49	NS			
Smoking	1.33	0.91 to 1.93	NS			
Dyslipidaemia	1.41	1.02 to 1.95	0.04			
Previous MI	1.35	0.98 to 1.87	NS			
CHF	1.20	0.82 to 1.75	NS	2,56	1.00 to 6.55	0.05
b-blockers	0.57	0.40 to 0.80	0.02			
Age	1.01	1.00 to 1.03	0.02	1.04	1.02 to 1.05	0.005
WMA rest	1.37	1.14 to 1.64	0.001			
NWMA peak	1.18	0.95 to 1.45	0.003			
NWMA rec	1.33	1.11 to 1.59	0.002	5.34	1.71 to 16.59	0.004

HTN: Hypertension
CHF: Congestive Heart Failure
NWMA rec: New Wall Motion Abnormalities at recovery

ited myocardial ischemia only during the recovery phase. Multivariate regression analysis showed that, new WMA in the recovery phase were the only independent predictors for single-vessel disease patients (odds ratio [OR] 6.24, 95% CI 2.61 to 14.9). The rate pressure product values at rest, peak and recovery were 8694 ± 286, 13910 ± 546 and 10648 ± 299 respectively. WMSI at rest was 1.78 ± 0.69, peak 1.90 ± 0.83 and at recovery 2.10 ± 0.95. Coronary angiography revealed 88 (47%) single vessel disease patients, 49 (26%) two-vessel disease patients and 39 (21%) three-vessel disease patients. All patients with angiographically single-vessel disease presented myocardial ischemia during the recovery phase of DSE; 58 during both peak and recovery phase and 30 only in the recovery phase after acute beta-blocker administration.

Intra- and interobserver variabilities

We observed good intraobserver agreement for images at rest (r = 0.90), low dose (r = 0.93), peak dose (r = 0.88), and recovery (r = 0.88, all p values <0.001). Moreover, global interobserver agreement was 88%.

Follow up

Follow up was successful for 187 patients. All cause mortality was 13% (25 patients), of which 10% (19 patients) was attributed to cardiac causes. Thirty-four (18%) patients suffered non-fatal myocardial infarction and 77 (41%) patients underwent late revascularization. Overall 130 (69%) patients had at least one cardiac event.

Predictors of late Cardiac Events

Univariate and multivariate predictors of late cardiac events (cardiac death, non-fatal myocardial infarction and late revascularizations) are summarized in table 2.

Univariable independent predictors of late cardiac events included age, dyslipidaemia, WMA at rest and new WMA at peak and recovery phase of DSE. Among clinical variables age, the presence of heart failure and diabetes were multivariable independent predictors of late cardiac events. Moreover myocardial ischemia estimation at recovery was the only DSE parameter, independently predicting late cardiac events in multivariate analysis. Similarly, although underpowered due to limited number of hard events, myocardial ischemia during the recovery phase was independently predicting in a trend line manner all-cause mortality and non-fatal myocardial infarction. Figure 1 illustrates the incremental contribution of myocardial ischemia at recovery phase of DSE over clinical data and ischemia at peak DSE, for prediction of late cardiac events.

Kaplan-Meier survival curves for the end point of late cardiac events in patients with myocardial ischemia at both peak and recovery phase of DSE, versus myocardial ischemia only in the recovery phase of DSE, are presented in figure 2.

Discussion:

In the present study we assess the incremental value of myocardial ischemia at the recovery phase of DSE for prediction of late cardiac events, in 187 patients with known or suspected CAD. During a mean follow up of 36 (±28) months, 130 (69%) patients had at least one cardiac event. Coronary angiography showed that patients with single-vessel disease were more accurately diagnosed by new WMA during the recovery phase compared to peak stress [OR 6.24, 95% CI 2.61 to 14.9]. Univariate analysis showed that among others, rest and DSE parameters were positively related to the risk of developing late cardiac events. Multivariable analysis results showed that clinical predictors of late cardiac events were diabetes, congestive heart failure and age. However the presence of myocardial ischemia (NWMA) during recovery phase was the only independent DSE predictor of late cardiac events. In fact this model proved to have the best predictive value for late cardiac events (HR 11.17, x^2

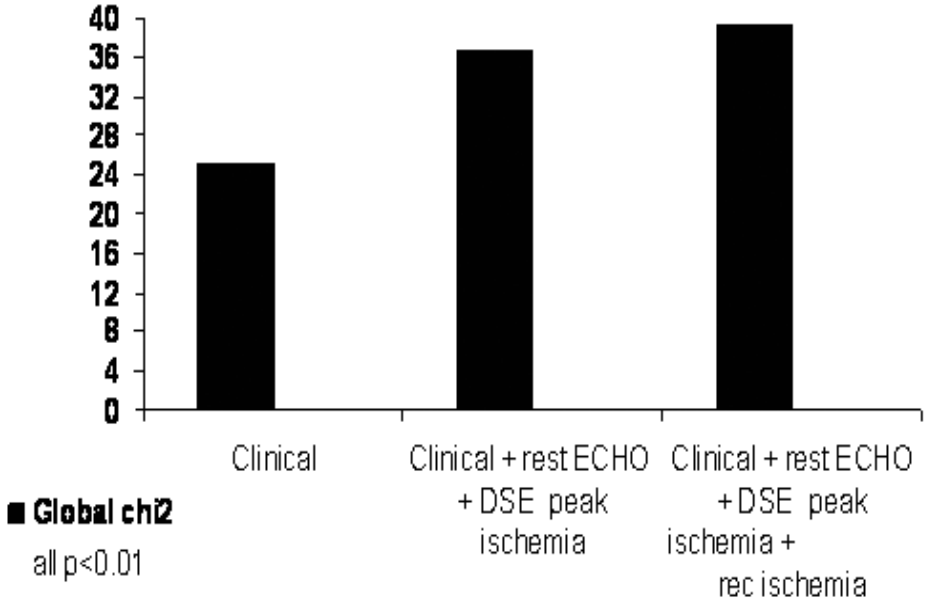

Figure 1: Incremental prognostic value of myocardial ischaemia at recovery phase over clinical data and ischaemia at peak DSE, for prediction of late cardiac events.

39.140) as shown in figure 1. Patients that exhibited ischemic response only in the recovery phase and after acute beta-blockade had a delayed event than those that presented ischemia at peak. The two survival curves crossed each other at 24 months of follow up. A possible explanation could be the fact that these patients were predominantly single-vessel disease patients (30 single-vessel disease patients vs 15 multi-vessel disease patients) with milder extent of ischemia than those with reversible wall motion abnormalities at peak DSE. Mathias et al[11] have demonstrated that injection of beta-blockers at the peak dose of DSE might enhance regional wall abnormalities and increase the sensitivity of the recovery images especially in single-vessel disease patients. So recovery phase mainly offers additional predictive information in patients that have a missed ischemic response at peak DSE.

Dobutamine and recovery phase of DSE

A possible explanation of our DSE results is that at the recovery phase we could better visualize the ischemic segments that already existed at peak stress but were masked by hyperdynamic contraction of mid- and epicardial layers. Dobutamine stimulates β1, β2, and α1-adrenergic receptors[12]. Acute β-blockade interacts with dobutamine β1 and β2 receptors leaving unopposed α1-adrenergic vasoconstriction[13] and therefore leading to reduction of coronary flow reserve[14]. This means that increased vasoconstriction can cause myocardial ischemia and that

