# NEW NON-INVASIVE IMAGING TECHNIQUES TO QUANTIFY VENTRICULAR FUNCTION: REAPPRAISAL OF DOBUTAMINE STRESS ECHOCARDIOGRAPHY

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# NEW NON-INVASIVE IMAGING TECHNIQUES TO QUANTIFY VENTRICULAR FUNCTION: REAPPRAISAL OF DOBUTAMINE STRESS ECHOCARDIOGRAPHY

NIEUWE NON-INVASIVE METHODEN VOOR HET KWANTIFICEREN VAN DE VENTRIKEL FUNCTIE: HERWAARDERING VAN DOBUTAMINE STRESS ECHOCARDIOGRAFIE

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**To my wife Lorenza**
**who accepted to lose**
**some years of our life**
**to let me do this**

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# INTRODUCTION AND OVERVIEW OF THE THESIS

## Background

The study of ventricular function has been addressed by several noninvasive and invasive techniques. Among the first, echocardiography and nuclear imaging have gained a widespread popularity and a good profile. In particular echocardiography has shown a widespread availability, is low-cost and safe (1). The introduction of sympathetic stressors, such as dobutamine, in combination with echocardiography, has significantly increased the potential of echocardigraphy in detecting functional response of the myocardium. This is especially so in the case of myocardial viability and ischemia (2-6). However, a major limitation of echocardiography remains its dependence on subjective operator interpretation. It requires an extensive learning curve on the part of the interpreter in evaluating the stressor effects on the dynamic response of ventricular function (7). Dobutamine stress echocardiography was the stressor selected in the present thesis and we addressed the problem of reducing its subjectivity, by introducing new quantitative techniques (8-9). So far, numerous attempts tried to quantify stress echocardiography, however this is beyond the goal of the present thesis. Examples are: centreline method in combination with invasive catheterization performed during exercise testing (10), automated edge detection applied to endocardial border contour detection (11). Recently Doppler tissue imaging addressed the task of measuring the myocardial tissue dynamics. In our opinion the introduction of Doppler tissue imaging and other quantitative techniques became recently feasible by software developments, such as the Digital Imaging and Communication in Medicine (DICOM 3) system for imaging digitalization. An ideal goal regarding this would be the development of partially automated echocardiography.

## Aim of the present thesis

This thesis is an insight investigation in some recently developed noninvasive imaging advances to quantitatively assess left or right ventricular function. The focus is on dobutamine stress echocardiography, with some reference to a recently developed nuclear imaging technique: $^{99m}$Technetium-tetrofosmin-$^{18}$F-fluorodeoxyglucose-single photon emission computed tomography (FDG-SPECT) (12). Among many attempts to pass from a subjective and qualitative to an objective and quantitative evaluation of ventricular function we analyzed Doppler tissue imaging. Left ventricular function, as stimulated by dobutamine, was studied by applying Doppler tissue imaging as a test on myocardial ischemia and contractile reserve, the latter being even more subjected to inter-observer variability, than the assessment of myocardial ischemia.

## Short overview of the dobutamine stress echocardiography criteria used in the present thesis

Dobutamine stress echocardiography is an established imaging technique. Our protocol complied with the standards of the American Society of Echocardiography (13). Dobutamine was intravenously administered with an infusion rate of 5 and 10 μg/kg/min for 5 min in the case of severe left ventricular dysfunction for assessment of contractile reserve, or just 10 μg/kg/min for 3 minutes in the case of normal left ventricular function, increasing by 10 μg/kg/min every 3 minutes up to a maximum dose of 40 μg/kg/min for evaluation of myocardial ischemia. In patients not achieving 85% of their age and gender predicted maximal heart rate and without evidence of myocardial ischemia, atropine was administered, starting with 0.25 mg intravenously and repeated up to a maximum of 2.0 mg within 4 minutes, while continuing the infusion of dobutamine (14).

**We aligned the scoring systems of dobutamine stress echocardiography and FDG-SPECT**

By echocardiography the left ventricle was divided in 16-segments (13) and visually assessed for both systolic wall thickening and inward wall motion. Each segment was graded on a 5-point scoring system: 1 = normo- or hyperkinesis; 2 = mild hypokinesis; 3 = severe hypokinesis; 4 = akinesis and 5 = dyskinesis; by an experienced observer blinded to the reference data. Myocardial viability was defined as an improvement, and myocardial ischemia as a worsening of wall motion of at least two adjacent ventricular segments at any step of the test, unless an akinetic segment at rest became dyskinetic at peak dobutamine stress (15). By FDG-SPECT analysis the left ventricle was also divided in 16-segments, corresponding to the echocardiographic segments, and semi-quantitatively scored according to the uptake of tetrofosmin and/or FDG using a 4-points scoring system: 0 = normal, 1 = mildly-moderately reduced, 2 = severely reduced and 3 = absent uptake. By adopting a similar scoring model for both imaging techniques we optimized the segmental assessment, combining myocardial perfusion, metabolic uptake and contraction, with further possibility to assign each myocardial segment to a coronary artery field.

**Reduction of inter-institutional variability** (*Chapter 1)*

In order to improve inter-institutional agreement, we adopted newly standardized guidelines for imaging and scoring, as derived from our multicentre experience (16). Image quality and severity of wall motion abnormalities were the strongest predictors of interinstitutional agreement. The variability achieved was less than in a similar previous study (7), thus emphasizing the importance of improving compliance to guidelines among the operators to improve agreement.

**Development of Doppler tissue imaging *(Chapters 2-3)***

We analyzed velocity colors in either 2D maps and M-mode display by reconstructing frame by frame the sequence of color changes along each cardiac cycle and each echocardiographic window or M-mode display. This analysis was performed off-line by freezing each subsequent frame of each echo view of the videotaped images. Each color represents a velocity range and a direction of motion. Velocities are depicted from red to orange and yellow when moving toward the transducer from low to high velocity values respectively. Conversely, they are depicted from blue to turquoise and green when moving away from the transducer. After a period of appropriate training we were able to recognize at a glance either in 2D or M-mode the following cardiac phases: isovolumic contraction, ejection phase, isovolumic relaxation, early diastole, diastasis and late diastole. However, we suffered the limitation of a qualitative eye-dependent approach. In absence of a quantitative software for Doppler tissue imaging, we reduced using pulsed wave Doppler tissue sampling, as the only quantitative approach not requiring any customized software (17-21).

**Quantification of ventricular function by using pulsed wave Doppler tissue sampling *(Chapters 2-3)***

Pulsed wave Doppler tissue sampling is a Doppler sample volume placed over a region of interest within the myocardium to display the corresponding velocity profile over time. Pulsed wave Doppler tissue sampling was performed with the Toshiba Powervision Echocardiographic System. The sample volume was used in apical echo views. Both electrocardiogram and phonocardiogram were simultaneously recorded with the pulsed wave Doppler tissue sampling velocity profile to obtain a precise timing of the cardiac cycle intervals, in order to measure the peak velocity of each interval by pulsed wave Doppler tissue sampling. Velocity measurements were made of ejection phase, early and late diastole by using an off-line computer assisted drawing system and the velocity values were expressed in cm/s. Early/late diastole velocity ratio was also

calculated. Five consecutive beats were analyzed and mean velocity values calculated, in order to minimize the measurement variability determined by respiration. Cardiac cycles with extrasystolic, post-extrasystolic beats or any disturbance of the rhythm were excluded. Recordings and measurements were repeated at baseline, low-dose (10 µg/kg/min) and peak-dose of dobutamine.

**Quantification of wall motion during dobutamine stress echocardiography**

***(Chapters 2-3)***

Quantitative data may be obtained by customized software from colour Doppler tissue imaging, however the temporal resolution is limited. In absence of customized software, we obtained velocity by using pulsed wave Doppler tissue sampling. Pulsed wave Doppler tissue sampling velocity values are significantly higher than by Doppler tissue imaging color analysis, because pulsed wave Doppler tissue sampling shows the peak velocity profile, while color Doppler tissue imaging averages velocity from the modal values (22-23). However, the major disadvantage of pulsed wave Doppler tissue sampling is that it requires repetitive sampling of different sites during stress, due to its limited spatial resolution. This can cause feasibility problems when performed in multiple sites and sequence of cardiac beats during the short time of dobutamine stress echocardiography, especially at peak test. Our best criterion of using pulsed wave Doppler tissue sampling in apical views by sampling only the basal segments and using systolic velocities and their percentage of variations during stress echocardiography, was a compromise to optimize spatial and temporal resolutions with its feasibility during dobutamine stress echocardiography. Our protocol was confirmed by others (23). We investigated different clinical settings of our pulsed wave Doppler tissue sampling protocol applied to dobutamine stress echocardiography (24-25).

**Advantages of longitudinal motion assessment by pulsed wave Doppler tissue sampling** ***(Chapters 2-3)***

An important advantage of the pulsed wave Doppler tissue sampling protocol, applied to the basal segments of each left ventricular wall in apical views, is the amplification effect of longitudinal ventricular velocity assessment (19, 26-27). By using pulsed wave Doppler tissue sampling at the basal level of left or right ventricular wall in apical echocardiographic images, the velocity of longitudinal displacement may be considered expression of the longitudinal myocardial contraction. These longitudinal velocities are higher than inward wall motion velocities measured in para-sternal views (23). This amplification effect is determined by the vectorial sum of the contraction velocity of each myocardial fiber interposed between the base and apex. The same protocol of pulsed wave Doppler tissue sampling was also analyzed in pigs using micro-manometers implanted in the sub-endocardial and sub-epicardial layers by Derumeaux et al (23). Both endocardial inward wall motion and longitudinal contraction contribute equally to ejection fraction (28) and add prognostic information (29).

A second advantage of this protocol is in reducing the divergence angle of longitudinal motion from the direction of Doppler beam, as both remain almost parallel each other. The relative fixation of the cardiac apex, which is used as a reference pivotal point, allows evaluation of all the myocardial segments moving towards it, thus towards the transducer, without the need of further corrections (30-32). The longitudinal approach minimizes the global cardiac translational movement, compared to the para-sternal approach and allows the use of the mitral annulus as a fixed and reproducible anatomical landmark. Another advantage is the higher temporal resolution of pulsed wave Doppler tissue sampling compared to either M-mode or 2D Doppler tissue imaging. A further advantage of pulsed wave Doppler tissue sampling is to measure higher velocity values, compared to color Doppler tissue imaging data which are auto-correlated, thus averaged from the modal velocities which are lower than the velocity of pulsed wave Doppler tissue sampling.

**Pitfalls of pulsed wave Doppler tissue sampling and Doppler tissue imaging**

***(Chapters 2-3)***

The angular dependence is the intrinsic main limitation of the Doppler technique. When the direction of movement diverges from the interrogating Doppler beam more than 20°, the accuracy of the velocity measurements becomes not acceptable and when the direction of movement is perpendicular to the Doppler beam, no measurement is achievable. A second limitation of Doppler tissue imaging is the global cardiac motion, particularly in the para-sternal views, as it distorts the accurate encoding of myocardial velocities. A third limitation is the presence of artifacts, such as side lobes, as their colour coding by Doppler tissue imaging affects the correct evaluation of the underlying image. A further limitation is the inability of Doppler tissue imaging to completely colour code every part of the ventricular wall, especially the walls imaged at the border of the echocardiographic sector. A possible explanation could be low intensity of the signals reflected from the myocardial backscatters (33). Therefore, the best assessment of the ventricular walls is performed when they are located in the central part of the sector, because a location close to the echocardiographic sector borders is affected by a lower spatial resolution. For further details about Doppler tissue imaging technique we refer to chapters 2 and 3.

**Pulsed wave Doppler tissue sampling assessed right ventricular dysfunction**

***(Chapter 4)***

Right ventricular shape entangles echocardiographic assessment (34-35). Moreover, the visual scoring usually misses the longitudinal component of motion (36). Pulsed wave Doppler tissue sampling, applied to the basal segments of right ventricular free wall in apical 4-chamber view exhibited a blunted pattern of increased velocities during dobutamine stress echocardiography in the case of right ventricular dysfunction, mainly determined by right coronary artery

disease. Thus, pulsed wave Doppler tissue sampling response predicted the presence of significant right coronary artery stenosis (37). An identical conclusion was reached more recently by Alam et al. (38). We could speculate about a more complex patho-physiological meaning to this finding. In agreement with Yamada et al (22) it is likely that a mixture of resting necrosis and jeopardized viability at low-dose, possibly resulting in some ischemia at peak-dose, is responsible for bi-phasic myocardial velocity of right ventricular free wall. This pattern resembles the bi-phasic pattern of myocardial segments during dobutamine stress echocardiography: the strongest predictor of myocardial viability. A potential application of this technique could be to quantify the right ventricular function at rest. It could also be used during stress in the follow-up of patients with a left ventricular dysfunction that is so severely impaired that it escapes reproducible assessment, thus requiring alternative measures. We used quantitative coronary artery angiography as a reference standard (39).

**Short overview of left ventricular functional reserve**

We studied myocardial viability using pulsed wave Doppler tissue sampling and dobutamine stress echocardiography with FDG-SPECT used as a reference. Ischemic left ventricular dysfunction increases morbidity, mortality rate and worsens quality of life (40). This data justifies the present enormous effort of recognizing myocardial viability (41-43). Among the therapeutic options, coronary revascularization appears to improve the left ventricular function. This reduces both morbidity and mortality, provided that an adequate proportion of viable myocardium is present. Myocardial viability encompasses myocardial stunning and hibernation. Many definitions of myocardial viability are available; these depend on the reference parameter or technique used. One widely used definition of myocardial viability is based on the presence of contractile reserve under inotropic stimulus. Another definition relies on preserved myocardial metabolic activity or tracer uptake, regardless of reduced coronary flow; this is called metabolic/perfusion mismatch. Among the many techniques used to

assess myocardial viability, echocardiography and nuclear imaging provides the best combination of accuracy and cost-effectiveness. If the aspect of resting dyssynergic myocardium is of value for predicting viability (44), the number of viable segments and the magnitude of their improvement the added value of predicting improvement of left ventricular ejection fraction (45). Among various stressors, dobutamine has become the most popular for recognizing myocardial viability. A top predictor of dobutamine stress echocardiography is the bi-phasic pattern (46) with improvement of wall motion and thickening in severely dyssynergic segments at low-dose dobutamine and worsening at peak. This is indicative of viable but jeopardized myocardium. Contractile reserve must be present in at least two adjacent segments for it to improve after coronary revascularization (47). Other techniques show a minor cost-effectiveness ratio, such as Positron Emission Tomography (PET), traditionally considered the gold standard of myocardial viability, and magnetic resonance imaging, presently promising to quantify regional ventricular dynamics. These techniques are expensive and of limited availability.

**We selected pulsed wave Doppler tissue sampling among many new techniques to detect myocardial viability**

Many new techniques are aiming to quantify myocardial viability. For example a quantitation of grey-scale imaging by video-densitometry has been studied for the recognization of myocardial viability (48), myocardial acoustic backscattering as acoustic quantification/colour kinesis (49), contrast echocardiography (50) and tracking of the speckle pattern within the myocardium have been investigated. Digital Imaging and Comunication in Medicine (DICOM 3) system has been introduced recently, and is the new standard of digital imaging and communication. It is consolidating efforts to quantify ventricular function. Among so many new approaches, we addressed pulsed wave Doppler tissue sampling to detect myocardial viability (33, 38).

**FDG-SPECT as a reference standard for myocardial viability**

FDG-SPECT is a new nuclear imaging technique that assesses simultaneously myocardial perfusion and membrane uptake, utilizing a double sequential intravenous injection of radionuclide tracers (12,51-53). Briefly an intravenous injection of $^{99m}$Technetium-tetrofosmin allows myocardial perfusion imaging. Then a dose of 500 mg of Acipimox (Byk, The Netherlands) is administered orally (57). Acipimox is a potent nicotinic acid derivative, blocks lipolysis and reduces free fatty acid plasmatic availability, thereby stimulating glucose and FDG uptake. A carbohydrate-enriched meal is given to stimulate insulin release and further FDG uptake. This protocol offers obvious practical advantages over the hyperinsulinemic euglycemic clamping, which consists of an intravenous infusion of insulin to activate glucose uptake from myocardial cell membranes together with glucose to maintain normoglycemia (55-56). A second intravenous injection introduces FDG and the resulting images of membrane uptake are matched with myocardial perfusion. The simultaneous imaging of dual isotope FDG-SPECT allows an optimal alignment of myocardial segments, thus increasing accuracy to detect myocardial viability.

**Pulsed wave Doppler tissue sampling increased sensitivity of dobutamine stress echocardiography to recognize myocardial viability versus wall motion *(Chapters 5-6)***

Nuclear imaging was found more sensitive than dobutamine stress echocardiography to detect myocardial viability. Pulsed wave Doppler tissue sampling appeared more sensitive than dobutamine stress echocardiography for detection of myocardial viability. This technique, combined with dobutamine stress echocardiography appears almost as sensitive as nuclear imaging. The patterns of pulsed wave Doppler tissue sampling overlapped those of dobutamine stress echocardiography with a higher prevalence of sustained improvement. By considering only low-dose dobutamine and a multi-segment approach of pulsed wave Doppler tissue sampling to left ventricle, this technique

showed its potential to quantify myocardial viability, with good correlation to FDG-SPECT (57-58). Our absolute velocity values reproduced those reported by Yamada et al (59).

**FDG-SPECT was the reference standard of dobutamine stress echocardiography for myocardial viability assessment** ***(Chapter 7)***

FDG-SPECT is used to study resting myocardial viability (1, 60-62). Compared to FDG-positron emission tomography (FDG-PET), it can be used as a cheaper and more available reference technique (63-66). FDG-SPECT exhibits patterns analogous to FDG-PET, with the only limitation of a semi-quantitative, instead of a quantitative scoring. A normal or moderately reduced perfusion/membrane uptake, a mismatch between hypo-perfusion or a normal or increased uptake is regarded as a sign of myocardial viability. Conversely, a minimal perfusion and uptake is indicative of non-viable myocardium. For evaluation of ischemia a stress protocol of FDG-SPECT could possibly be developed. Of all nuclear techniques FDG-SPECT appears more sensitive than dobutamine stress echocardiography in detecting myocardial viability. This technique detects myocyte membrane activity, while actomyosine function is lost, as this requires a higher metabolic activity of the cell (67). Notwithstanding different myocardial viability mechanisms assessed by echocardiography and nuclear techniques, we found a good correlation between dobutamine stress echocardiography and FDG-SPECT when using a similar scoring model. The maximum agreement for the two techniques evaluating myocardial viability was found for the bi-phasic pattern during dobutamine stress echocardiography.

**Safety of dobutamine stress echocardiography in patients with severe left ventricular dysfunction** ***(Chapter 8)***

In patients with severe left ventricular dysfunction (ejection fraction <35%) dobutamine stress echocardiography low-high dose protocol is safe and feasible (68-69). Our findings answer some concerns expressed by Rahimtoola (70) and

Nagueth and Zoghbi (71), concerning the safety of dobutamine stress echocardiography in severely dysfunctional left ventricles. Atropine addition is required in 1/3 of the tests and may be infused safely, as the most frequent side effects: hypotension and arrhythmias (72-79), do not relate to either atropine or ischemia induction. Thus, a low-high dose protocol can be used in these patients. It increases accuracy in the detection of myocardial viability by inducing ischemia after initial improvement. This is essential for both predicting a worse prognosis (80) and making the decision about coronary revascularization (81).

**Ejection fraction improvement during low-dose dobutamine predicted myocardial viability *(Chapter 9)***

Volume changes during dobutamine stress echocardiography have been found to predict coronary artery disease and unfavorable outcome (82-85). In our experience an increase of ejection fraction >10% at low-dose dobutamine stress echocardiography, especially if followed by worsening at peak-dose (bi-phasic response), accurately predicts functional recovery after revascularization. This is defined as an increase of ejection fraction >5%, measured by $^{99m}$Technetium ventriculography (86). Left ventricular-function improvement after revascularization is proportional to the degree of ejection fraction improvement at low-dose dobutamine stress echocardiography, linearly related to the number of viable segments. Thus ejection fraction appears to overestimate viability less, when compared to wall motion score index by dobutamine stress echocardiography (87-88) and nuclear tests (89).

**The angiographic success of percutaneous transluminal coronary angioplasty in chronic totally occluded coronary arteries could be immediately confirmed by dobutamine stress echocardiography *(Chapter 10)***

Patients with angina and chronic totally occluded coronary arteries were traditionally recanalized by coronary artery bypass grafting (CABG) (90).

Recanalization by percutaneous transluminal coronary angioplasty (PTCA) showed higher failure rate (91-93) and restenosis rate. However, the proven advantage of revascularization in reducing ischemia has supported continuous efforts in developing new technologies. As a new alternative approach excimer laser guide-wire was introduced in 1993 (94-97). In this approach the guide-wire contains laser fibres that are activated whenever an obstacle stops the advancement of the guide-wire. We studied the functional impact of the angiographic success of percutaneous transluminal coronary angioplasty by comparing a dobutamine stress echocardiography performed the day before, with a dobutamine stress echocardiography performed the day after a successful recanalization. We were able to confirm that a significant improvement of both stress-induced ischemia and resting dyssynergy occurs after a successful angiographical procedure (98-99).

**Dobutamine stress echocardiography predicted hypotension during hemodialysis *(Chapter 11)***

The prevalence of coronary artery disease among patients with terminal renal dysfunction is as high as 50% (100). However, exercise stress testing in this population is generally unfeasible. Therefore, dobutamine stress echocardiography appears a safe and feasible alternative in detecting myocardial ischemia (101-103). An additional role of dobutamine stress echocardiography performed before hemodialysis could be the prediction of hypotension during hemodialysis. This occurs in about 30% patients (104). We found evidence that the absence of dobutamine-induced contractile reserve, expressed as the failure of stroke index to increase during low-dose dobutamine stress echocardiography, appears predictive of hypotension during hemodialysis (105). Even if the patho-physiological mechanism of this finding remains to be explored, this marker could possibly stratify a higher risk group of patients.

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# CHAPTER 1

# STANDARDIZED GUIDELINES FOR THE INTERPRETATION OF DOBUTAMINE ECHOCARDIOGRAPHY REDUCE INTERINSTITUTIONAL VARIANCE IN INTERPRETATION

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## ABSTRACT

Subjective interpretation of dobutamine echocardiograms provides only moderate interinstitutional observer agreement if non-unified data acquisition and assessment criteria are applied. The present study was assigned to evaluate parameters associated with low interinstitutional observer agreement in the interpretation of dobutamine echocardiograms and to analyze whether standardized interpretation criteria improve interinstitutional observer agreement. 150 dobutamine echocardiograms (dobutamine up to 40 µg/kg body weight per min and atropine up to 1 mg) were evaluated at five centers. Clinical, procedural, and echocardiographic parameters were included in the analysis of variables with significant impact on interinstitutional agreement. Standardized interpretative criteria were established, and 90 dobutamine echocardiograms were reanalyzed by three observers using a standardized image display. Multivariate analysis demonstrated low image quality (Odds ratio [OR] 0.19, 95% Confidence interval [CI] 0.08-0.45, p=0.0002), low severity of the induced wall motion abnormality (OR 0.17, 95% CI 0.07-0.40, p<0.0001) and a low peak rate-pressure product (OR 0.93, 95% CI 0.43-2.27, p=0.0382) to result in a low interinstitutional agreement. Standardization of image display in cine loop format and of dobutamine stress echo interpretation criteria resulted in improvement of test result categorization as normal or abnormal, with a kappa value of 0.50, compared with 0.39 using the original subjective interpretation. In conclusion, image quality, the severity of induced wall motion abnormalities and the obtained rate-pressure product have a significant impact on the interpretation homogeneity of dobutamine echocardiograms. Standardization of image display in cine loop format and of reading criteria results in improved interinstitutional agreement in interpretation of stress echocardiograms.

## INTRODUCTION

Dobutamine echocardiography (DE) has proven to be an accurate method for the non-invasive diagnostic of coronary artery disease (1-2). Beside a high diagnostic accuracy consistency of test result interpretation by different observers is of critical importance to facilitate communication of test results. In a multicenter study we demonstrated significant differences between experienced centers in the interpretation of DE if non-unified image display and reading criteria are applied (3). Higher interobserver interpretation agreement on DE has been reported for observers of the same institution indicating that implicit agreement on reading criteria might result in improved homogeneity in the interpretation of test results (4-8). Improved agreement between different centers on interpretation of test results could be demonstrated for perfusion scintigraphy after standardization of image display and interpretation (9). The purpose of this study was (i) to analyze the reasons for the relatively low interinstitutional agreement in the interpretation of DE and determine clinical, procedural and echocardiographic parameters which predict low interinstitutional agreement, (ii) to evaluate whether standardized image display and reading criteria result in improved consistency between readers of different institutions in the interpretation of DE.

## METHODS

**Patients:** Thirty consecutive patients scheduled for angiography due to suspected coronary artery disease underwent DE at each of five experienced institutions with a high volume of stress echocardiograms. Patients with previous Q wave myocardial infarction, congestive heart failure, severe congenital or acquired valvular heart disease or documented cardiomyopathy were excluded from the study. No patient was excluded on the basis of poor echocardiographic image quality. Thus, a total of 150 DE from 146 patients (116 men, 30 women; mean [±SD] age 46±12 years) were studied. Four patients underwent a second examination after interventional therapy had been performed. Medical therapy

included nitrates in 78 patients, calcium antagonists in 48 patients and beta blocking agents in 45 patients. One hundred thirteen patients had angina at the time of examination. A non-Q wave myocardial infarction had been previously documented in 14 patients, and in 26 patients previous myocardial revascularization had been performed (20 with coronary angioplasty, 6 with coronary artery bypass grafting).

**Dobutamine stress protocol:** Dobutamine was infused intravenously, starting at a rate of 5 μg/kg body weight per min, increasing the dosage every 3 min to 10, 20, 30 and 40 μg/kg per min. In case 85% of age-predicted maximal heart rate was not reached and the test was negative, 0.25 mg atropine was given every minute up to a maximum of 1.0 mg atropine i.v. Blood pressure and 12-lead electrocardiograms (ECG) were recorded at baseline and at the end of each dobutamine stage or before the premature cessation of the test. The presence of horizontal or downsloping ST-segment depression of at least 0.1 mV, 0.08 s after the J point versus baseline recordings was considered diagnostic for ECG evidence of myocardial ischemia. Endpoints were maximal pharmacologic stress, development of new wall motion abnormalities, a heart rate of 85% of age-predicted maximal heart rate, progressive and severe angina, dyspnea, severe ventricular arrhythmias, > 0.2 mV of downsloping ST segment depression, development of hypotension (decrease in systolic blood pressure ≥ 20 mm Hg) and significant hypertension (systolic blood pressure > 240 mmHg).

**Stress echo image acquisition:** Patients were placed in the left lateral decubitus position before, during and after dobutamine infusion. Imaging was performed in the parasternal long- and short-axis as well as apical 2- and 4-chamber views in each patient. Images at rest and peak stress conditions were stored for review and exchange between centers. Individual centers maintained their standard practice of image acquisition, resulting in videotape recorded images in 82 studies and digitized images in quad-screen cine loop format in 68 studies. All

recorded echo studies were transferred to S-VHS-videotapes to have a uniformly readable media for off-line analysis.

**Stress echocardiographic interpretation:** At each of the five involved centers all 150 DE studies were evaluated by a physician experienced in stress echocardiography. Image interpretation was performed without the knowledge of clinical or angiographic data, data on the maximal dobutamine or atropine dosage or the reason for stress test termination. For wall motion analysis, the left ventricle was divided into 16 segments according to the recommendations of the American Society of Echocardiography (10) and each segment was scored using a 4-point scale: 1= normal, 2= hypokinetic, 3= akinetic, 4= dykinetic. An abnormal DE was defined as an increase in score from rest to stress in at least one segment. Echo image quality was assessed semi-quantitatively on a five point scale: A=complete endocardial definition; B=visualization of all segments but not adequate as A; C=inadequate visualization of one or two segments but adequate visualization of adjacent segments within the same coronary territory; D=inadequate visualization of ≥3 segments but adequate visualization of adjacent segments of the same territory; E=inadequate visualization of one or more whole territories.