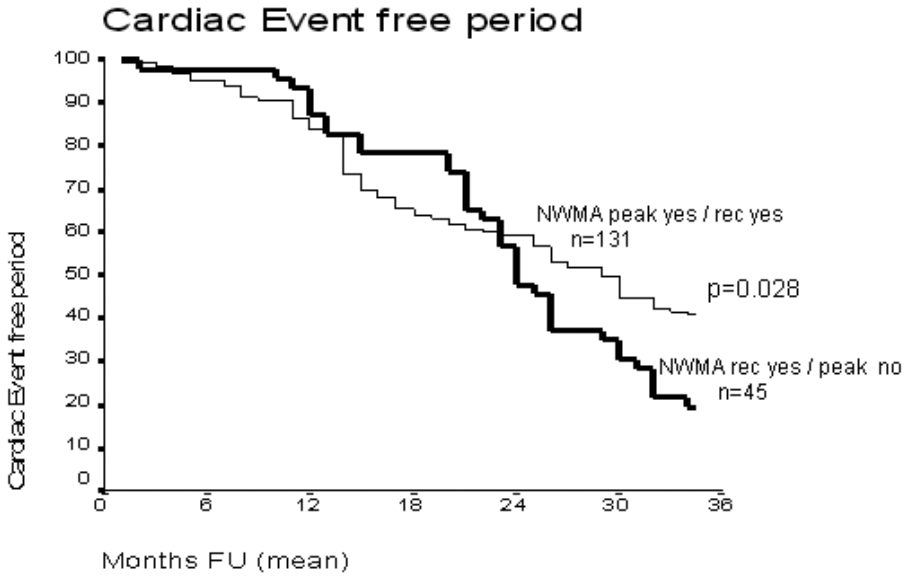

Figure 2: Kaplan-Meier survival curves demonstrating the late cardiac event free period in patients with myocardial ischaemia at both peak and recovery phase of DSE, versus ischaemia only in the recovery phase of DSE.

could also explain the paradoxical enhancement of wall motion abnormalities at the recovery phase. Moreover we found that the value of rate-pressure product during the recovery phase, as a measure of oxygen consumption rate, was less than its value at peak stress, but more than the value at rest. This indicates a prolonged ischemic effect of dobutamine during the recovery phase.

We also have to mention the potential role that myocardial stunning (with or without the influence of beta-blockers) may have in producing NWMA in recovery. Wall motion abnormalities in recovery that are not apparent at peak stress may be due to worsening of post-stress abnormalities with stunning.

Comparison with previous studies

Several studies have demonstrated that DSE can be used as a prognostic tool for a large pool of patients[3,15,16], alternatively to other stress modalities[1,2,17]. So far there has been evidence that myocardial ischemia based on reversible wall motion abnormalities at peak DSE, predict patients that have increased risk of developing late cardiac events, even if they are asymptomatic after coronary intervention[18]. There are also a number of studies demonstrating the predictive value of myocardial ischemia at peak DSE, in several subgroups of patients[18-25]. Peak dobutamine wall motion score index, which measures the sum of resting and stress-induced wall motion abnormalities, has been shown to be incremental to clinical data in the prediction of all causes of mortality[15,16]. This is related to the "combined" information of DSE, which provides information on left ventricular function at rest, functional improvement at low-dose dobutamine in segments with rest dyssynergy, and the presence and extent of myocardial ischemia at peak

DSE[3,15,16,25]. Nevertheless, to our knowledge this is the first study assessing the incremental value of myocardial ischemia in the recovery phase of DSE in a predictive model, for prognosis of late cardiac events despite the fact that there were only a modest number of hard events (death and MI).

A possible clinical implication of the present study is that future development of quantitative automatic wall motion scoring systems could include recovery phase in addition to peak images scoring.

Study limitations

During follow-up, only 19 patients died due to cardiac causes. That was a small number of patients to provide valuable prediction model for cardiac mortality. On the other hand that could be attributed to the substantial progress in the treatment of CAD. As our hospital is a referral centre, 55% of our study population had undergone a revascularization procedure and 53% had suffered an MI prior to DSE. That could explain the high prevalence of disease of the study population and the small number of normal subjects.

Conclusions

In conclusion observation and scoring of individual segments at recovery phase, as part of the regular DSE scoring, improve the assessment of myocardial ischemia in CAD patients and provide incremental prognostic value for cardiac events, when compared to peak.

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Value of Myocardial Viability Estimation by Dobutamine Stress Echocardiography in Assessing Risk Preoperatively Before Non-Cardiac Vascular Surgery in Patients with Left Ventricular Ejection Fraction <35%

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CHAPTER **5**

Value of Myocardial Viability Estimation by Dobutamine Stress Echocardiography in Assessing Risk Preoperatively Before Non-Cardiac Vascular Surgery in Patients with Left Ventricular Ejection Fraction <35%

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Abstract

Patients with heart failure (HF) scheduled for vascular surgery have increased risk for adverse postoperative outcome, stratification usually depends on dichotomous risk factors. We sought to develop a quantitative prognostic model for HF patients using wall motion patterns during dobutamine stress echocardiography (DSE).

We studied 295 consecutive patients (mean age: 67±12 years) with ejection fraction ?35%. During DSE wall motion patterns of dysfunctional segments were scored as scar, ischemia or sustained improvement. Cardiac death and myocardial infarction were noted perioperative and during 5 year follow-up. Of 4572 dysfunctional segments; 1783 (39%) had ischemia, 1280 (28%) sustained improvement and 1509 (33%) scar. In 212 patients ≥1 ischemic segments were present; 83 had only sustained improvement. Perioperative and late cardiac events were 20% and 30% respectively. Using multivariate analysis the number of ischemic segments were associated with perioperative cardiac events (odds ratio (OR) per segment 1.6; 95%CI 1.05-1.8),

Running head: Patients with heart failure scheduled for non-cardiac surgery. *Total word count*: 2782
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while the number of segments with sustained improvement were associated with improved outcome (OR per segment 0.2; 95%CI 0.04-0.7). Multivariate independent predictors of late cardiac events were age and ischemia. Sustained improvement was associated with improved survival. We demonstrated that DSE provides an accurate risk stratification of HF patients undergoing vascular surgery.

Keywords: Heart Failure, Dobutamine Stress Echocardiography, vascular surgery.

Introduction

Preoperative cardiac risk assessment for patients undergoing major vascular surgery is a challenging entity. Patients are mainly stratified according to the number of dichotomous cardiac risk factors [1, 2]. At present risk stratification of patients with HF scheduled for vascular surgery mainly depends on resting left ventricular (LV) function, as it is shown that patients with LV dysfunction have a reduced long-term survival after major vascular surgery [3, 4, 5]. However, the presence of myocardial viability; i.e. dysfunctional segments that improve after inotropic stimulation might enhance preoperative risk stratification. A quantification of dobutamine stress echocardiography (DSE) results would help in this aspect. We tried according to the Bayesian principle to change the pretest probability in more precise post test quantification of risk and therefore stratify HF patients more accurately. The aim of our study is to assess the prognostic implications of ischemia or sustained improvement, as the 2 main patterns of response of viable tissue to DSE, in patients with known LV ejection fraction < 35%, undergoing major vascular surgery.

Methods

The study population included 295 consecutive patients with known LVEF?35%, who were referred to the Erasmus MC (Rotterdam, the Netherlands) for major vascular non-cardiac surgery, between June 1999 and June 2001. All patients underwent DSE examination for evaluation of viability. Diabetes mellitus was defined as fasting plasma glucose level of ≥126 mg/dl on at least two occasions and/ or requirement for insulin or oral hypoglycaemic agents, according to the criteria by the American Diabetes Association [6]. Hypercholesterolemia was defined as total cholesterol of 200 mg/dl or use of a cholesterol-lowering agent. Hypertension was defined as systolic blood pressure ≥ 140 mmHg, diastolic blood pressure ≥ 90 mmHg, or use of antihypertensive medication. The local medical ethics committee approved the study protocol. Patients gave an informed consent for the study.