**Quantitative coronary angiography:** Coronary angiography was performed on all patients. Analysis of all coronary angiograms was performed with electronic calipers by an independent angiographer. Significant coronary artery stenosis was considered present when ≥ 50% reduction of vessel diameter was observed in at least one major coronary artery.

**Analysis of reasons for interpretation heterogeneity:** In order to evaluate possible reasons for different interpretation of stress echo images and to elucidate factors increasing the likelihood of interpretation heterogeneity the degree of agreement was analysed depending on clinical, procedural and echocardiographic variables. Clinical parameters consisted of the patient age, antianginal therapy prior to dobutamine stress test (nitrates, calcium antagonists,

β-receptor blocking agents) and the findings of the coronary angiogram. Procedural parameters consisted of maximal dobutamine dosage, additional administration of atropine, premature termination of pharmacologic stress, achieved rate-pressure product (RPP), achievement of the targeted heart rate. Echocardiographic variables consisted of the result of the echo study (positivity vs. negativity), the size of the induced wall motion abnormality (four or more segments of induced wall motion vs smaller area of induced dyssynergy), the degree of induced dyssynergy (hypokinesis/akinesis/dyskinesia) and the image quality of stress echocardiograms. These variables were determined using the majority assessment of the five echo readers. Furthermore, it was analyzed whether interpretation agreement was more determined by the image acquisition or the image interpretation process.

**Standardized cine loop display and reading criteria:** Three of the five centers reanalyzed 90 DE after standardizing image display and reading criteria. A joint reading session on 30 DE was performed by the three reanalyzing centers to improve homogeneity in stress echo reading before reanalyzing the DE. In addition to the general reading criteria, further interpretive guidelines were stipulated to reach improved homogeneity in cases of uncertainty: (1) Basal inferior and basal septal hypokinesis are not identified as being abnormal unless an adjacent segment is also affected by a new dyssynergy or there is a clear deterioration of function to akinesia or dyskinesis, (2) induced delayed contraction should be used as an index of ischemia in the absence of conduction disturbance, (3) the identification of ischemia was based upon anticipated coronary territories, (4) significant resting wall motion abnormalities (hypokinesia in at least three segments or akinesia in at least one segment) should also suggest an abnormal test and the presence of coronary disease. The 90 DE reanalyzed subsequently were displayed in a standardized digitized cine loop format. Thus, all stress echocardiograms were digitized from the initial videotape recorded study. This allowed direct comparison of rest and stress images in quad-screen format. The time interval between the first and second

reading of the 90 echocardiograms by the three selected centers was at least 12 months.

**Statistical analysis:** All analysis was carried out using the SAS software package. Continuous data are presented as mean±SD, and categorical data are presented as frequency. Concordant interpretation of stress echocardiograms was defined as the presence of identical reading by four or all five of the interpreting centers. Chi-square test was performed to test for significant differences. Univariate and multivariate logistic regression analysis were performed to determine clinical, stress procedural and echocardiographic parameters with significant impact on the interobserver agreement in test interpretation, with low interobserver agreement being defined as agreement of less than four of the five centers on positivity or negativity of a test result. Univariate parameters with significant impact (p value < 0.2) on interobserver agreement were entered into the multivariate model. A level of 0.05 was considered statistically significant.

The kappa test was used to test the hypothesis that agreement was greater than by chance alone (11). The coefficient of agreement (kappa) was graded as follows: 0 to 0.2 = poor to slight; 0.21 to 0.4 = fair; 0.41 to 0.6 = moderate; 0.61 to 0.8 = substantial; 0.81 to 1.0 = nearly perfect.

## RESULTS

Pharmacologic stress included a maximal dobutamine dosage of 35±8 µg/kg/min and additional atropine administration in 53 patients. The maximal obtained RPP was 20136±5245 mmHg/min. Concordant interpretation of DE was obtained in 109 studies.

**Clinical parameters influencing interpretation agreement:** Age and medication with nitrates, calcium antagonists or beta-receptor antagonists were no parameters with impact on interpretation agreement by univariate analysis. Severity of coronary artery disease by angiography was a univariate parameter with significant impact on interpretation agreement (p=0.0181) (Table I).

**Table I.** Clinical, procedural and echocardiographic parameters with significant impact on interpretation agreement of dobutamine echocardiograms

| | P |
|---|---|
| Vessel disease | 0.0181 |
| Rate pressure product | 0.0179 |
| Dobutamine echo result (pos/neg) | 0.0280 |
| Extent of wall motion abnormality | <0.0001 |
| Severity of wall motion abnormality | <0.0001 |
| Image quality | <0.0001 |

**Procedural parameters influencing interpretation agreement:** While maximal dobutamine dosage, additional administration of atropine, maximal heart rate, achievement of target heart rate, and premature stop of dobutamine stress were no univariate predictors of interpretation agreement, the maximal achieved RPP during stress test was a univariate parameter with significant impact on interpretation agreement (p=0.0179).

**Echocardiographic parameters influencing interpretation agreement:** Concordant agreement of at least four centers on positivity or negativity of a study was more frequent for agreement on negativity and less frequent for positivity of a test. The extent of a wall motion abnormality was a significant univariate parameter influencing the interpretation agreement with higher agreement for induced wall motion abnormalities of four or more segments than for smaller segments of dyssynergy. The degree of dyssynergy also influenced the interpretation agreement. Hypokinesis was associated with a lower interpretation agreement. Image quality was another univariate parameter with significant impact on interobserver interpretation agreement; in studies with highest image quality concordant interpretation (agreement of at least four of five centers) was achieved in 100%, while it was only achieved in 43% of those with lowest image quality (Table I).

**Multivariate predictors of interpretation agreement:** Image quality, severity of induced wall motion abnormality and maximal RPP were independent variables with significant impact on interpretation agreement (Table II).

**Table II.** Multivariate predictors of interpretation agreement

| | Majority agreement on stress echo result | | |
|---|---|---|---|
| | OR | 95% CI | P |
| Image quality | 0.19 | 0.08-0.45 | <0.0001 |
| Severity of wall motion abnormality | 0.17 | 0.07-0.40 | 0.0002 |
| Rate-pressure product | 0.92 | 0.43-2.27 | 0.0382 |

CI: confidence interval, OR: odds ratio

**Acquisition vs. interpretation of stress echocardiograms:** Omission of those 30 studies submitted by one center did not result in a significant change of interpretation agreement for the remaining 120 studies (Table III). However, omission of one analyzing center resulted in an increase of concordant interpretation (agreement of at least four of five centers) from 110/150 studies (73%) to 116/150 studies (77%; agreement of at least three of the remaining four centers) and even 130/150 (86%) (Table III). Thus, significant increases in agreement ($p<0.01$) could be obtained depending on which of the five centers was omitted from interpretation. The greater impact of interpretation vs acquisition on test agreement is reflected by different mean kappa values obtained for each of the five centers. The mean kappa value indicating the interpretation agreement of one center with the other four centers ranged from 0.26 to 0.47.

**Table III.** Influence of omission of specific centers from acquisition and reading of dobutamine echocardiograms on the concordance of interpretation

| | CoI of all 5 centers | CoI after omission of center from acquisition of studies | Change in CoI P | CoI after omission of center from reading | Change in CoI P |
|---|---|---|---|---|---|
| Center 1 | 73% | 74% | n.s. | 84% | <0.05 |
| Center 2 | 73% | 72% | n.s. | 86% | <0.01 |
| Center 3 | 73% | 74% | n.s. | 81% | n.s. |
| Center 4 | 73% | 73% | n.s. | 77% | n.s. |
| Center 5 | 73% | 73% | n.s. | 80% | n.s. |

CoI: Concordant interpretation

**Standardization of image display and stress echo reading criteria:** Table IV demonstrates the effect of standardized stress echo reading criteria and standardized image display on interpretation agreement. For categorization of test results as normal or abnormal, the kappa value increased from 0.39 (original agreement of the three centers on the 90 test studies) to 0.50.

**Table IV.** Effect of digitization and unification of image display as well as standardized stress echo reading criteria on agreement of dobutamine echo interpretation for 90 stress echocardiograms evaluated by three centers

| | Agreement before standardization | | Agreement after standardization | |
|---|---|---|---|---|
| | Kappa | 95% CI | Kappa | 95% CI |
| Center 1 vs Center 2 | 0.26 | 0.09-0.44 | 0.42 | 0.23-0.61 |
| Center 1 vs Center 3 | 0.50 | 0.36-0.64 | 0.56 | 0.38-0.73 |
| Center 2 vs Center 3 | 0.42 | 0.29-0.56 | 0.51 | 0.33-0.69 |
| Mean | 0.39 | | 0.50 | |

Considering the majority opinion (two or more) on DE result of the three reanalyzing centers for the detection of angiographically defined coronary artery disease in the patients with the 90 reanalyzed DE diagnostic accuracy was non-significantly changed using standardized image display and reading criteria. Sensitivity, specificity and accuracy were 78%, 87% and 81% respectively, without standardization and 76%, 88% and 80%, respectively, with standardization.

## DISCUSSION

Differences in interpretation are a well known limitation of most diagnostic procedures in cardiology. Low levels of interobserver agreement have been reported for exercise ECG (12-13), perfusion scintigraphy (14) as well as coronary angiography (15-16). Recently we reported a relatively moderate agreement between readers of five institutions in the interpretation of DE (3).

Reasons for the moderate agreement on DE interpretation between readers of different institutions were analyzed in this study.

**Causes of interpreter variance:** In this study image quality, severity of induced wall motion abnormality and maximal RPP were found to be the only independent parameters influencing the interobserver agreement. This result stresses the importance of acquiring the best possible image quality. The finding that the severity of induced wall motion abnormalities was the second major parameter influencing the interobserver agreement points to the difficulty in differentiating between normal and pathologic in borderline situations. The known substantial variations in segmental left ventricular wall motion response to dobutamine stress within each patient add to the difficulties (17,18). Despite the differences in both echo acquisition and interpretation at different centers, differences in acquisition techniques between these experienced centers had only minor effects on the degree of agreement, and it was the interpretation which was the source of most of the variance. The importance of the observer in the subjective process of stress echo interpretation has been stressed before (19). This study indicates that some readers have a tendency to "under-read" resulting in more false negative results while others have a tendency to "over-read" resulting in more false positive studies.

**Standardized image display and reading criteria:** While some of the factors causing interobserver variability in interpretation of stress echocardiograms might reflect aspects such as the normal regional variability of left ventricular function in response to dobutamine stress and impaired image quality, other factors may be easier to alter. Minor induced wall motion abnormalities might be transformed to more significant wall motion abnormalities if patients are always stressed maximally, implying that the protocol should not be terminated because of the development of new minor wall motion abnormalities.

The commonly used stress echo reading criteria - scoring wall motion according to four grades and regarding deterioration of wall motion by one scale in at least one segment as pathologic - do not consider the normal inhomogeneity in wall

motion response and leave enough room for different reading practices. In this respect, joint reading sessions for multicenter studies, or the availability of interpretation examples to guide individual practitioners may enhance interpretive concordance, especially with small and less pronounced wall motion abnormalities. In our study, uniform criteria were aimed at preventing disagreement on hypokinetic basal inferior and septal wall motion abnormalities and interpretation of delayed contraction. Furthermore, it was required that wall motion analysis should take the anatomy of coronary perfusion beds into account, e.g. a separate new wall motion abnormality in the middle septal segment was disregarded if the apical septal segment did not demonstrate a new wall motion abnormality.

Further efforts to improve image quality or endocardial border definition and techniques allowing a quantification of endocardial or myocardial wall motion are required. Improved endocardial border definition has been described with contrast echocardiography (20) and second harmonic imaging (21), while color-coded endocardial wall motion analysis (22) and color-coded tissue Doppler analysis (23) have been used to quantify endocardial or myocardial wall motion. However, the value of these approaches in the context of routine stress echocardiography needs to be proven.

**Limitations of the study:** Only patients without significant wall motion abnormalities at rest were included in this study. The observer variability might be higher in patients with more difficult to read DE. This study does not differentiate between the relative effects of a standardized image display and those of uniform interpretation citeria.

**Conclusion:** Low interobserver agreement in the interpretation of DE is mainly due to studies with low image quality and studies with minor wall motion abnormalities, in which varieties in reading habits result in different test result interpretation. Substantial efforts should be undertaken to acquire stress echo studies with high image quality and obtain pronounced wall motion abnormalities during stress testing. At present, conformity in data acquisition is

higher than conformity in DE interpretation. Standardized image acquisition and reading criteria result in improved interinstitutional agreement on DE interpretation.

*We gratefully acknowledge the expert statistical analysis of Thorsten Reineke*

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# CHAPTER 2

# DOPPLER TISSUE IMAGING IN THE NEW ERA OF DIGITAL ECHOCARDIOGRAPHY

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## ABSTRACT

Doppler tissue imaging is one of the most recent technical achievements of clinical echocardiography. Different Doppler modes are encompassed by Doppler tissue imaging: tissues velocity, pulsed wave-Doppler, acceleration, phase, synchronicity and energy modes. With the exception of the energy mode, all are based on the Doppler shift, according to the strength of the Doppler signals from the tissues. The most widely used is the tissue velocity, in which the velocity of moving tissue is calculated in relation to the transducer from the Doppler shift and displayed as colour-encoded velocity maps in M-mode and two-dimensional imaging formats. Both curved M-mode, applied on two-dimensional images, and three-dimensional reconstruction appear among the most promising applications of velocity mode for the quantitative assessment of regional left ventricular function. A second Doppler mode, pulsed wave-Doppler tissue imaging, displays the velocity profile of a region of interest versus time. The velocity data are displayed with high temporal resolution, but with the disadvantage of a low spatial resolution. A third Doppler mode, tissue acceleration, displays the differences in velocity between subsequent frames in colour-encoded maps. A clinical application has been found in the electrophysiologic field. Other Doppler modes, phase and synchronicity, still require clinical assessment. Lastly, the tissue energy or power mode displays the strength of the Doppler signal from the tissues as gradations of the colour intensity in colour-encoded maps. One of its fields of application appears the study of myocardial perfusion with contrast agents. The development of new dedicated algorithms for colour quantification, along with the beginning of the new era of digital echocardiography, should help to bring Doppler tissue imaging into the clinical arena.