The DSE protocol was approved by the Hospital Ethical Committee and was performed in accordance with well-established protocols [7, 8]. Studies were performed using a Sonos 5500 imaging system (Phillips Medical Systems, Eindhoven, The Netherlands). Patients underwent a resting 2-dimensional echocardiographic examination from the standard apical and parasternal views. Images were recorded on videotape and also digitized for comparison of different stages. Dobutamine was administered intravenously by infusion pump, starting at 5 mg/kg/min, followed by 10 mg/kg/min for 5 minutes and increasing by 10 mg/kg/min every 3

minutes to a maximum of 40 mg/kg/min (stage 5), and continued for 6 minutes. The dobutamine infusion was stopped if a target heart rate (85% of a theoretic maximal heart rate (men: (220 – age) x 85%; women: (200 – age) x 85%) was achieved. If the target heart rate was not achieved and patients had no symptoms or signs of ischemia, atropine (starting with 0.25 mg, increased to a maximum of 2.0 mg) was given intravenously at the end of stage 5 while the dobutamine administration was continued. During the test, a 12-lead electrocardiogram was recorded every minute. Blood pressure was measured every 3 minutes. Metoprolol was administered (1,0 to 5,0 mg) intravenously according to heart rate response and systolic blood pressure, and after peak stress images were acquired to achieve a recovery phase, defined as heart rate within 10% range of resting heart rate. The criteria for stopping the test were: (1) achievement of the target heart rate (2) severe and extensive NWMA, (3) horizontal or downsloping ST depression of ≥0.2 mV measured 80 ms after the J point, or ST-segment elevation of ≥0.2 mV in the absence of Q waves, (4) symptomatic decline in systolic blood pressure of more than 40 mmHg, or a systolic blood pressure ≤ 90 mmHg, (5) hypertension (blood pressure >240/140 mmHg), (6) the occurrence of sustained cardiac arrhythmias, (7) severe angina pectoris, and (8) intolerable adverse effects considered to be the result of dobutamine or atropine. Two experienced investigators performed off-line assessment of echocardiographic images without knowledge of the patient's clinical and coronary angiography data, but with knowledge of the doses of dobutamine and atropine used. Interobserver and intraobserver agreement for analysis of DSE studies were reported previously (92% and 94%, respectively) [9]. Regional function was scored according to a 16 segment, five point scoring model: 1, normal; 2, mildly hypokinetic; 3, severely hypokinetic; 4, akinetic; and 5, dyskinetic. Wall-motion score index (WMSI) (total score divided by the number of segments scored) was calculated, at rest, low dose and during peak stress. Myocardial viability was assessed in severely dysfunctional segments; 4 types of wall motion responses were observed: (1) biphasic pattern (ischemia): improvement of wall motion at 5, 10, or 20 mg/kg/min dobutamine with worsening at higher dosages; (2) worsening only (ischemia); (3) sustained improvement; (4) no change or scar. Severely dysfunctional segments exhibiting a biphasic, sustained, or worsening response were considered viable, whereas segments with unchanged wall motion were considered scarred.

Evaluated end points were all cause mortality, cardiac death and non-fatal myocardial infarction. Cardiac death was defined by clinical data of acute myocardial infarction and/or significant cardiac arrhythmias and/or refractory congestive heart failure, together with electrocardiographic and autopsy studies when available. Elevations of cardiac isoenzyme levels and development of new electrocardiographic changes defined a non-fatal myocardial infarction. In patients with more than one cardiac event, the worst event was chosen: documented cardiac death (worst) and nonfatal infarction (less worst). Perioperative cardiac events were considered as those events that occurred within 30-days after surgery. Follow-up data were obtained in 2006 .The mean period of long-term follow-up was 60 months (± 24) after DSE. Physicians who were unaware of patients' stress test results assessed events. The present status was determined by contacting the patient's general physician and/or review of the hospital records. The date of the last interview or review was used to calculate the follow-up time.

The t-test was used for continuous variable and chi –square test was used for categorical

variables. Characteristics were summarized as percentages for categorical variables and as mean ± standard deviation for continuous variables. Univariate and multivariate analysis of clinical and echocardiographic variables with the end points were assessed using logistic regression analysis for the 30 day post-surgery period and the Cox proportional hazards model for long-term follow-up. All clinical variables and representative DSE variables were considered in the model, regardless of their univariate significance. Variables were selected in a stepwise forward selection manner with entry and retention set at a significance level of 0.05. The fitted model included age only for the purpose of adjustment; all other models were based on the variables selected in the stepwise algorithm, which were replaced by dichotomous versions to facilitate ease of clinical use. The risk of a variable was expressed as hazard ratio (HR) or odds ratio (OR) with a 95% confidence interval (CI). The probability of cardiac death free survival was calculated by the Kaplan-Meier method and the resulting curves were compared by the log rank test [10].

Results

The patients' demographics and clinical characteristics are presented in Table 1. The patients' medication was continued during the study.

During DSE the heart rate increased significantly from rest to peak stress. The rate pressure product values at rest, low, and peak were 8694 ± 286, 13910 ± 546 and 17028 ± 351 respectively. In 91% of patients target heart rate was reached. Atropine was added at peak stress in 97 patients as the majority was on chronic beta-blocker therapy. The mean maximal dobutamine dose was 38 ± 8 mcg/kg/min. Side effects included hemodynamically stable sustained ventricular tachycardia (>10 complexes) in 4 (1%) patients , non-sustained ventricular tachycardia (<10 complexes) in 14 (5%), atrial fibrillation in 4 (1%), and severe hypotension (decrease of systolic blood pressure >40 mmHg) in 4 (1%). No myocardial infarction or ventricular fibrillation was recorded during or attributed to DSE. The WMSI at rest was 2.08 ± 0.50, at low dose 1.39± 0.44, and at peak dose 1.89 ± 0.55. From the 4572 dysfunctional segments, 1783 (39%) exhibited an ischemic response, 1280 (28%) had sustained improvement and in 1509 (33%) the motion patterns was unchanged during DSE and therefore were defined as scar. As expected all these patients with LV dysfunction of ischemic etiology had several degrees of scar tissue. 212 patients had one or more ischemic segments, while 83 patients experienced only a sustained improvement during DSE. In 26 patients with severe ischemia during DSE and symptomatic angina not relieved by medication, cardiac revascularization procedure preceded non-cardiac surgery.

During the early perioperative period i.e. within 30-days after operation, 6 patients died, 34 patients suffered non-fatal acute myocardial infarction and 54 patients experienced an ischemic cardiac event (elevated isoenzyme levels). From these 54 patients, 47 (87%) had presented ischemia during DSE and 7 (13%) presented sustained improvement ($p< 0.001$). From the 34 patients with acute myocardial infarction the respective numbers were 29 (83%) and 5 (15%) ($p< 0.001$). Four (15%) out of 26 patients that underwent coronary revascularization prior to vascular surgery suffered a non-fatal myocardial infarction.

Univariate significant predictors of perioperative cardiac events were cholesterol ≥200mg/dl

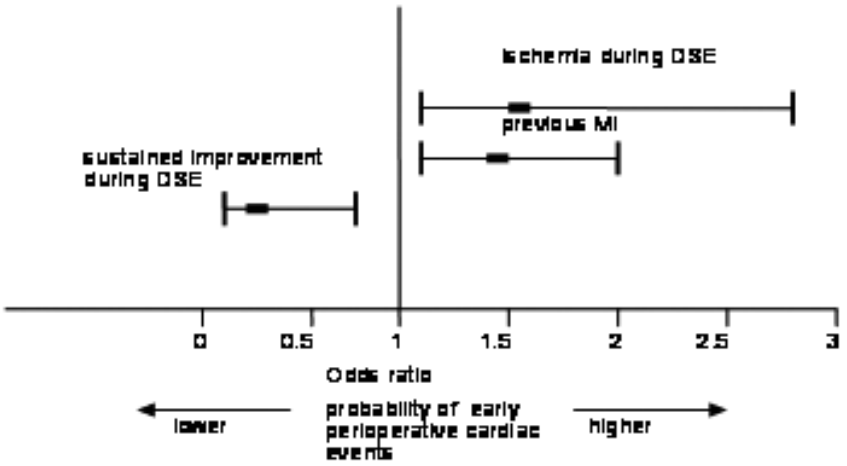
Table 1: Study population characteristics (n=295)

Males	234 (79%)
Females	61 (21%)
Age (Years)	67 ±12
Hypertension	87 (29%)
Diabetes Mellitus	53 (18%)
Previous Myocardial Infarction	158 (54%)
Cholesterol ≥ 200 mg/dl	77 (26%)
Smoking	114 (39%)
Angina	27 (9%)
Previous Percutaneous Coronary Intervention	21 (7%)
Previous Coronary Artery Bypass Grafting	56 (19%)
Cardiac Medications	
Angiotensin Converting Enzyme -inhibitors	100 (34%)
Aspirin	23 (8%)
Statins	18 (6%)
β-blockers	99 (34%)
Calcium channel-blockers	79 (27%)
Nitrates	71 (24%)
Diuretics	59 (20%)
Digoxin	28 (9%)

(OR 1.71, 95%CI 1.03-2.85, p=0.04) and ischemia during DSE (OR 2.77, 95%CI 1.15-6.64, p=0.001).