## BACKGROUND

Echocardiography provides unique anatomical and functional informations of the heart which are superior to e.g. nuclear imaging techniques with respect to availability, radiation and costs (1). Anatomical informations of the cardiac structures have improved with the introduction in echocardiography of new imaging technologies: three-dimensional echocardiography, contrast echocardiography, high resolution imaging and acoustic backscatter-derived imaging: e.g. acoustic quantification. Parallel efforts have been made to obtain detailed informations on myocardial function. However, for both these anatomical and functional informations the subjective nature of the echocardiographic examination remains the limiting factor. Different strategies have been developed to overcome this problem. For example, in stress echocardiography the ventricular function evaluation has been improved by semiquantitative scoring systems. However the reduction in interobserver and interinstitutional variation has globally been moderate, regardless of an effective learning curve (2). To make the situation worse, echocardiographically "silent" myocardial ischemia, such as subendocardial infarctions or syndrome X, contribute increasing discrepancies between operators. All the echocardiographic techniques, primarily introduced to improve the anatomical informations, have been soon after adopted to improve the functional informations. In this context Doppler tissue imaging combines important features: its ability of measuring intramural myocardial function, its low attenuation rate by the interposed chest wall, its high spatial and temporal resolutions and its suitability for a three-dimensional quantification of the myocardial function. However, its clinical diffusion has been hampered by limitations, mainly related to an inadequate digital imaging processing.

This review will be focused on Doppler tissue imaging, ranging from its conception to the most recent developments and potential applications. The data derived from our clinical experience were obtained by using the Toshiba Powervision ultrasound system.

## DOPPLER TISSUE IMAGING TECHNOLOGY

In 1989 Isaaz et al (3) first reported the use of a modified pulsed wave-Doppler to measure the myocardial velocities of the ventricular posterior wall.

In 1992 the Doppler tissue imaging technique was independently developed by McDicken et al. (4) and Yamazaki et al. (5).

According to the same principles of colour Doppler flow imaging, Doppler tissue imaging utilizes the multigated pulsed Doppler technology to calculate tissue velocity at consecutive points along multiple scan lines. These velocities are displayed both in M-mode and two-dimensional formats using a colour scheme (4). Each image unit or pixel displays one colour representing a mean velocity value. Cardiac structures have a velocity range of 6-24 cm/s, 8 to 10 times lower than blood flow and an amplitude ~40 decibel (dB) higher than blood flow. Therefore, to obtain Doppler tissue imaging, the high-pass filter, employed in colour Doppler flow imaging to remove the low velocity Doppler signals from cardiac structures, must be removed, to allow these signals to enter the auto-correlator, where complex computations are performed, resulting in Doppler output data as mean velocities and variances. To eliminate the low amplitude Doppler signals from the blood flow, it is sufficient decreasing the overall gain. In this way blood flow signals are eliminated and only high amplitude signals from the tissues are processed by the auto-correlator.

The low tissue velocities allow Doppler tissue imaging to operate at low level of pulse repetition frequency (PRF/8-16), far below the Nyquist or aliasing limit, which is one half the pulse repetition frequency (PRF/2). Therefore, aliasing never occurs. When tissue velocities exceed the preset velocity range, homogeneous colours are displayed. When operating at very low velocities, like in the dyssynergic myocardial segments, the preset velocity range of the instrument must be widened to discriminate between different levels of colour within the colour band. In this setting the highest velocities enter the non informative homogeneous colour band. For the operator would be useful to recognize within this homogeneous colour band when the Nyquist limit is

exceeded and aliasing occurs. Therefore, the ongoing trend is to add the colour-encoding of aliasing (6).

A problem of Doppler tissue imaging analysis is a change in velocities and hence in colours faster than the standard frame rate. This can be solved by increasing the frame rate, usually limited to 25 frames/s when videotape recording are used. Toshiba Powervision Doppler tissue imaging system, by using digital parallel processing techniques, allows two-dimensional Doppler tissue imaging scanning with a 3.75 MHz transducer and a 60° sector at 40-60 frames/s, which is equal to or greater than the standard grey-scale two-dimensional image frame rate. A even higher temporal resolution is achieved by Doppler tissue imaging in M-mode, where the scanning rate is as high as 90 multigated lines/s (Figure 1). This technology is the core of both tissue velocity and tissue acceleration mode.

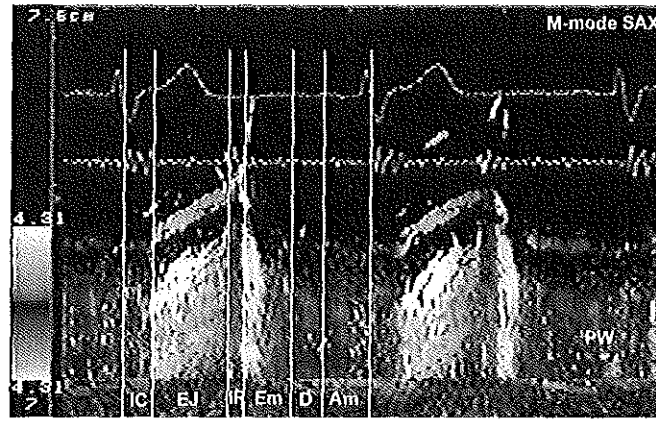


**Fig 1:** Healthy subject. Doppler tissue imaging in parasternal short-axis M-mode. The posterior wall is encoded in red-yellow during the ejection phase and blue-green during the relaxation phase. The colours in the endocardial layers are brighter than those in the epicardial layers, indicating a higher velocity of motion. The cardiac cycle phases are indicated by vertical lines. IC: isovolumic contraction, EJ: ejection phase, IR: isovolumic relaxation, Em: early diastole, D: diastasis, Am: late diastole. PW: posterior wall, M-mode SAX: M-mode parasternal short axis view.

An alternative display of velocity is obtained by pulsed wave-Doppler tissue imaging. This technology allows to place a small sample volume in a point of

interest of the myocardium and to display its velocities over time with a temporal resolution of 4 ± 3 ms. Thus, it is possible to measure with the highest echocardiographic accuracy instantaneous peak velocities of each cardiac phase. Although this not an imaging modality, to date the trend is to include it in the general definition of Doppler tissue imaging.

A different Doppler technology is involved in tissue energy mode. In this case colour images are not derived from the phase shift of the Doppler signal, but from the integration of the power spectrum of the Doppler signal, which reflects the composition of the tissue. Therefore, yet using part of the Doppler signal path within the ultrasound machine, tissue energy mode measures only the strength of the returning ultrasound signal. For this reason these images are both angle and velocity independent. They are available in two-dimensional format, at a 30-60 frames/s and logarithmically compressed. The main advantage of this imaging modality is its ability to recognize signals from the background noise, which is less intense than the background of grey-scale format.

## EXPERIMENTAL STUDIES

The validation of Doppler tissue imaging has been performed using "tissue-mimicking" phantoms rotated in a water bath at different constant speeds, similar to the velocities of normal and pathologic myocardium (7,8). The correlation found between the velocities of these phantoms and the velocities measured by Doppler tissue imaging is very high. Only in the very low or high velocity range a distorted estimation and a poor spatial resolution occur (5,9). The spatial resolution of velocities of single layers of gel phantoms sliding one on the other, as displayed in two-dimensional velocity maps, is 3x3 mm when using a 2.5 MHz transducer and a low transmit pulse repetition frequency (9). A three-dimensional velocity reconstruction has been tested on phantoms with a spatial resolution of 1 x 1 mm (10).

Phantoms of different composition have been used to validate the Doppler energy mode and a close correlation has been found with the integrated tissue backscatter imaging (11).

Animal studies have shown that 1 minute after coronary occlusion in pigs, decreased wall velocities are visually detected by Doppler tissue imaging in the ischemic area, with reversion to normal after reperfusion (11). The analysis of velocity changes during ischemia by pulsed wave-Doppler tissue imaging offers a higher temporal resolution, allowing an earlier detection of velocity changes (12). After 10 seconds of ischemia both a significant reduction of early diastolic peak velocity and a reduction of early/late diastolic ratio occur, followed by an increase in late diastolic peak velocity (13).

The presence of transmural velocity gradients (the increase of velocity from epi- to endocardium) has been validated with the implantation of piezoelectric crystals in the endocardial and epicardial layers in dogs (14). A decrease of transmural velocity gradients with the development of ischemia has been detected (14).

The use of Doppler energy maps in pigs has shown an enhancement of contrast-associated coronary perfusion in the left ventricular walls after a peripheral intravenuous injection of SHU508A (Levovist) (11). Following a right atrial injection of 8 ml of Levovist in pigs, Doppler energy mode has been more sensitive than grey-scale imaging, calculated as background-subtracted peak videodensitometry, in detecting dipyridamole-induced coronary artery hyperaemia, reduced perfusion or immediate reperfusion (15).

## CLINICAL APPLICATIONS

Doppler tissue imaging may be applied to all echocardiographic views. Thus far its application has been focused on the standard parasternal and apical views.

In parasternal views the posterior wall exhibits higher velocities than the anterior wall. The total anterior displacement of the heart during systole adds to the posterior wall velocities and subtracts from the inward endocardial velocities of

the anterior wall. Therefore for an accurate measurement of myocardial velocities in parasternal views a correction formula or the measurement of the velocity gradient should be introduced. Myocardial velocity gradient mapping displays only the increase of velocity from subepicardial to subendocardial layers, without velocity relation to the transducer. In this way it is possible to eliminate the interference introduced by the global cardiac movement (16,17). However its application is limited to the anterior and posterior segments in parasternal views, the only exhibiting a direction of contraction and relaxation parallel to the Doppler beam.

In apical views all the standard segments are displayed. In these views Doppler tissue imaging is able to detect the longitudinal motion of the cardiac base toward and away from the apex, which may be considered as a fixed reference point (18). A velocity gradient is also present in apical views, with the maximal velocities at the cardiac base and a progressive decrease toward the apex. As the velocity component perpendicular to the interrogating sound beam is not measured, the horizontal inward wall motion in apical views is partially missed. Both the horizontal inward wall motion and the longitudinal shortening are known to play an equivalent role for the global ejection fraction (19), therefore an integrated assessment of their resulting velocity vector should be desirable .

## QUALITATIVE OR VISUAL ASSESSMENT OF DOPPLER TISSUE IMAGING

The first approach to Doppler tissue imaging has been visual. A scheme encodes tissue velocities in colours. Each colour represents a velocity range and a direction of motion. The lowest velocities toward the transducer are displayed as red, the intermediate velocities as orange and the highest velocities as yellow, with intermediate hues. The lowest velocities away from the transducer are displayed as blue, the intermediate as turquoise and the highest velocities as green. Myocardial segments with velocities too low to reach the colour threshold

are imaged in black and white. A multicolour scheme is also used to display the acceleration maps.

A non-colour non-imaging approach is offered by pulsed wave-Doppler tissue imaging, which allows the sampling of a selected point in the myocardium and the display of its velocity versus time.

For display of tissue energy maps, a mono- or bichromatic (red/blue) scheme is used, with an increase in brightness parallel to the increase in Doppler signal intensity from tissue.

Velocity and energy data can be represented both in M-mode, to improve temporal information, and two-dimensional imaging, to improve spatial information. Acceleration data may be displayed only in two-dimensional imaging.

A frame by frame analysis of Doppler tissue imaging has been accomplished in our laboratory to study the normal myocardial contraction and relaxation sequences, by using as a reference both electrocardiogram and phonocardiogram. The phases of the cardiac cycle are visually recognizable in both M-mode and two-dimensional Doppler tissue images: isovolumic contraction, ejection phase, isovolumic relaxation, early diastole, diastasis and late diastole. In M-mode the systo-diastolic phases may be detected with high temporal resolution (Figure 1). As an example, it is possible to discriminate the velocity ratio of the early versus the late diastole by visually comparing the colour ratio of the corresponding cardiac phases. The M-mode motion pattern has been well correlated with ejection and filling parameters (20). In parasternal views the systolic septal wall motion is displayed in blue (posterior direction) and the posterior wall motion in red-yellow (anterior direction). During diastole opposite colours are displayed (Figures 2 and 3). In apical views red-to-yellow colours spread from base to apex during both isovolumic contraction and ejection phase in systole and blue-to-green colours do the same during isovolumic relaxation, early and late diastole. The apical area usually remains encoded in grey or dark hues of colour, as it is almost immobile. Virtually no

motion is present during diastasis, therefore the ventricular walls are not colour-encoded during this phase.

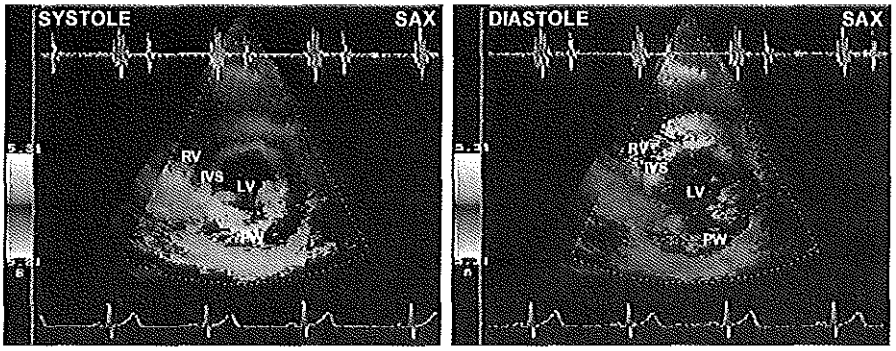


**Fig 2:** Healthy subject. The parasternal short axis view shows in mid systole a red encoded posterior wall and a blue encoded anterior wall (left panel). A pattern of opposite colours is visible in early diastole (right panel). PW: posterior wall, LV: left ventricle, IVS: interventricular septum, RV: right ventricle, SAX: parasternal short axis view.