Multivariate analysis showed that an increased number of segments with sustained improvement during DSE compared to the number of ischemic segments was associated with an improved postoperative outcome. The only multivariable independent predictors of early perioperative cardiac events were previous myocardial infarction (OR 1.5, 95%CI 1.05 -2.3), ischemia (OR 1.6, 95%CI 1.05 -2.8) and sustained improvement during DSE (OR 0.2, 95%CI 0.04-0.7) (Figure 1). For perioperative all-cause mortality the only independent predictor in multivariate analysis was age (OR 1.03, 95%CI 1.05-1.1).

Long term follow up was successful for all patients. All cause mortality was 43% (128 patients), and 70% (89 patients) of that was attributed to cardiac causes. Thirteen (4%) patients had non-fatal myocardial infarction. Overall 102 (35%) patients had at least one hard cardiac event. From the 128 patients that died from all causes, only 21 had sustained improvement during DSE. Furthermore only 11 patients with sustained improvement during DSE died from cardiac causes and another 3 had a non-fatal myocardial infarction. From the 26 patients that



DSE: Dobutamine Stress Echocardiography
MI: Myocardial Infarction

Figure 1: Diagram showing the independent multivariate predictors for cardiac events within 30 days following major vascular surgery in patients with LV ejection fraction < 35%.

underwent coronary revascularization prior to vascular surgery, 6 died from all causes and 7 had late cardiac events, 4 of which were fatal myocardial infarction.

Univariate analysis for all-cause mortality showed that beta-blockers use was associated with an improved outcome (HR 0.61, 95%CI 0.42-0.89, p=0.006). Sustained improvement (HR 0.71, 95%CI 0.49-1.01, p=0.09) and ischemia (HR 1.21, 95%CI 0.83-1.76, p=0.30) during DSE, were not significant univariable predictors. However in a multivariate model of clinical and echocardiographic parameters the only independent predictors of all-cause mortality were age (HR 1.05, 95%CI 1.02-1.07) and ischemia (HR 1.06, 95%CI 1.02-1.12) during DSE.

Univariable predictors of cardiac events are summarized in table 2. Angina was not significant univariate predictor for any events (HR 1.0, 95%CI 0.56-1.68, p=0.55). In the multivariate model age (HR 1.05, 95%CI 1.02-1.08) and ischemia during DSE (HR 1.9, 95%CI 1.1-4.0), were independent predictors of cardiac events, whereas sustained improvement (HR 0.5, 95%CI 0.3-0.9) proved to be protective.

Kaplan-Meier curves for the end point of cardiac events in patients with sustained improvement versus ischemia during DSE are illustrated in figure2.

Discussion

This study demonstrates the independent prognostic value of wall motion patterns during DSE in patients with LV dysfunction undergoing major vascular surgery, for the prediction of cardiac events within 30 days after surgery, and for all-cause mortality and hard cardiac events

Table 2: Uniavariate predictors of cardiac events (cardiac death and myocardial infarction) in heart failure patients undergoing major vascular surgery

Univariable predictors	Hazard Ratio	95% Confidence Interval	p Value
Previous myocardial infarction	1.51	1.00 to 2.31	0.05
Hypertension	1.15	0.75 to 1.78	0.51
Smoking	1.05	0.70 to 1.57	0.84
Age	1.00	0.59 to 1.71	0.99
Diabetes mellitus	1.00	0.60 to 1.70	0.99
Beta-blockers	0.62	0.38 to 0.95	0.04
Statins	0.62	0.35 to 1.09	0.07
Ischemia during low-high dobutamine stress echocardiography	1.65	0.93 to 2.92	0.06
Sustained improvement during low-high dobutamine stress echocardiography	0.72	0.43 to 1.22	0.25

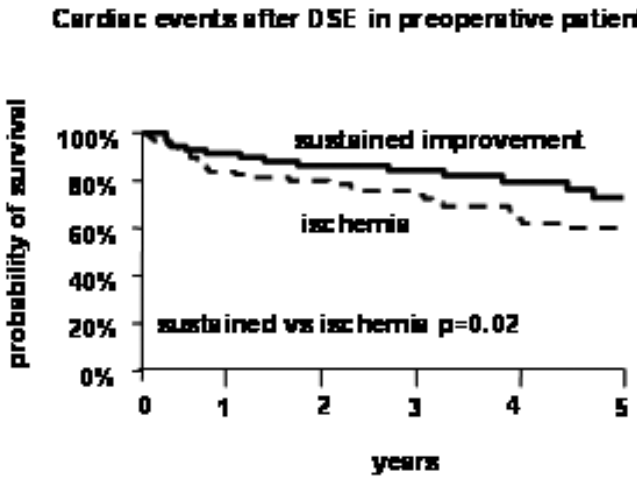
during a long-term mean follow-up of five years.

Our results showed that sustained improvement during DSE provided a protective effect in both early perioperative period and long-term cardiac events. On the contrary ischemia proved to be hazardous in both early and long-term follow up periods. When patients with sustained improvement were compared to patients with ischemia during DSE they had significantly less events in the early perioperative period ($p< 0.001$). Moreover the difference in survival during long-term follow-up regarding cardiac events between the two different viability responses during DSE was also significant ($p=0.02$) (Figure 2).

Ischemia during DSE also predicted decreased survival in all-cause mortality.

Furthermore the beneficial effect that beta-blockers exert in patients' survival [11] was reconfirmed in our study for both all-cause mortality and late cardiac events.

It is extensively reported that cardiovascular complications are the leading cause of death after non-cardiac surgery [12, 13, 14]. That was also the case in our study. We found that 70% of total mortality was attributed to cardiac causes. Furhtermore patients with resting LV dysfunc-



DSE: Dobutamine Stress Echocardiography
LVEF: Left Ventricular Ejection Fraction

Figure 2: Kaplan-Meier curve showing survival from cardiac events in patients with LV ejection fraction < 35%, undergoing major vascular surgery, with sustained improvement vs ischemia during low-high DSE.

tion have greatly reduced long-term survival following non-cardiac surgery [14, 15, 16, 17, 18]. Regarding early perioperative outcome this has not been clearly shown maybe due to the inability of resting LV ejection fracrion to provide information regarding severe underlying coronary artery disease [14]. Therefore by utilizing DSE we further stratified those patients with resting LV dysfunction, according to their viability profile. Viable patients with sustained improvement suffered much less cardiac events during the first 30 days following surgery compared to patients with an ischemic response in low-high DSE. This is in accordance with a previous study by Landesberg et.al [19]. Although these authors used thallium scan and not DSE, they similarly found that ischemia was associated with an increased incidence of troponin elevation during the early perioperative period [19, 20]. Also in a previous study from our group it was shown that the presence of new wall motion abnormalities during DSE was a powerful determinant of an increased risk for perioperative events [14, 21]. Other studies also have demonstrated similar results [22, 23, 24]. However the present study is the only study to our knowledge demonstrating a clear benefit for patients with LV dysfunction and with sustained improvement during DSE, regarding the early perioperative outcome. Especially, patients with predominantly sustained improvement are at lower risk and might respond favorable to low-dose inotropic stimulation during surgery. On the other hand, in patients with predominantly an ischemic response, beta-blockers or revascularization could be considered. Previous studies have evaluated the role of extended ischemia detection in stress echocardiography either with dobutamine [11, 14, 25] or dipyridamole [26] and its correlation with late cardiac events in patients undergoing non-cardiac

surgery. Furthermore it has been shown that the extent of fixed and reversible perfusion defects on dipyridamole thallium scintigraphy is a significant indicator of late cardiac risk [23, 27]. We also found similar results regarding the probability of all-cause mortality and long-term cardiac events. However our study population was more homogeneous as it consisted only of patients with known LV dysfunction of ischemic origin. Moreover we tried to investigate a further possible stratification of these patients according to their viability response during DSE. By extensive internet search of medical libraries we came to the conclusion that our study is the first to our knowledge demonstrating a beneficial effect of a sustained improvement response during DSE for viability estimation in this group of patients for the end point of long-term cardiac death.

A possible limitation of our study is that as an observational one, it relied mainly upon medical records and administrative data meaning that the effects of some cardiac risk factors could be biased. Nevertheless most of the predictive values that we found are in concordance with previous studies both from our and other institutions. Another possible limitation could be the fact that we did not investigate the impact of response to dobutamine according to the type of surgery. However the aim of our study was to provide a more accurate stratification of risk of patients with LV dysfunction irrespective of the type of scheduled surgery.