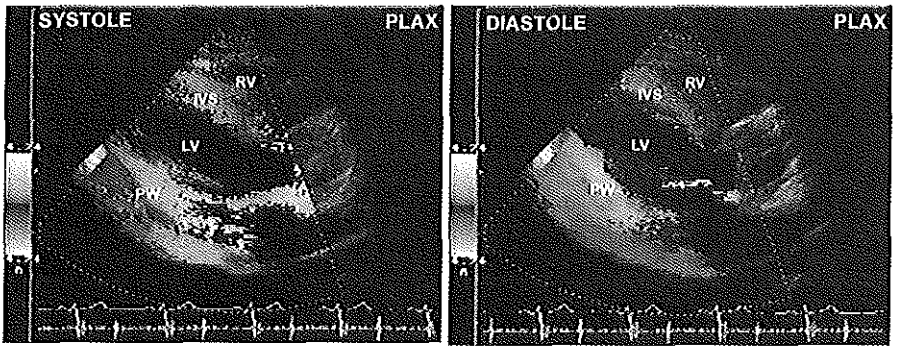


**Fig 3:** Healthy subject. The parasternal long axis view shows the posterior wall encoded in red-yellow and the anterior septum in blue-green in systole (about 80-120 ms after the QRS). An opposite color pattern is evident in diastole. PW: posterior wall, LV: left ventricle, IVS: interventricular septum, RV: right ventricle, PLAX: parasternal long axis view.

The qualitative experience acquired from the visual analysis of normal subjects may be useful as a reference to describe pathological patterns. As an illustration, a left ventricular hypertrophy exhibits an asynchronous contraction pattern in the septum, with blue and red colours in adjacent myocardial layers (Figure 4, A), a septal myocardial infarction shows no colours in the akinetic area (Figure 4, B),

and a global hypokinetic left ventricle is characterized by darker hues of red and blue (Figure 4, C). As a further example, by comparing the appearance of the corresponding colours, in hypertrophic cardiomyopathy the onset of relaxation in early diastole has been found delayed in the septum relative to the other walls (21).

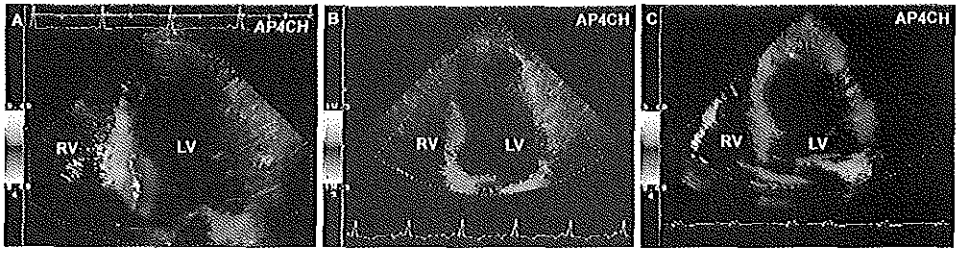


**Fig 4:** Doppler tissue imaging frames in early systolic apical four chamber view in cardiac patients. A: patient with left ventricular hypertrophy: an asynchronous contraction pattern is visible in the septum with blue and red colours in adjacent myocardial layers. B: patient with a septal myocardial infarction: the akinetic area shows no colours. C: patient with low ejection fraction: dark hues of red are visible all over the left ventricular walls. LV: left ventricle, RV: right ventricle, AP4CH: apical four chamber view.

## QUANTITATIVE ASSESSMENT OF DOPPLER TISSUE IMAGING

The visual assessment of Doppler tissue imaging appears less important than the quantitative manipulation of imaging data. Many algorithms have been developed and others are under consideration to elicit quantitative informations from Doppler tissue imaging and especially to convert colours in velocities (16). In comparison with other technologies, Doppler tissue imaging appears superior e.g. to the tracking of the speckle pattern within the myocardium, an angle-independent technique providing informations on intramural myocardial velocities, but unlikely to be introduced in the near future, because of the sophisticated algorithms required (22).

Most of the velocity measurements are made in M-mode tissue Doppler imaging, because of its high temporal resolution, as based on its high sampling rate. This allows accurate measurements of velocities and time intervals versus

time. A good correlation has been found between parasternal M-mode Doppler tissue imaging and the endocardial motion profile of the echocardiogram (17) or the transmitral Doppler velocity profile (23). One example of parameter calculated in M-mode tissue Doppler imaging is the mean transmural velocity, defined as the mean of all the velocities calculated along an individual M-mode line from epicardium to endocardium. From all the mean transmural velocities over one cardiac phase interval a maximal or peak velocity may be calculated. Therefore, each cardiac phase may be represented by a peak velocity. In healthy subjects the peak systolic velocities of both the anterior septal and the posterior walls, calculated in parasternal views, show a wide range of normal values (17).
An alternative approach is the display of transmural velocity gradient maps. These are obtainable by using a software which refers to the centre of ventricular contraction all the colour-encoded sampling lines. According to this algorithm the transmural velocity gradient is colour-encoded from the subepicardium to the subendocardium. Its best feasibility is for the anterior and posterior segments of left ventricle in parasternal views, according to the Doppler angle-dependence. The transmural velocity gradient is represented in systole with the same colours in both anterior and posterior walls and with opposite colours in diastole, therefore eliminating the interference from the global cardiac movement relative to the Doppler transducer (7,24). As an example, in conditions of right ventricular volume overload, like in presence of atrial septal defect, the cardiac translocation is increased. In this setting the myocardial velocity gradient coding is able to detect a normal contraction pattern of the left ventricle (25). During myocardial ischemia, a reduction of transmural systolic and diastolic velocity gradients has been recorded (7). In dilated cardiomyopathies a reduction of transmural velocity gradient has been found to correlate with their severity (26,27). In patients with hypertrophic cardiomyopathy, both systolic and early diastolic velocity gradients exhibit lower values than in athletes or normal subjects (28). The myocardial velocity gradient may be also displayed in three-dimensional format (29).

Another quantitative application of Doppler tissue imaging, pulsed wave-Doppler tissue imaging, allows a temporally accurate velocity measurement of both systolic and diastolic cardiac phases from a point of interest within the myocardium. As an example, in healthy subjects the regional myocardial relaxation has been found preceding the starting of early diastolic transmitral flow, with a resulting shortened isovolumic relaxation time (30). In our laboratory we have mainly developed the pulsed wave-Doppler tissue imaging approach by sampling the basal part of each ventricular wall in standard apical views. The velocity values obtainable in apical views are different from those obtainable in parasternal views and also from one wall to another. In our experience and in agreement with Sun et al (31), the velocity range of healthy subjects in apical views is wider than in parasternal views and the velocity values exhibit regional heterogeneity (32). For this reason, time intervals or ratios are occasionally preferred to absolute velocity values. In patients with cardiomyopathies peak velocity values were found lower than in healthy subjects (33).

An angle-corrected curved M-mode is under consideration in order to sample colour two-dimensional images, as stored on a digital support at a high frame rate, thus combining both temporal and spatial high resolutions. Another important development is the display of myocardial velocities in three-dimensional format for the assessment of intramural contractile function, by reconstructing the three-dimensional velocity vectors, as obtained by three-dimensional colour Doppler tissue images (34).

## CLINICAL APPLICATIONS OF DOPPLER VELOCITY MODE

Both chronic and acute ischemic myocardial segments may be studied by Doppler tissue imaging. Rest or stress induced dyssynergic segments appear as darker hues of colour in M-mode and two-dimensional displays (11).

M-mode tissue Doppler imaging during dobutamine stress has measured decreased velocity values during early diastole and systole in ischemic segments at peak stress (35).

Pulsed wave-Doppler tissue imaging has also been used during dobutamine stress echocardiography by sampling the 6 basal segments of each wall in the standard apical views, with the addition of the right ventricular free wall (Fig 5), or by sampling 12 or 16 segments (36,37).

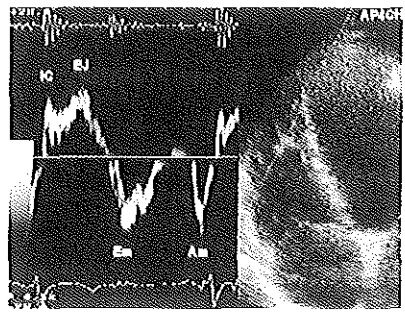


**Fig 5:** Resting frame showing a sample volume of pulsed wave-Doppler tissue imaging located on the basal part of the right ventricular free wall in apical 4-chamber view (Right side). The velocity profile shows systolic velocities over the baseline and early and late diastolic velocities below the baseline (Left side). IC: isovolumic contraction, EJ: ejection phase, Em: early diastole, Am: late diastole, AP4CH: apical four chamber view.

In our opinion, to date, pulsed wave-Doppler tissue imaging, especially by sampling the basal segments in apical views, offers many advantages compared to other quantitative approaches non supported by adequate algorithms. A first advantage is the amplification of the velocity profile determined by the many myocardial fibres interposed between the cardiac base and the cardiac apex, with a consequent improvement of measurement accuracy. Moreover, the direction of contraction is always close to the direction of the Doppler beam, while in short axis view the velocity of contraction of the posterior septum and lateral walls is not detectable, as perpendicularly oriented to the Doppler beam. Another advantage is the relative fixed position of the cardiac apex, relative to the transducer, therefore reducing the bias determined by the global cardiac

translational movement. This translation is more evident in parasternal than in apical views, because the heart moves toward the thoracic anterior wall during systole and in the opposite direction during diastole, as a result of the interventricular interaction, mainly oriented in the horizontal axis. A further advantage of pulsed wave-Doppler tissue imaging is the presence of the mitral annulus, an important intra-patient reproducible anatomical landmark.

Pulsed wave-Doppler tissue imaging is able to detect the onset of ischemia, as a prolongation of isovolumic relaxation time, a reduction of early diastolic peak velocity, a delayed time to peak early diastolic velocity and an increase of late diastolic velocity, all preceding the reduction of systolic peak velocity. Modifications of systo-diastolic parameters, as measure by pulsed wave-Doppler tissue imaging, have been correlated with the severity of the coronary stenosis (38). At peak stress a decreased early diastolic velocity higher than 2 cm/s and a decreased early/late diastolic ratio correlate with regions supplied by coronary arteries with more than 50% of stenosis diameter (36). In our experience patients with an history of more than 50% of stenosis diameter in the proximal or medium part of the right coronary artery exhibit a blunted (less than 25%) increase of the ejection phase velocity from low dose to peak dobutamine, when measured in the basal part of the right ventricular wall in apical four chamber view, compared to patients without right coronary disease, who exhibit a sustained increase of the ejection phase velocity. Therefore, these different patterns may be helpful in predicting the presence of a significant right coronary disease (39).

A presence of viability in dyssynergic myocardium may be demonstrated by comparing rest and low dose dobutamine infusion as an appearance of brighter velocity colours in colour-encoded displays (40,41) and increased velocities in pulsed wave-Doppler tissue imaging recordings. In patients with poor left ventricular function we found a correlation between the ejection velocities of pulsed wave-Doppler tissue imaging in the basal segment of each ventricular wall in apical views and the corresponding wall motion score index. Therefore,

an agreement exists between the longitudinal and the horizontal components of ventricular contraction. The same results may be confirmed during dobutamine stress echocardiography at each step of the test (42). Moreover, a sustained improvement from low dose to peak dobutamine seems to correlate with the presence of viability and a blunted increased with the absence of viability, as defined by the standard wall motion score index for each ventricular wall (43). By using three-dimensional Doppler tissue imaging at rest, viable segments exhibit systolic, early and late diastolic peak velocities higher than non viable segments. The increase of velocity from rest to low dose is also higher in viable than in non viable segments (44).

Myocardial segments with chronic coronary artery stenosis exhibit at rest reduced early diastolic velocity, reduced early/late diastolic ratio and prolonged isovolumic relaxation time (45).

In patients with microvascular angina the myocardial segments have shown an increased isovolumic relaxation time and an increased early/late diastolic ratio (37).

During percutaneous coronary angioplasty pulsed wave-Doppler tissue imaging in apical views is able to detect, as early as 30 second after the beginning of occlusion (46), a decrease of early diastolic peak velocity and early/late diastolic ratio, followed by a decrease of late diastolic peak velocity (47). Similar results have been confirmed with colour M-mode in short axis view (48), able to detect a decrease of myocardial velocity gradient and a disappearance of heart cycle intervals during acute coronary occlusion, with reversion during reperfusion (49).

In hypertrophic cardiomyopathy a prolongation of isovolumic relaxation time and an early/late diastolic ratio higher than 1 in the septum, compared to an early/late diastolic ratio lower than 1 in the lateral wall, have been correlated with regional diastolic dyssynergies (50).

A prolongation of the isovolumic relaxation time is also measured in amyloidosis. In this cardiac disease peak systolic and diastolic velocities appear

both flattened and delayed, while in two-dimensional imaging an intramural reduction of colour in the interventricular septum is described, probably due to the infiltrative process (50).

Pulsed wave-Doppler tissue imaging has shown that the ventricular relaxation seems relatively preload independent, as the pattern of early diastole, recorded by pulsed wave-Doppler tissue imaging, is different from the simultaneous pattern of transmitral Doppler velocity profile (51).

In patients with poor quality of grey-scale images, Doppler tissue imaging is able to measure the left ventricular volumes with the Simpson`s formula. A validation was made by Sutherland et al. (52) against volumes obtained by two-dimensional echocardiography and the interobserver agreement was improved by Doppler tissue imaging. For the right ventricular volumes the best correlation has been found between the area-length method in apical view and the volumes measured by magnetic resonance imaging (53).

A low intra- and inter-observer variability for the left ventricular volume assessment has been reported with three-dimensional echocardiography (54). A three-dimensional echocardiographic reconstruction of the left ventricle may be also obtained by using the Doppler energy mode (55,56). By converting the colour Doppler tissue images in grey-scale format is also possible to evaluate the regional left ventricular mass (24). However, the most promising three-dimensional application is the colour velocity display, allowing the quantitative regional analysis of left ventricular function in correlation with the corresponding coronary artery fields, or the analysis of left ventricular systo-diastolic volume variations in correlation with myocardial velocities of contraction and relaxation. Many cardiac pathologies will be addressed by this approach (57). The three-dimensional technology combined with Doppler tissue imaging results also helpful in the assessment of right ventricular volumes (58).

In our experience a correlation exists between the pulsed wave-Doppler tissue imaging ejection velocity, as measured at the basal part of ventricular walls in

apical views, and the resting ejection fraction, obtained by radionuclide ventriculography.

## CLINICAL APPLICATIONS OF DOPPLER ACCELERATION MODE

In the Wolff-Parkinson-White syndrome, the mapping of the insertion of left-sided accessory atrio-ventricular pathways appears a clinical application of the acceleration maps (59). During radiofrequency ablation procedures it is also possible to monitor on line the successful ablation of the accessory pathway (60).

Other potential applications in the electrophysiological domain seem the location of both focus and sequence of the atrial activation.

## CLINICAL APPLICATIONS OF DOPPLER ENERGY MODE

Doppler energy maps used in combination with echo-contrast agents appear promising in the study of myocardial perfusion. However, to date, the effectiveness of a peripheral intravenous injection of contrast agent in measuring perfusion changes of left ventricular walls in the clinical setting remains low (11). A potential exists to combine second harmonic technology to Doppler energy imaging.

Another application is the tissue characterization by measuring the integrated backscatter levels. However, the current logarithmically compressed format of Doppler energy imaging hampers a fine discrimination of different backscatter levels (61).

Doppler energy appears superior to grey-scale imaging in patients with poor transthoracic acoustic views because of its high signal-to-noise ratio and superior border detection. Its potential for a backscatter-based three-dimensional echocardiographic reconstruction of the left ventricle is under investigation (55).

## FURTHER CLINICAL APPLICATIONS OF DOPPLER TISSUE IMAGING

Further clinical applications of Doppler tissue imaging are here illustrated by few examples.

Pulsed wave-Doppler tissue imaging with the sample volume on the mitral annulus shows early diastolic peak velocities lower in constrictive pericarditis than in restrictive cardiomyopathy (62). With the same technique, late diastolic peak velocities have shown a correlation with the left atrial stroke volume (63) and left atrial appendage cycle length has been transthoracically determined in atrial fibrillation, in order to predict a successful cardioversion (64).

In heart transplanted patients, colour M-mode, placed over the subendocardial posterior wall, exhibits a decrease of early diastolic velocity during mild acute rejection and a further decrease during moderate-severe rejection (65). Furthermore, in heart transplanted patients, atrial contraction exhibits highest velocities only when the recipient atrium contracts in late diastole, simultaneously to the donor atrium. However, all the atrial velocities remain lower than in normal subjects, indicating a poor contribution of atrial contraction to left ventricular filling (66).

In the assessment of aortic function a reduced time to peak velocity both in systole and diastole helps to distinguish patients with arterial hypertension and coronary artery disease from healthy subjects (67).

Other applications are the assessment of regional diastolic syndromes (68), infarct-induced thrombi (69), endocardial vegetations (70) cardiomyoplasties (71), and other cardiac parameters, as obtained for example by transesophageal echocardiography (72).

## LIMITATIONS

The angular dependence is the intrinsic main limitation of the Doppler technique: when the direction of movement diverges from the interrogating Doppler beam more than 20°, the accuracy of the velocity measurements

becomes not acceptable and when the direction of movement is perpendicular to the Doppler beam, no colour and hence no measurement is achievable.

A second limitation of Doppler tissue imaging is the global cardiac motion, particularly in the parasternal views, as it distorts the accurate encoding of myocardial velocities.

A third limitation is the presence of artefacts, such as side lobes, as their colour-encoding by Doppler tissue imaging affects the correct evaluation of the underlying image.

A further limitation is the inability of Doppler tissue imaging to completely colour-encode every part of the ventricular wall, especially the walls depicted at the border of the echocardiographic sector. A possible explanation seems a low intensity of the signals reflected from the myocardial backscatters (9). Accordingly, the best assessment of the ventricular walls is performed when they are located in the central part of the sector, because a location close to the echocardiographic sector borders is affected by a lower spatial resolution.

## FUTURE PERSPECTIVES IN THE ERA OF DIGITAL ECHOCARDIOGRAPHY

Doppler tissue imaging offers the potential to study in a quantitative way aspects of myocardial dynamics to date missed by other noninvasive clinical techniques.

A possible competiton to Doppler tissue imaging could arise from techniques, like the tracking of the speckle pattern within the myocardium to calculate intramural myocardial velocities, as its angle-independence represents an advantage over Doppler tissue imaging. However, algorithm limitations render unlikely an imminent introduction in echocardiography of this technique and its low signal-to-noise ratio remains a disadvantage in comparison with Doppler tissue imaging. Other approaches to the ventricular function assessment, like colour kinesis, are waiting adequate algorithms and comparative studies with Doppler tissue imaging.

The high spatial resolution offered by two-dimensional Doppler tissue imaging and the high temporal resolution offered by pulsed wave-Doppler tissue imaging will be combined with the development of new algorithms (73). Pulsed wave-Doppler tissue imaging, a time-consuming a spatially limited approach, is likely to be replaced in the near future by e.g. the angle-corrected curved M-mode, applied on two-dimensional velocity maps recorded at a frame rate high enough to guarantee a useful temporal resolution. With this approach the early recognition of diastolic abnormalities induced by myocardial ischemia during stress echocardiography should become a clinical routine reality. Real time border detection will be another interesting development of this technique. Transthoracic three-dimensional reconstruction will allow the assessment of regional myocardial function and the introduction of new cardiac functional indices. A three-dimensional on-line system, for a real-time reconstruction of the left ventricle, will be the subsequent step. Doppler acceleration maps will help in electrophysiologic studies and procedures. Phase and synchronicity parameters still wait for their assessment. Second harmonic Doppler power imaging in combination with myocardial contrast agents will help in the quantification of myocardial perfusion.

All these improvements are moving parallel to the beginning of the new era of digital medicine. The new standard of digital imaging and communications in medicine (DICOM 3.0 Standard) is a set of rules that allows medical images with all associated informations to be exchanged between imaging equipments, computers, institutions and individual operators. Traditional videotapes and cine films will be replaced by writable CD-ROM and digital database. In the case of echocardiographic images, a new era of digital storing, processing and worldwide exchanging will start.

By having Doppler tissue images in high frame rate colour digital format, a substrate to perform sophisticated calculations of myocardial function parameters will be provided. Easily retrievable images will allow serial intra-or

inter-patients comparisons. Both CD-ROM-stored and network-transmitted images will permit any level of colour processing at any PC-equipped location.

In conclusion, either the development of new Doppler tissue imaging-dedicated algorithms or the beginning of the new era of digital echocardiography appear the intermingled master-keys to enter Doppler tissue imaging in the clinical arena.

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# CHAPTER 3

# TISSUE DOPPLER IMAGING AND THE QUANTIFICATION OF MYOCARDIAL FUNCTION

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## ABSTRACT

Tissue Doppler imaging (TDI) has recently been introduced in clinical echocardiography. Most widely used are tissue velocity maps, in which the velocity of moving tissue is calculated relative to the transducer from the Doppler shift and displayed as colour-encoded velocity maps in either M-mode or two-dimensional image formats (Doppler velocity mode). This allows detection and quantification of dyssynergic areas of the myocardium. Additionally, the velocities may be studied with pulsed wave-tissue Doppler sampling (PW-TDS) which displays the velocity of a selected myocardial region versus time with high temporal resolution. Less often used, are tissue acceleration maps which display acceleration or velocity change of subsequent frames as different colours (Doppler acceleration mode). These maps may find application in clinical electrophysiology. Another TDI modality is tissue energy imaging, which is based on the integration of the power spectrum of the Doppler signals from the tissue. This technique provides maps of Doppler energy which are represented as colour brightness. Such maps offer potential for the study of myocardial perfusion. TDI modalities have promise to become clinically useful for quantifying myocardial function.

Abbreviations:
TDI = tissue Doppler imaging.
PW-TDS = pulsed wave-tissue Doppler sampling.


## INTRODUCTION

TDI is a new imaging technique to assess cardiac function. Parallel to improved techniques for the imaging of cardiac structures i.e: two- and three-dimensional echocardiography, contrast echocardiography, acoustic backscatter and improved blood flow representation by colour Doppler flow imaging, efforts have been made to obtain detailed information on the myocardial function. TDI

uses the Doppler shift data from the myocardium to obtain both qualitative and objective or quantitative informations on ventricular wall dynamics.

## TDI TERMINOLOGY

Tissue Doppler imaging (TDI) is the most accepted term to refer to the imaging of myocardium. It encompasses three major colour display modes of the Doppler shift processing method: 1) tissue velocity imaging; 2) tissue acceleration imaging and 3) tissue energy or power imaging. Pulsed wave-tissue Doppler sampling (PW-TDS) is a technique not imaging the myocardium, but displaying velocities over time from a sample volume.

## TDI METHODOLOGY

TDI is based on the same principles applied in colour Doppler flow imaging. In short, colour Doppler flow imaging utilises multigated pulsed Doppler technology to calculate blood velocity at consecutive points along multiple scan lines and displays these velocities in M-mode or two-dimensional formats using a colour scheme (1).

Blood flow within a cardiac chamber has a 8 to 10 times higher velocity and a lower amplitude of Doppler signals compared to cardiac structures. Therefore a high-pass filter must be employed to remove the low velocity Doppler signals from cardiac structures. These filtered data are processed in an auto-correlator, which performs complex computations and yields Doppler output data as mean velocities and variances.

TDI development progressed from 1992-1994 with clinical applications being demonstrated threafter (1-2). Doppler signals from the myocardium have a velocity range of 6-24 cm/s and an amplitude ~40 dB higher than those derived from the blood pool. The principle of TDI is based on selecting the low velocities of cardiac structures by bypassing the high-pass filter and on rejecting the low amplitude Doppler signals from the blood pool, by decreasing the overall gain. In this way blood flow signals are eliminated and only the high

amplitude-low velocity signals from tissue are processed in the auto-correlator (3). This technique enables TDI to be more sensitive than colour Doppler flow imaging and less affected by the attenuation caused by chest wall structures. However, the principle of image reconstruction is the same, displaying more than 16 millions of colours, each one conveyed by a single pixel, representing the smallest unit of colour imaging and a single velocity value. Thus, TDI technique, as requiring special programs, is implemented only in upgraded echocardiographic systems.

Moreover, TDI differs from colour Doppler flow imaging, because aliasing never occurs. Due to the low velocities of tissue motion, TDI usually operates at one sixteenth the pulse repetition frequency (PRF/16), far below the Nyquist or aliasing limit which is one half the pulse repetition frequency (PRF/2). Therefore, the Doppler frequency shift data from tissue are always far below the Nyquist limit. When velocity of tissue exceeds the pre-set velocity range of the instrument, uniform rather than inverted colours are displayed. In this case, by widening the colour band series, it is possible to extend the discrimination among different colour levels.

A problem for TDI analysis is the rapid change in velocities and hence in colours. This can be solved by increasing the frame rate. A maximum of 25 frames/s is allowed when videotape recordings are used, but digital processing techniques, such as in the Toshiba Powervision TDI system, allow two-dimensional TDI scanning with a 3.75 MHz transducer and a 60° sector at 40-60 frames/s. Moreover, a high temporal resolution of TDI is achieved in the TDI M-mode where the scanning rate is as high as 90 multigated lines/s (Figure 1).

Tissue velocities are encoded by using a multicolour scheme. In tissue velocity maps each colour represents a range of velocities and a direction of motion. These bi-directional maps display the lowest velocities toward the transducer as red, intermediate velocities as orange and the highest velocities as yellow, with intermediate hues. Velocities away from the transducer are displayed in blue, progressing to turquoise and further to green at the highest velocities.

Myocardial segments with velocities too low to reach the threshold to be encoded in colour are imaged in grey, or in black when the background tissue image is subtracted.

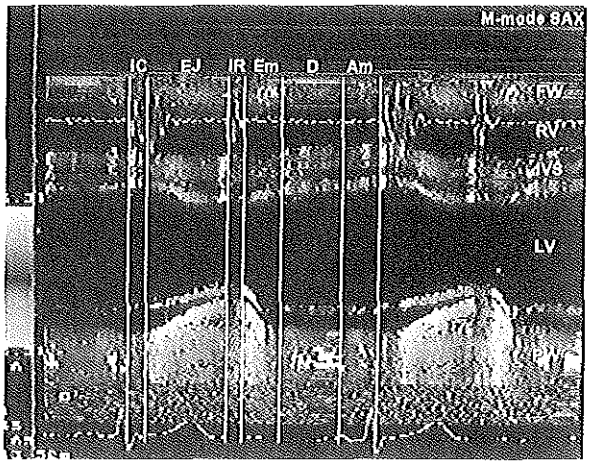


**Fig 1:** M-mode TDI obtained from a healthy subject. The parasternal short-axis M-mode recording shows the posterior wall encoded in red-yellow in the ejection phase and blue-green in the relaxation phase, while the interventricular septum shows opposite colours in the corresponding phases. The colours in the endocardial layers are brighter than those in the epicardial layers, indicating a higher velocity of motion. Brighter colours in the posterior wall indicate higher velocities than those in the septal wall. This is explained by the anterior cardiac motion in systole, relative to the fixed transducer, adding velocity to the posterior wall and subtracting velocity from the septum. The phases of contraction and relaxation of the posterior wall are indicated by vertical lines. The same lines should be slightly shifted to mark the corresponding phases of the septum, according to its earlier activation. IC: isovolumic contraction, EJ: ejection, IR: isovolumic relaxation, Em: early diastole, D: diastasis, Am: late diastole, PW: posterior wall, LV: left ventricle, IVS: interventricular septum, RV: right ventricle, FW: free wall of the right ventricle.

This technology is the core of both tissue velocity maps (Doppler velocity mode) and tissue acceleration maps (Doppler acceleration mode).

Doppler acceleration mode displays acceleration or velocity change of subsequent frames as different colours (Doppler acceleration mode). These maps may be represented only in two-dimensional image format, according to a multicolour scheme. M-mode may not display acceleration because it does not represent a temporal sequence of frames.

PW-TDS is also based on the Doppler shift principle, however it does not display velocities in image format, but as a profile versus time by sampling a region of interest in the myocardium (Figure 2) (4). In contrast with TDI, PW-TDS can be obtained with minor adaptations from all the echocardiographic systems.