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Prognostic Significance of Renal Function in Patients Undergoing Dobutamine Stress Echocardiography

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Nephrol Dialysis Transplant (in press)

CHAPTER **6**

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Abstract

Background: Dobutamine stress echocardiography (DSE) is used for risk stratification of patients with suspected coronary artery disease (CAD). However the prognostic value of DSE among the entire strata of renal function has yet to be determined. We assessed the prognostic value of renal function relative to DSE findings.

Methods: We studied 2292 patients, divided in 1015 (44%) patients with normal renal function (creatinine clearance (CrCL)>80ml/min) and 1277 (66%) with renal dysfunction, classified as mild (CrCl:60-80ml/min) in 647, moderate (CrCl:40-60ml/min) in 403 and severe (CrCl<40ml/min) in 227 patients. All underwent DSE for evaluation of known or suspected CAD and were followed for a mean of 8 years.

Results: New wall motion abnormalities during DSE and mildly, moderately and severely abnormal CrCl were powerful independent predictors for all cause mortality, cardiac death and hard cardiac events (cardiac death and non-fatal myocardial infarction). Kaplan-Meier curves demonstrated that patients with normal DSE and renal dysfunction have greater probability for

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cardiac death and hard cardiac events compared to those with normal renal function. The warranty of a normal DSE in the presence of mild, moderate and severe renal dysfunction was 48, 36 and 6 months respectively.

Conclusions: The presence and severity of renal dysfunction has additional independent prognostic value over DSE findings. The low risk warrantee period after a normal DSE is determined by the severity of renal dysfunction.

Keywords: Dobutamine Stress Echocardiography, prognosis, renal function.

Running title: DSE and renal function

Introduction

Cardiovascular disease is the major cause of death in patients with renal dysfunction [1]. In particular, coronary artery disease (CAD) is an important predictor of mortality in chronic renal failure patients [2]. Dobutamine stress echocardiography (DSE) is a widely used non-invasive imaging technique for detection of CAD [3]. Several studies have demonstrated the high predictive value of DSE for long-term cardiac events in patients with normal renal function [4]. It has also been suggested as a tool for risk stratification of patients with chronic renal failure, specifically in patients undergoing evaluation for kidney transplantation [5]. However the value of wall motion abnormalities (WMA) during DSE among the entire strata of renal function has yet to be determined. The identification of clinical variables that influence prognosis in addition to abnormalities on DSE is important to optimize risk stratification in a given patient. The aim of this study was to assess the prognostic value of renal function relative to DSE findings in patients with known or suspected CAD.

Subjects and Methods

Study population and baseline measurements

The study population included 2292 consecutive patients with known or suspected CAD who were referred at the Erasmus MC (Rotterdam, the Netherlands) for DSE between 1993 and 2003. Diabetes mellitus was defined as fasting plasma glucose level of ≥126 mg/dl on at least two occasions and/or requirement for insulin or oral hypoglycaemic agents, according to the criteria by the American Diabetes Association [6]. Hypercholesterolemia was defined as total cholesterol of 200 mg/dl or use of a cholesterol-lowering agent. Hypertension was defined as systolic blood pressure of 140 mmHg, diastolic blood pressure of 90 mmHg, or use of antihypertensive medication. Heart failure was defined according to the New York Heart Association classification.

Renal function assessment

Serum creatinine was assessed by a nonkinetic alkaline picrate (Jaffe) method. Creatinine clearance (CrCl) was computed with the Cockcroft-Gault [7] equation: CrCl (ml/min) = (140-

age) X weight (kg) ÷ 72 X serum creatinine (mg/dl) (X 0.85 for women) and standardized for body surface area using the Dubois formula. This equation has close correlation with measured creatinine clearance and gives a more accurate assessment of renal function than serum creatinine alone.

By this definition patients were divided in 4 groups; normal renal function (CrCl > 80ml/min) and mild (CrCl = 60-80ml/min), moderate (CrCl = 40-60ml/min) and severe (CrCl < 40ml/min) renal dysfunction. The local medical ethics committee approved the study protocol. Patients gave an informed consent to undergo the study.

Dobutamine stress echocardiography

The DSE protocol was approved by the local medical ethics committee and was performed in accordance with well-established protocols [8]. Studies were performed using a Sonos 5500 imaging system (Phillips Medical Systems, Eindhoven, The Netherlands). Patients underwent a resting two-dimensional echocardiographic examination from the standard apical and parasternal views. Images were recorded on videotape and also digitized for comparison of different stages. Dobutamine was then administered intravenously by infusion pump, starting at 5 mg/kg/min, followed by 10 mg/kg/min for 5 minutes and increasing by 10 mg/kg/min every 3 minutes to a maximum of 40 mg/kg/min (stage 5), and continued for 6 minutes. The dobutamine infusion was stopped if a target heart rate (85% of a theoretic maximal heart rate (men: (220 – age) x 85%; women: (200 – age) x 85%) was achieved. If the target heart rate was not achieved and patients had no symptoms or signs of ischemia, atropine (starting with 0.25 mg, increased to a maximum of 2.0 mg) was given intravenously at the end of stage 5 while the dobutamine administration was continued. During the test, a 12-lead ECG was recorded every minute. Blood pressure was measured at the end of every dobutamine infusion stage.

The criteria for stopping the test were: (1) achievement of the target heart rate (2) severe and extensive new WMA, (3) horizontal or downsloping ST depression of ≥0.2 mV measured 80 ms after the J point, or ST-segment elevation of ≥0.2 mV in the absence of Q waves, (4) symptomatic decline in systolic blood pressure of more than 40 mmHg, or a systolic blood pressure £ 90 mmHg, (5) hypertension (blood pressure >240/140 mmHg), (6) the occurrence of sustained cardiac arrhythmias, (7) severe angina pectoris, and (8) intolerable adverse effects considered to be the result of dobutamine or atropine. Two experienced investigators performed off-line assessment of echocardiographic images without knowledge of the patient's clinical and coronary angiography data, but with knowledge of the doses of dobutamine and atropine used. Interobserver and intraobserver agreement for analysis of DSE studies were reported previously (92% and 94%, respectively) [9]. Regional function was scored according to a 16 segment, five point scoring model: 1, normal; 2, mildly hypokinetic; 3, severely hypokinetic; 4, akinetic; and 5, dyskinetic. Wall-motion score index (WMSI) (total score divided by the number of segments scored) was calculated, at rest, low dose and during peak stress. Digital screen format was used to compare images. When there was disagreement between the two assessors, a third investigator viewed the images without knowledge of the previous assessments, and a majority decision was reached.

Follow-up

During follow-up, the end-points of the study were all-cause mortality, cardiac death and hard cardiac events [cardiac death or non-fatal myocardial infarction (MI)]. Clinical information was obtained by outpatient visits, by mailed questionnaires, by telephone interviews or by reviewing hospital records and the electronic patient database. Survival status was obtained by approaching the referring physician or the municipal civil registries. Cardiac death was defined as death caused by acute myocardial infarction, cardiac arrhythmias, or congestive heart failure. Sudden unexpected death was included as cardiac death.

Statistics

The t-test was used for continuous variable and chi –square test was used for categorical variables. Characteristics were summarized as percentages for categorical variables and as mean ± standard deviation for continuous variables. Univariate and multivariate analysis of clinical and echocardiographic variables with the end points were assessed using the Cox proportional hazards model. All clinical variables and representative DSE variables were considered in the model, regardless of their univariate significance. Variables were selected in a stepwise forward selection manner with entry and retention set at a significance level of 0.05. The fitted model included age only for the purpose of adjustment; all other models were based on the variables selected in the stepwise algorithm, which were replaced by dichotomous versions to facilitate ease of clinical use. The risk of a variable was expressed as a hazard ratio (HR) with a corresponding 95% confidence interval (CI). The probability of all-cause mortality, cardiac death and hard cardiac events free survival was calculated by the Kaplan-Meier method and the resulting curves were compared by the log rank test [10, 11].

Results

The patients' demographics and clinical characteristics are presented in Table 1.

According to renal function the total study population was divided in 1015 (44%) patients with normal renal function and 1277 (66%) with renal dysfunction. This was classified as mild in 647 patients, moderate in 403 patients and severe in 227 patients. The overall prevalence of hypertension was 36%. The respective percentages for mild, moderate and severe renal dysfunction were 34%, 44% and 53%. The prevalence of diabetes in these groups was 13%, 15%, and 21% respectively.