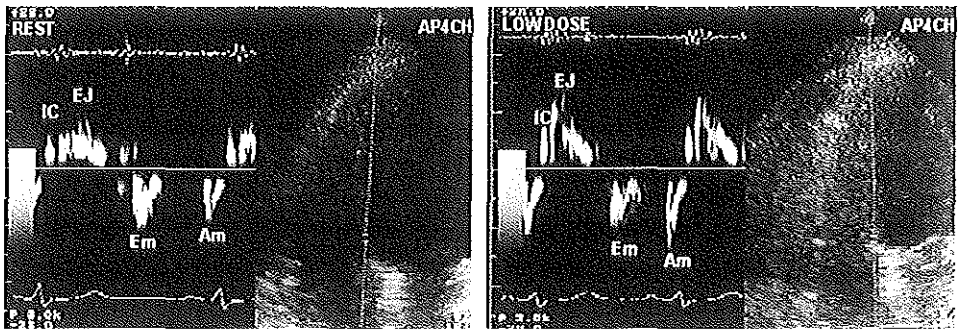


**Fig 2:** PW-TDI with the sampling on the basal part of a dyssynergic posterior-septal wall in apical four chambers (AP4CH) view. The velocity profile (left panel) shows systolic velocities over the baseline and early and late diastolic velocities below the baseline. During infusion of 10 µg/kg/min of dobutamine (right panel) systolic velocities increase, expressing a contractile reserve, while diastolic Em/Am ratio inverts, possibly predicting a further development of posterior-septal ischemia. IC: isovolumic contraction, EJ: ejection, Em: early diastole, Am: late diastole, AP4CH: apical four chamber view.

A different Doppler technology is involved in tissue energy maps. They are not derived from the phase shift of Doppler signals, but from their intensity, as obtained from the integration of the power spectrum of the Doppler signals, reflecting the composition of the tissue (Doppler energy mode). These Doppler signals, therefore, are both angle and velocity independent (non-directional). For display of tissue energy imaging, a mono- or bichromatic (red/blue) scheme is used, with a progressive increase in brightness.

## EXPERIMENTAL VALIDATION BY PHANTOM STUDIES

Validation of TDI velocities was performed using "tissue-mimicking" phantoms rotated in a water bath at a series of constant speeds, such as encountered in

normal and pathologic myocardium (5,6). A good correlation was found between the velocities of these phantoms and the velocities measured by TDI, but overestimation and poor spatial resolution was encountered in the very low velocity ranges (2,7). Accurate representation of velocities of single layers of gel phantoms sliding one on the other was demonstrated (7). Both axial and lateral resolutions of the two-dimensional velocity maps were 3x3 mm when using a 2.5 MHz transducer and a low transmit pulse repetition frequency (7).

Tissue energy imaging was also validated by using phantoms and the images obtained closely resembled those obtained with integrated tissue backscatter imaging (8).

## VALIDATION BY ANIMAL STUDIES

Experimental studies in pigs showed that decreased wall velocities were visually detected by TDI in a ischemic area 1 min after coronary occlusion with reversal after reperfusion (8). PW-TDS allowed a more accurate time analysis of velocity changes during ischemia (9). Transmural velocity gradients (the velocity increased from epi- to endocardium) and their decrease parallel to ischemia were validated with the implantation of piezoelectric crystals in the subendocardial and subepicardial layers in dogs (10).

Using Doppler energy maps in pigs, contrast-enhanced perfusion in the left ventricular walls was demonstrated after a peripheral intravenuous injection of SHU508A (Levovist) (8).

## CLINICAL APPLICATION OF DOPPLER VELOCITY MODE

When using TDI most information on myocardial contraction is obtained in apical and parasternal views, because they allow the assessment of the complex left ventricular contraction and relaxation from two perpendicular transducer positions (see Figures 3-5).

Since only the velocity component relative to the interrogating sound beam is measured, the perpendicular motion, such as e.g. the inward motion in the lateral

walls, is not recorded. In parasternal images the posterior wall exhibits higher velocities and velocity gradients than the antero-septal segments. Total cardiac anterior displacement during systole adds to the posterior wall velocities and subtracts from the inward posterior velocities of the anteroseptal wall. In normal subjects there is a velocity gradient within the myocardium which gradually increases from subepicardial to subendocardial layers in parasternal views (11,12) and decreases from base to apex in apical views (13) (See Figures 1 and 5).

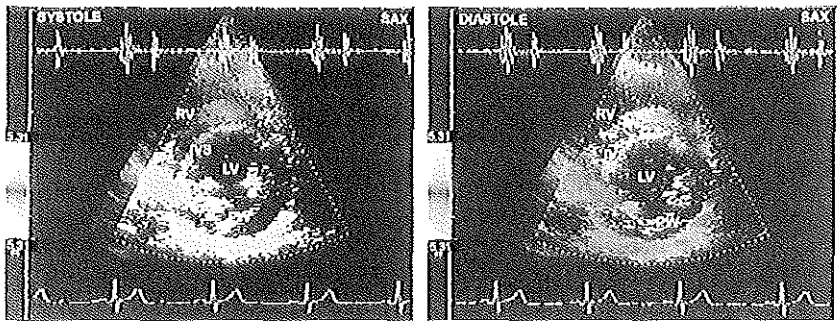


**Fig 3:** TDI velocity maps obtained from a healthy subject in the parasternal short axis (SAX) view. In early systole (about 80-120 ms after QRS: left panel) the posterior wall is encoded in red-yellow and the anterior wall in blue. In early diastole (right panel) this colour pattern is the opposite. PW: posterior wall, LV: left ventricle, IVS: interventricular septum, RV: right ventricle.

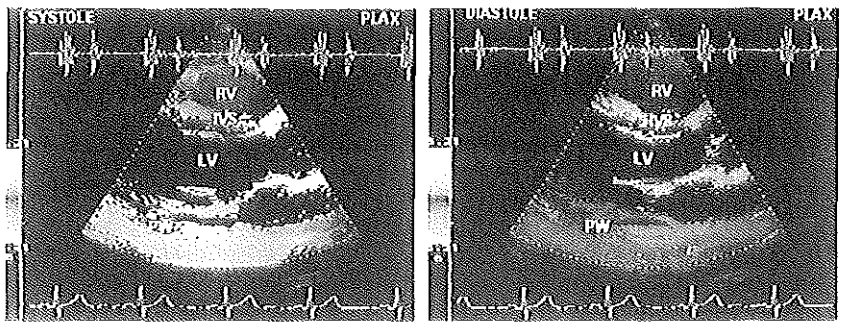


**Fig 4:** TDI velocity maps obtained from a healthy subject in the parasternal long axis (PLAX) view. In early systole (about 80-120 ms after QRS) the posterior wall is encoded in red-yellow and in diastole in blue-green. An opposite colour pattern is visible in the interventricular septum. PW: posterior wall, LV: left ventricle, IVS: interventricular septum, RV: right ventricle.

The importance of TDI to measure both equatorial and longitudinal regional myocardial dynamics was suggested by the observation that both the endocardial inward motion and the longitudinal shortening contribute equally to the ejection fraction (14) and the quantitative regional assessment of ventricular asynergy adds independent prognostic data to the global ejection fraction (15). TDI may therefore offer advantages for comprehensive assessment of both global and regional ventricular wall function.

## VISUAL ASSESSMENT OF DOPPLER VELOCITY MODE

In our experience, frame by frame analysis of TDI allows the study of the myocardial contraction and relaxation sequences. All phases of the cardiac cycle can be visually identified from two-dimensional TDI images. In apical views the red-yellow colours spread from base to apex in systole, while the blue-green colours spread from base to apex in early and late diastole (Figure 5).

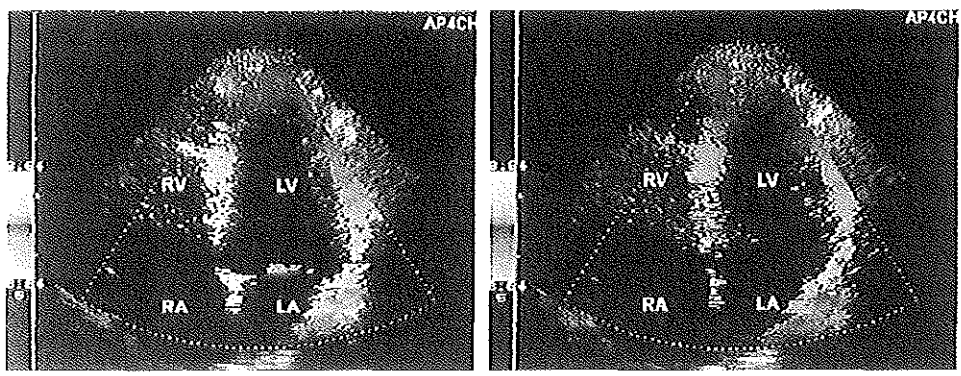


**Fig 5:** TDI velocity maps obtained from a healthy subject in the apical four chamber (AP4CH) view. In systole the walls are encoded in red-yellow and in diastole in blue-green. In both cardiac phases the basal segments are moving faster than the other segments, therefore encoded in brighter colours. The apex is almost immobile and encoded in dark colours. LV: left ventricle, RV: right ventricle, LA: left atrium, RA: right atrium.

The ventricular walls appear often red-yellow during the isovolumic contraction, which coincides with the rapid change of shape of the left ventricular cavity during this phase (16). The apical area usually remains encoded in grey or dark blue, as it is almost immobile (13). Virtually no motion is present during the diastasis phase, therefore the ventricular walls are not colour-encoded during this phase. It is possible to discriminate the velocity ratio of the isovolumic contraction versus the ejection phase and of early diastole versus late diastole by visually comparing the colour ratio of the corresponding cardiac phases. In the parasternal view the systolic antero-septal wall motion is displayed in blue-green (posterior direction) and the posterior wall motion in red-yellow (anterior direction). During diastole these colours are inverted (Figures 1,3) (17). The myocardial velocity during the rapid filling phase shows higher intensities of blue. The same colour pattern is seen during atrial contraction when the filling velocity is increased. A higher temporal resolution of the motion of selected areas of the myocardium is obtained when the M-mode is used and the motion pattern correlated well with ejection and filling parameters (Figure 1) (18).

We used the qualitative experience acquired from normal subjects as a reference to study pathological patterns. As an example, hypo- and akinetic segments are characterized by darker hues of red or blue (Figure 6). Dyskinetic segments are characterized by colours opposite to the neighbouring segments (Figure 6A). In dilated cardiomyopathy the absence of colors or the presence of dark hues of colors indicate very low velocities (Figure 6B). In patients with left bundle branch block, the early red-yellow colours indicating contraction are delayed in the septum, as compared to the opposite wall according to a later activation (Figure 6C) (19).

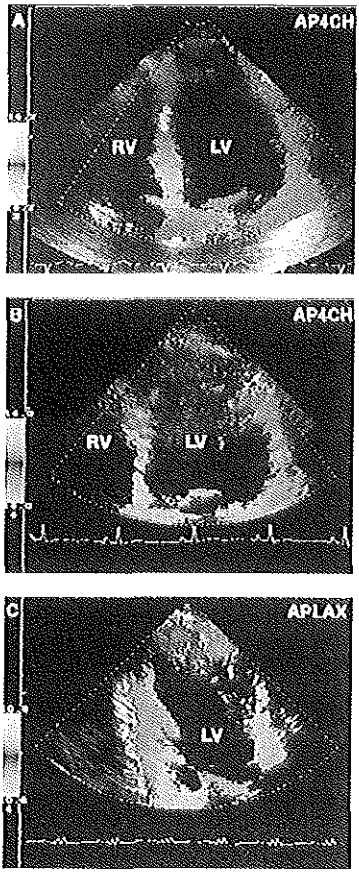


Fig 6: TDI velocity maps in different cardiac conditions obtained at a similar timing range (80-120 ms after the onset of QRS) of systole. **6A:** Myocardial infarction of the mid-distal segments of the posterior-septum in apical four chamber (AP4CH) view. The darkest or absent colours indicate the infarcted segments. A a dyskinetic basal segment of the posterior wall during early systole is encoded in blue, as moving away from the transducer, while the adjacent segments are encoded in red, as moving towards the transducer. **6B:** Dilated cardiomyopathy. Absent colours or only dark hues of red indicate very low velocities in all segments, caused by systolic impairment. **6C:** Left bundle branch block in apical long axis (APLAX) view. In this frame, approximately 80 ms after the onset of QRS, the activation of the basal part of the septum appears delayed and interrupted, compared to the posterior wall. This indicates a delayed pattern of contraction. AP4CH: apical four chamber view, APLAX: apical long axis view, LV: left ventricle, RV: right ventricle. APLAX: apical long axis view, LV: left ventricle, LA: left atrium

## QUANTITATIVE ASSESSMENT OF DOPPLER VELOCITY MODE

More intriguing than the visual assessment of TDI is the TDI quantification. Theoretically, each of the more than 16 millions of colours by which TDI is displayed can be converted in a corresponding velocity value. Obviously, an average must be calculated among many pixels representing a region of interest. As an example, an on-line algorithm in the Toshiba Powervision system allows the measurement of 4 velocities from 4 colour-encoded regions of interest. Dedicated algorithms were developed to obtain similar quantitative data off-line (11). Most often measurements of velocities were made from M-mode TDI recorded in the parasternal views. Due to its high sampling rate, accurate measurements of velocities and time intervals were possible. A good correlation was found with both endocardial motion profile echocardiograms (12) and

transmitral Doppler velocity profiles (20). Examples of parameters calculated in M-mode TDI were the mean transmural velocity, defined as the mean of all velocities measured along an M-mode line from epicardium to endocardium and the maximal or peak transmural velocity, defined as the maximal velocity of all mean transmural velocities in each cardiac phase: isovolumic contraction (IC), ejection (EJ), isovolumic relaxation (IR), early diastole (Em), diastasis (D) and late diastole (Am) (21). In healthy subjects studied in these different phases of cardiac cycle the peak systolic velocities of the posterior and the antero-septal walls showed a wide range of values (12). Preejection left ventricular peak velocities measured by colour M-mode on the posterior wall correlated with ejection fraction (22). These values were lower in patients with cardiomyopathies (23). Another dedicated software allowed the reconstruction of transmural velocity gradient maps. According to this algorithm the multigated colour-encoded velocities along each sampling line were not referred to the transducer but to the center of the ventricle or centre of contraction, thus in systole the transmural velocity gradient from the subepicardium to the subendocardium was oriented toward the center of the ventricle. A velocity gradient of opposite direction was present during diastole. In short axis view all the walls appeared in red-yellow during systole and blue-green during diastole, therefore eliminating the interference from cardiac translational movement relative to the Doppler transducer (5,24). The independence from the translational motion allowed the assessment of myocardial contraction even in presence of atrial septal defect, characterized by exaggerated translation of the left ventricle (25). A reduction of transmural systolic and diastolic velocity gradients was recorded during myocardial ischemia (5) or correlated with the severity of dilated cardiomyopathy (26,27). Also velocity gradients suffered, however, from the angular dependence, which allowed their best application to the anterior and posterior walls in short axis views.