Patient Characteristics and Hemodynamic response

During DSE the heart rate increased significantly from rest to peak stress. The target heart rate was reached in 91% of patients. Atropine was administered in 206 patients. The mean maximal dobutamine dose was 38 ± 8 mcg/kg/min. Side effects included hemodynamically stable sustained ventricular tachycardia (>10 complexes) in 23 (1%) patients , non-sustained ventricular tachycardia (<10 complexes) in 115 (5%), atrial fibrillation in 23 (1%), and severe hypotension (decrease of systolic blood pressure >40 mmHg) in 23 (1%).

Table 1: Study population characteristics (2292 patients).

Demographics	
Males	1504 (66%)
Females	788 (34%)
Age	61 ± 8
Body Mass Index	25.6 ± 2.5
Body Surface Area	1.88 ± 0.5
Renal Function	
Normal	1015 (44%)
Mild dysfunction	647 (28%)
Moderate dysfunction	403 (18%)
Severe dysfunction	227 (10%)
Cardiac risk factors and history	
Hypertension	809 (36%)
Congestive Heart Failure	343 (15%)
Diabetes Mellitus	315 (14%)
High Cholesterol	727 (33%)
Smoking	666 (30%)
Angina	589 (26%)
Previous Myocardial Infarction	805 (35%)
Previous revascularization PCI	356 (16%)
CABG	346 (15%)
Cardiac Medication	
ACE-inhibitors	131 (6%)
Angiotensin receptor blockers	666 (30%)
β-blockers	809 (36%)
Nitrates	315 (14%)
Diuretics	143 (6%)
Digoxin	727 (33%)

The WMSI was 1.47 ± 0.60 at rest and 1.55 ± 0.67 at peak stress. Rest WMA were observed in 1469 (64%) patients and new WMA at peak stress were present in 1546 (68%) patients (Table 2).

Long term follow up

During a mean long-term follow up of 8 years, 543 patients (24%) died, which included 128 (13%) patients with normal CrCl, 145 (22%) with mild renal dysfunction, 156 (39%) with moderate and 114 (50%) with severe renal dysfunction. Cardiac death occurred in 324 patients (14%);

Table 2: Dobutamine Stress Echocardiography results according to renal function.

	Normal renal function (1015 patients)	Mild renal dysfunction (647 patients)	Moderate renal dysfunction (403 patients)	Severe renal dysfunction (227 patients)
Rest WMA*	610 (60%)	400 (62%)	300 (74%)	159 (70%)
NWMA[x]	640 (63%)	429 (66%)	314 (78%)	163 (72%)
WMSI[+] at rest	1.47 ± 0.61	1.55 ± 0.67	1.72 ± 0.71	1.63 ± 0.67
WMSI[+] at peak	1.40 ± 0.54	1.47 ± 0.60	1.63 ± 0.65	1.55 ± 0.61

***WMA**: Wall Motion Abnormalities
[x]**NWMA**: New Wall Motion Abnormalities
[+]**WMSI**: Wall Motion Score Index

the respective numbers among the strata of CrCl was 65 for normal CrCl (6% of normal), 91 for mild renal dysfunction (14% of mild), 102 for moderate (25% of moderate) and 66 for severe renal dysfunction patients (29% of severe). Ninety-two (4%) patients suffered non-fatal MI. Overall 416 (18%) patients had at least one hard cardiac event.

Predictors of all-cause mortality, cardiac death and hard cardiac events

Table 3 summarizes the hazard ratios after multivariate analysis for predictors of all-cause mortality, cardiac death and hard cardiac events either unadjusted or adjusted for age, sex, prior MI, prior CABG, prior PCI, congestive heart failure, typical angina, diabetes, hypertension, high cholesterol and smoking. Ischemia during DSE and mildly, moderately and severely abnormal CrCl were powerful independent predictors for all end points.

The incremental values (all $p < 0.001$) per 20 ml/min decrease of CrCl over new WMA during DSE for the end points of all-cause mortality, cardiac death and hard cardiac events and the respective improvements in global x^2 are shown in figure 1.

Kaplan-Meier curves for the end point of all-cause mortality in patients with normal DSE, new WMA, ≤ 4 abnormal segments and > 4 abnormal segments during DSE among the entire strata of renal function are shown in figure 2 (all $p<0.001$).

Figure 3 demonstrates the Kaplan-Meier curves for cardiac death and hard cardiac events in patients with normal DSE among the entire strata of renal function (all $p<0.01$). Patients with normal DSE and renal dysfunction have greater probability for both cardiac death and hard cardiac events compared to those with normal renal function.

Kaplan-Meier curves for cardiac death and hard cardiac events in patients with new WMA and > 4 abnormal segments during DSE among the entire strata of renal function are demonstrated in figure 4 (all $p<0.001$).

Table 3: Multivariate analysis for the end-points of all cause mortality, cardiac death and hard cardiac events (cardiac death or nonfatal MI). Hazard Ratios (HR) associated with levels of the creatinine clearance (CrCl) in 2292 patients.

	HRs, 95%CIs unadjusted	HRs, 95%CIs adjusted†
All cause mortality		
NWMA during DSE	1.8 (1.5-2.1)	1.5 (1.2-1.8)
Normal CrCl	1.0	1.0
Mildly abnormal CrCl	2.0 (1.5-2.5)	1.4 (1.1-1.9)
Moderately abnormal CrCl	3.9 (3.0-4.9)	2.3 (1.8-3.1)
Severely abnormal CrCl	5.5 (4.2-7.1)	3.5 (2.7-4.7)
Cardiac death		
NWMA during DSE	2.7 (2.1-3.6)	1.8 (1.3-2.4)
Normal CrCl	1.0	1.0
Mildly abnormal CrCl	2.4 (1.7-3.3)	1.7 (1.2-2.4)
Moderately abnormal CrCl	5.0 (3.7-6.9)	2.8 (2.0-4.1)
Severely abnormal CrCl	6.1 (4.3-8.7)	3.8 (2.1-4.6)
Cardiac death or MI		
NWMA during DSE	2.3 (1.8-3.0)	1.6 (1.2-2.0)
Normal CrCl	1.0	1.0
Mildly abnormal CrCl	2.0 (1.5-2.6)	1.5 (1.1-2.1)
Moderately abnormal CrCl	3.6 (2.7-4.7)	2.3 (1.6-3.1)
Severely abnormal CrCl	4.8 (3.5-6.5)	3.3 (2.4-4.7)

†*Adjusted for age, sex, prior MI, prior CABG, prior PCI, CHF, typical angina, diabetes, hypertension, high cholesterol, smoking.*

Discussion

This study showed the predictive value of renal function relative to DSE findings during a long-term mean follow up of 8 years. Ischemia during DSE was an independent predictor of

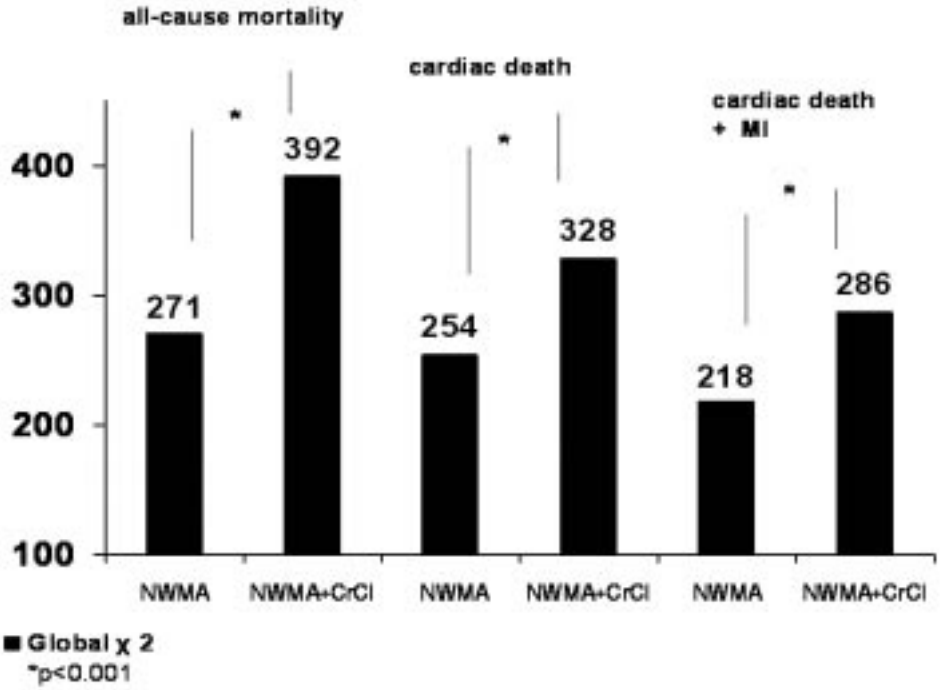

Figure 1: Incremental value of a 20ml/min decrease of CrCl over NWMA during DSE for the end points of all-cause mortality, cardiac death and hard cardiac events (cardiac death + MI).

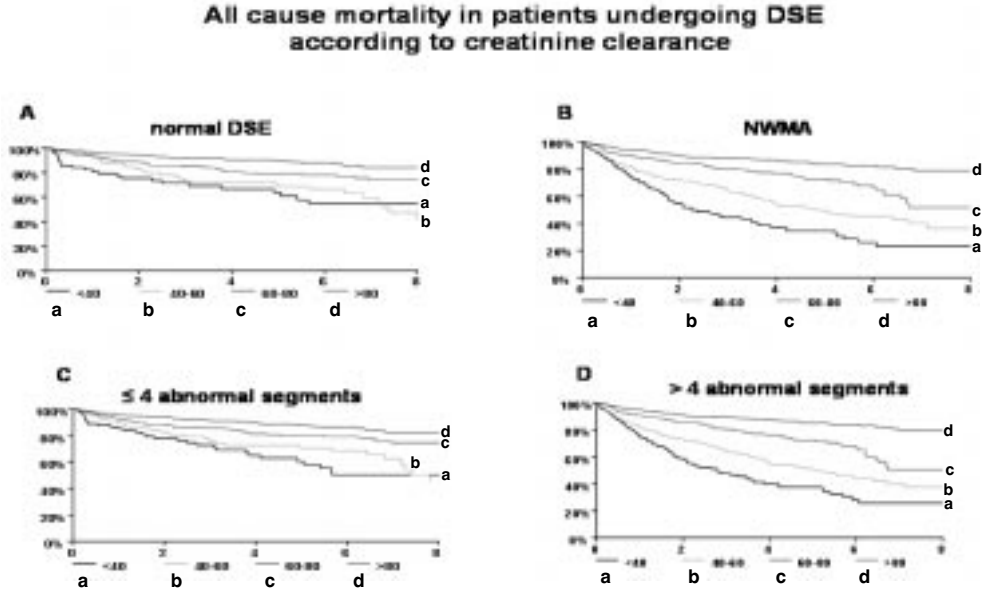

Figure 2: Kaplan-Meier curves for all-cause mortality in patients with (A) normal DSE, (B) NWMA, (C) ≤ 4 abnormal segments and (D) > 4 abnormal segments in DSE and according to renal function, for a period of 8 years.

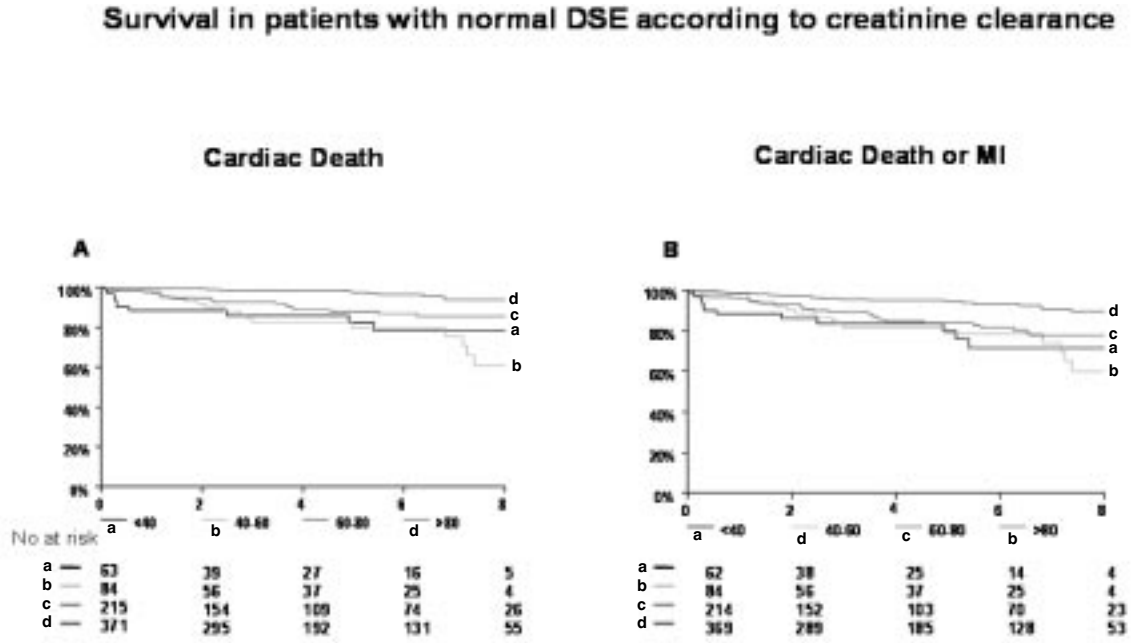

Figure 3: Kaplan-Meier curves for cardiac death (A) and hard cardiac events (B) in patients with normal DSE and according to renal function, for a period of 8 years. Patients with normal DSE and renal dysfunction have greater probability for both cardiac death and hard cardiac events compared to those with normal renal function. The warranty of a normal DSE in the presence of mild, moderate and severe renal dysfunction was respectively 48, 36 and 6 months.

mortality and hard cardiac events among the entire strata of renal function (table 2). The global x^2 increased significantly when CrCl, was added to the model (figure1). The degree of renal dysfunction was an additional determinant of survival and hard events among patients with normal as well as those with abnormal DSE (figures 2, 3, 4). Based on survival curves, we suggest that patients with severe renal dysfunction should repeat DSE every 6 months even in the absence of new WMA during the baseline DSE. In patients with mild or moderate renal dysfunction and normal DSE at baseline we recommend that it should be repeated every 36 and 48 months respectively (figure 3).

Comparison to previous studies

The American Society of Transplantation has reported guidelines for the pre-transplant evaluation of patients with severe renal dysfunction [12]. They included the use of non-invasive cardiac stress testing, however, it remained unclear which test to use due to the lack of firm support for a single test. Some studies have suggested that DSE is superior to exercise ECG for diagnosis of CAD in patients with renal dysfunction [13] and has also prognostic value in this setting [14, 15, 16]. We also demonstrated the prognostic value of DSE among the entire strata of renal function. In addition, patients with significant renal dysfunction are often unable to perform treadmill exercise testing. Furthermore the presence of left ventricular hypertrophy makes

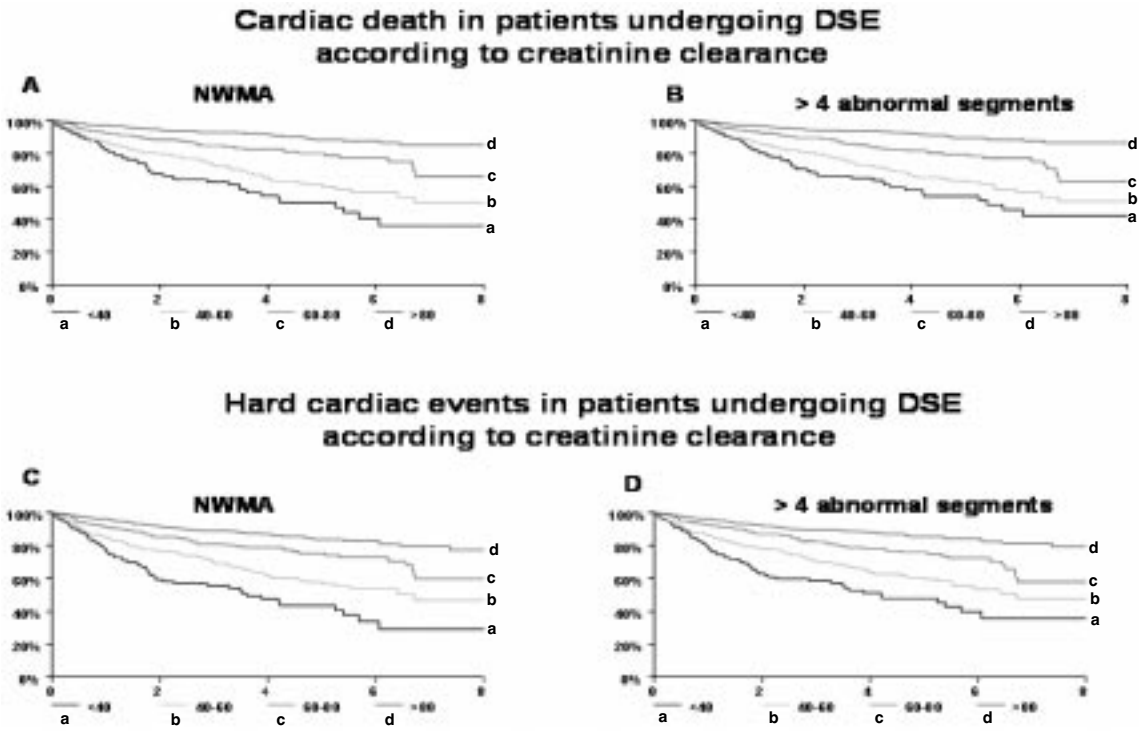

Figure 4: Kaplan-Meier curves for cardiac death (A and B) and hard cardiac events (C and D) in patients with NWMA and > 4 abnormal segments in DSE and according to renal function, for a period of 8 years.

any ST-segment interpretation on ECG less reliable [13]. The theoretical advantages of DSE in renal dysfunction include maintained sensitivity and specificity in hypertension [17] and bundle branch block [18].

It is known that early renal failure is associated with changes in traditional and non-traditional cardiovascular risk factors [1, 2]. Moreover patients with renal dysfunction may have only atypical or no symptoms of CAD, due to limited activity levels [2]. Avoidance of coronary angiography and potentially nephrotoxic contrast material is also critical in these patients. Therefore given its safety and low cost, DSE could be used as a screening tool in detecting occult CAD before development of myocardial infarction or sudden cardiac death in patients with renal dysfunction [19].

A previous study has shown that the accuracy for detecting CAD and the prognostic implications of positive results of DSE in patients with renal dysfunction appear similar to the general population [19]. We similarly found that new WMA during DSE were independent predictors for decreased survival but the addition of CrCl added significantly to the power of the predictive model (table 2, figure 1).

Although the prognosis of patients with renal dysfunction and normal DSE was better than for patients with new WMA, the event rate remained substantial for all end points. This could be explained by the high risk profile of our population and by the known high prevalence of cardiac

events in patients with renal failure even in the absence of coronary artery disease at baseline because uremia itself provides an atherogenic milieu [16].

In two of the largest prognostic series, the prognostic value of a normal DSE in renal dysfunction appears to be limited to about 2 years [4, 20]. We have shown in an even larger study population with a longer follow-up period that the predictive value of a normal DSE in the presence of mild, moderate and severe renal dysfunction is limited to 48, 24, and 6 months, respectively.

In conclusion we found that renal dysfunction has additional independent prognostic value over DSE findings, irrespective of the presence and severity of wall motion abnormalities. The low risk period after a normal DSE is determined by the presence and the severity of renal dysfunction.

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Summary and Conclusions

In this thesis we have demonstrated the role of dobutamine stress echocardiography in the clinical practice.

In the first part of the thesis we discuss the limitations and advantages of the current methodology of dobutamine stress echocardiography evaluation. We show that a new, objective technique for the evaluation of wall motion abnormalities is feasible (chapter 1). This technique, called automated coupled contour and robust myocardial tracking, is evaluated in a multicenter study. This seems promising for the improvement of the sensitivity of dobutamine stress echocardiography without losing its specificity. In addition, the use of this technique can resolve one of the major drawbacks of dobutamine stress echocardiography, the subjective wall motion evaluation. This is a major cause for a high inter- and intraobserver variability.

Furthermore, we show that a change in the time of wall motion evaluation during dobutamine stress echocardiography is a simple and reliable way to improve the sensitivity of the test without losing its specificity. The evaluation of wall motion abnormalities in the recovery phase of dobutamine stress echocardiography, after intravenous beta-blockade at peak stress, has the potential to improve the diagnostic accuracy of the test. We demonstrate that this modest change of the traditional protocol did not lengthen the duration of the test and importantly, improved the sensitivity for the detection of coronary artery disease (chapter 2) and myocardial viability (chapter 3).

In the second part of the thesis we show that wall motion abnormalities assessed during the recovery phase of dobutamine stress echocardiography have important long term prognostic value (chapter 4). Patients with heart failure symptoms represent a high risk population, especially if noncardiac surgery is indicated. In order to stratify these patients we have developed a prediction model based on wall motion abnormalities during incremental dobutamine infusion. With the use of this model we were able to stratify patients with heart failure prior to vascular surgery. Wall motion abnormalities indicative for myocardial viability, ischemia or a biphasic response were associated with adverse outcome. However, patients

that primarily demonstrated a sustained improvement had a favorable outcome (chapter 5). In the last chapter we show the diagnostic accuracy of dobutamine stress echocardiography in a large patient population with renal dysfunction.

In conclusion, in this thesis we show that wall motion abnormalities assessment during the recovery phase of dobutamine stress echocardiography is associated with an improved accuracy for the detection of coronary artery disease in everyday clinical practice.

Samenvatting en Conclusies

Dit proefschrift beschrijft de rol van dobutamine stress echocardiografie voor de beantwoording van vragen uit de dagelijkse klinische praktijk. In het eerste deel van dit proefschrift beschrijven we de beperkingen en voordelen van de huidige stress echocardiografie beoordeling. Tevens demonstreren wij een nieuwe analyse techniek (hoofdstuk 1). Deze techniek genaamd “automated coupled contour and robust myocardial tracking” werd geëvalueerd bij patiënten in meerdere centra. De eerste resultaten lijken belovend, de sensitiviteit voor het aantonen van coronair afwijkingen is toegenomen, zonder vermindering van de specificiteit van de test. Deze techniek probeert ook één van de onvermijdelijke beperkingen van stress echocardiografie, een hoge interobserver variabiliteit, op te lossen. Hiervoor wordt gebruik gemaakt van een objectieve evaluatie van wandbewegingsstoornissen.

We laten zien dat de evaluatie van wandbewegingsstoornissen tijdens de herstelfase van dobutamine stress echocardiografie, na intraveneuze bètablokkade tijdens maximale stress, een eenvoudige en betrouwbare manier is om de sensitiviteit van de huidige test te verbeteren zonder de specificiteit te verminderen. We tonen aan dat deze simpele verandering van het traditionele protocol de duur van de test niet verlengd. De sensitiviteit voor de detectie van coronair vaatlijden (hoofdstuk 2) en voor inschatting van vitaliteit (hoofdstuk 3) werd tevens sterk verbeterd.

In het tweede deel van dit proefschrift demonstreren wij de waarde van wandbewegingsstoornissen tijdens de herstelfase van de dobutamine stress echocardiografie als onderdeel van de beoordeling voor het voorspellen van lange termijn uitkomst (hoofdstuk 4). In een selecte groep van patiënten die een vaatoperatie moesten ondergaan, ontwikkelden wij een predictie model voor het voorspellen van postoperatieve complicaties. In dit model gebruiken wij verschillende patronen van wandbewegingen tijdens toenemende dobutamine dosering. De aanwezigheid van wandbewegingsstoornissen die myocard vitaliteit aantonen identificeert hoog risico patiënten. Dit leidt tot een betere risicostratificatie (hoofdstuk 5). In het laatste hoofdstuk

van dit proefschrift hebben wij de voorspellende waarde van dobutamine stress echocardiografie onderzocht voor het aantonen van coronair lijden bij patiënten met een gestoorde nierfunctie, geschat door middel van kreatinine klaring.

Concluderend, in dit proefschrift hebben wij met eenvoudige methoden de klinische toepassing van dobutamine stress echocardiografie verbeterd voor de hedendaagse klinische praktijk.

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