Another quantitative application of TDI is possible with PW-TDS. The zero baseline and the velocity profile of PW-TDS offer reference points to measure peak velocities, time intervals and time velocity integrals.

## VISUAL AND QUANTITATIVE CLINICAL APPLICATIONS OF DOPPLER VELOCITY MODE

Patients with myocardial ischemia during stress were studied by dobutamine TDI. Rest or stress induced dyssynergic segments appeared with darker hues of colour in M-mode and two-dimensional displays (8). At the onset of ischemia, a reduction of early diastolic peak velocity and an increase of late diastolic peak velocity was recorded with PW-TDS, preceding the reduction of systolic wall velocity and these changes correlated with the severity of coronary artery stenosis (Figure 2) (28). Increased isovolumic relaxation time by PW-TDS appeared an early index of regional ischemia (29). During coronary angioplasty myocardial velocities and velocity gradients decreased, while colour-coded heart cycle intervals were lost (30). An interesting application was the sampling of all segments from the standard apical views during dobutamine stress echocardiography. Off-line measurements of velocities from infarcted segments in early and late diastole showed reduced values at rest and peak stress (31). At peak stress decreased velocities of early diastolic phase with a corresponding decreased early/late diastolic velocity ratio correlated with regions supplied by coronary artery stenosis >50% of diameter (31). In our experience, the the application of PW-TDS to dobutamine stress echocardiography protocol is limited by the 3 minutes available for each dobutamine step. The time required to sample 5-10 heart cycles at each dobutamine step, including adjustements of image quality, angulation and echocardiographic system settings, prevents its application to each of 16 ventricular segments. A compromise is sampling the basal part of each ventricular wall in apical view, close to the mitral or tricuspid annulus, thus obtaining data which reflect the entire wall dynamics. Patients with

stenosis >50% of diameter in the proximal or medium part of the right coronary artery exhibit a blunted increase of the ejection phase velocity from low dose to peak dobutamine, when measured by PW-TDS sampled at the right ventricular free wall close to the tricuspid annulus in apical four chamber view. A different pattern is obtained from patients without right coronary artery disease, who exhibit a sustained increase of the ejection phase velocity. Therefore, the blunted pattern may predict a significant right coronary artery disease (32).

The presence of myocardial contractile reserve could be demonstrated at low dose dobutamine infusion when myocardial contraction and velocities were elicited. This resulted in brighter colours (33) on two-dimensional maps and increased velocities on PW-TDS recordings, as compared to resting values. Viability in hibernating myocardium also exhibited less decrease of E/A ratio at rest (34). In our preliminary experience, by sampling the dyssynergic myocardium at the level of mitral annulus in standard apical views with PW-TDS the ejection phase velocity is increased from rest to low dose dobutamine in walls showing improved thickening to confirm the presence of longitudinal viability (Figure 2).

M-mode TDI allowed the study of myocardial velocities of wall segments in different phases of the cardiac cycle and their timing was validated against invasive pressure recordings (11). Decreased peak velocities during early diastole were demonstrated in ischemic segments during dobutamine stress (35).

Left ventricular volumes could be measured by applying Simpson's formula in patients with poor quality of grey scale images using TDI and were validated by Sutherland et al. (36) against volumes obtained by two-dimensional echocardiography. Measurement of volumes by TDI improved the inter-observer agreement, because of the higher sensitivity of Doppler imaging. A good correlation was also established with three-dimensional echocardiography (37). Left ventricular mass could also be calculated by combining TDI with three-dimensional echocardiography (38).

The usefulness of investigating diastolic parameters by TDI was reported in many examples. Early diastolic parameters measured by PW-TDS at the mitral annulus level showed a correlation with the invasively measured time constant of isovolumic relaxation (39). This approach appeared relatively pre-load independent in evaluating diastolic function (40).

The differential diagnosis of restrictive cardiomyopathies from constrictive pericarditis appeared related to lower early relaxation velocities in the restrictive disease, measured by PW-TDS sampled at the level of lateral mitral annulus (41).

In dilated cardiomyopathy an increased early diastolic myocardial velocity gradient by TDI detected a restrictive pattern (42). Conversely, a reduced early diastolic myocardial velocity gradient discriminated hypertrophic cardiomyopathy from hypertensive, athlete and normal hearts (43).

An early recognition of acute rejection in heart transplanted patients was suggested by decreased isovolumic relaxation time, early diastolic relaxation velocity and deceleration time, as measured by PW-TDS (44).

## CLINICAL APPLICATIONS OF DOPPLER ACCELERATION MODE

In the Wolff-Parkinson-White syndrome, the ventricular insertion of accessory atrio-ventricular pathways could be recognized as an early appearance of colour in the acceleration maps (45). According to acceleration colour-encoding, this early appearance represented an early variation of myocardial velocities versus time. Other examples of electro-physiological applications were the location of focus and sequence of atrial activation (46) and the on-line monitoring of successful radio-frequency ablation procedures, as disappearance of early colour activation in the pre-activated area (47).

## CLINICAL APPLICATIONS OF DOPPLER ENERGY MODE

The use of echo-contrast agents with Doppler energy maps potentially increased the sensitivity of both myocardial perfusion (8) and endocardial border

definition in suboptimal echocardiographic images, as compared to standard grey-scale images or TDI alone (48).

## LIMITATIONS

The major limitation of any Doppler technique is its angular-dependence: when the velocity direction diverges from the interrogating Doppler beam, more than 20°, the accuracy of the measurements becomes not acceptable and when the direction of movement is perpendicular to the Doppler beam, no colour and therefore no measurement, is obtainable.

Cardiac translational movement is a second limitation, particularly in the parasternal views, as it distorts the accurate encoding of myocardial velocities and it moves the walls under the sample volume of PW-TDS, therefore rendering almost impossible keeping it on the same endocardial, transmural or epicardial positions. The three-dimensional twisting contraction of the heart still escapes from a correct evaluation. The algorithm for the intramyocardial velocity gradient imaging has overcome this problem, but it remains affected by the angle dependence. Less influenced by the global cardiac movement are the standard apical views, able to assess the longitudinal component of contraction toward a relatively fixed apex. However, in these views the horizontal component of contraction is missed, as a result of the Doppler angular-dependence.

Another limitation, sometimes encountered with TDI, is its inability to completely colour-encode the ventricular wall, especially the lateral and anterior walls in apical views. Possible explanations are a low intensity of the signals reflected from the myocardial backscatters or a reduced spatial resolution, determined by the eccentric position of these ventricular walls in the echocardiographic two-dimensional sector (7). Usually the best assessment is obtained from walls located in the central part of the sector.

Artifacts, such as side lobes, represent a further limitation, as they are colour-encoded by TDI and prevent the evaluation of the underlying image.

Finally, the lack of a high frame rate digital storage with corresponding quantification software and of guide-lines for TDI clinical standard applications remain at the present further limitations.

## FUTURE PERSPECTIVES AND CONCLUSIONS

As a recently introduced technique and although some technical limitations, partially liable to be eliminated, TDI offers the potential to study in a qualitative and quantitative way aspects of myocardial dynamics so far missed by other non-invasive clinical techniques. By using either Doppler velocity mode or PW-TDS it is possible to interpret regional systolic and diastolic events, as they are reflected by different intramyocardial or transmural measurable velocities, e.g. viable or ischemic reactions elicited by stress tests. The colour application may be helpful in the three-dimensional rendering of left ventricular volumes. Doppler acceleration mode may contribute to electrophysiologic studies and procedures. By adding Doppler energy mode to echo-contrast agents may be improved the non-invasive assessment of regional myocardial perfusion. However, for a clinical impact, especially for stress echocardiography, larger number of studies are required. A recently introduced simple software seems able to rapidly exploit TDI potential for quantification of myocardial dynamics in the setting of stress echocardiography (49).

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# CHAPTER 4

# USEFULNESS OF PULSE-WAVE DOPPLER TISSUE SAMPLING AND DOBUTAMINE STRESS ECHOCARDIOGRAPHY FOR THE DIAGNOSIS OF RIGHT CORONARY ARTERY NARROWING

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## ABSTRACT

To study the feasibility and diagnostic accuracy of right coronary artery (RCA) narrowing by right ventricular (RV) pulse-wave Doppler tissue sampling during dobutamine stress echocardiography (DSE), 30 patients (mean age 55 ± 10 years, 26 men) with suspected coronary artery disease, underwent DSE (up to 40 µg/kg/min with additional atropine in submaximal heart rate responses). Pulse-wave Doppler tissue sampling of RV free walls close to the tricuspid annulus was performed in the apical 4-chamber view. The maximum velocity during the ejection phase, early, and late diastole was measured. Data from 5 consecutive beats were averaged. The measurements were repeated at rest, low dose (10 µg/kg/min) and at peak dobutamine stress. The results were evaluated for the prediction of significant proximal or medium RCA narrowing (≥50% diameter stenosis, assessed by quantitative coronary angiography within the previous 3 months). A progressive increase of the ejection phase velocity (>25% between 10 µg/kg/min and peak stress) was predictive of a normal RCA, whereas a blunted increase and/or decrease (<25% of increase) was predictive of significant RCA narrowing: sensitivity (95%CI): 82% (68-96), specificity: 78% (67-93), positive predictive value: 69% (52-86), negative predictive value: 88% (75-100), accuracy: 79% (65-94). Pulse-wave Doppler tissue sampling provided analyzable data in 100%, whereas the visual assessment of gray-scale images was possible only in 90%. Thus, in patients with suspected RCA narrowing, pulse-wave Doppler tissue sampling during DSE was able to diagnose significant RCA narrowing.


## INTRODUCTION

Right ventricular (RV) function is a prognostic determinant of many heart diseases (1-3). However, both RV anatomy and function escape from a reliable echocardiographic examination, mainly because of a complex shape (4-5). Visual assessment of the RV free wall by echocardiography in apical 4-chamber

in most instances leads to an underestimation of mild hypokinesia, due to an asymmetrical contraction of the RV walls toward its center (6). Pulse-wave Doppler tissue sampling displays tissue velocity profiles of areas of interest with high temporal resolution. By sampling the RV free wall close to the tricuspid annulus in the apical 4-chamber view, pulse-wave Doppler tissue sampling estimates longitudinal RV dynamics, expressed as motion velocities of the cardiac base towards and away from the cardiac apex (7), which is used as a fixed reference point (8). This longitudinal assessment usually escapes from the visual scoring (9). Aim of our study was to diagnose right coronary artery (RCA) narrowing by pulse-wave Doppler tissue sampling during dobutamine stress echocardiography (DSE).

## STUDY PATIENTS AND METHODS

**Patient selection.** The study population included 30 consecutive patients (mean age 55 ± 9.5 years, 26 men) referred for evaluation of suspected coronary artery disease who fulfilled the following criteria: 1) a recent (within 3 months) coronary angiography, with no change in clinical conditions, 2) no relevant valvular heart disease, pulmonary or systemic hypertension resulting in moderate-severe left and/or right ventricular hypertrophy, cardiovascular shunts or any cardiac disease interfering with either cardiac preload or afterload and 3) a left ventricular ejection fraction >45%, as assessed by echocardiography. The antianginal medication was not a criterion of exclusion.

**Coronary angiography.** Coronary angiography was performed within 3 months before DSE. Significant coronary artery disease was defined as a diameter stenosis ≥50%. The stenosis diameter was quantified using the Quantitative Coronary Angiographic method previously described by our center (10). According to the absence or presence of a significant RCA narrowing patients were respectively divided into group 1 and 2.

**Assignment of the myocardial segments to coronary arteries.** The present study focused on the RV function. We assigned RV free wall to RCA, according to an angiographically proven RCA dominance in all our patients. A standard assignment was applied to match the 3 coronary arteries to the 16 left ventricular segments (11).

**Dobutamine stress echocardiography.** Dobutamine was intravenously administered with an infusion rate of 10 μg/kg/min per min for 3 minutes, increasing by 10 μg/kg/min every 3 minutes up to a maximum dose of 40 μg/kg/min. In patients not achieving 85% of their for age and gender predicted maximal heart rate and without symptoms or signs of myocardial ischemia, atropine was administered, starting with 0.25 mg intravenously and repeated up to a maximum of 2.0 mg within 8 minutes, while continuing the infusion of dobutamine. Throughout dobutamine infusion the electrocardiogram (3 leads) was continuously monitored and recorded (12 leads) at one minute intervals. The criteria to interrupt DSE were: achieved 85 % of the maximal predicted target heart rate, achieved maximal dose of both dobutamine and atropine infusions, extensive new wall motion abnormalities, horizontal or downsloping ST-segment depression >0.2 mV 80 ms after the J point compared with the baseline, ST-segment elevation >0.1 mV 80 ms after the J point in patients without prior myocardial infarction, severe angina, symptomatic reduction in systolic blood pressure >40 mm Hg from baseline, hypertension (blood pressure >240/120 mm Hg), significant arrhythmias or any serious side effect regarded as being due to dobutamine infusion.

**Grey scale echocardiographic imaging.** The left ventricle was divided in 16 segments and visually assessed for both systolic wall thickening and inward wall motion. Each segment was graded on a 5-point scoring system (1 = normo- or hyperkinesia; 2 = mild hypokinesia; 3 = severe hypokinesia; 4 = akinesia and 5 = dyskinesia ) by an experienced observer blinded to the angiographic data. Ischemia was defined as a deterioration in score at any step of

the test in one or more segments, unless an akinetic segment at rest and low dose dobutamine became dyskinetic at peak dobutamine stress. Left ventricular wall motion score index was defined as the sum of the scores of the individual segments divided by the total number of segments. The RV free wall was evaluated for the quality of the visual assessment.

**Pulse-wave Doppler tissue sampling.** Pulse-wave Doppler tissue sampling was performed with the Toshiba Powervision echocardiographic system (Toshiba Corp., Otawara-Shi, Japan), using a 2.5 MHz transducer and a pulse repetition frequency of 45-60 KHz. Pulse-wave Doppler tissue sampling was sampled from the RV free wall close to the tricuspid lateral annulus in the apical four-chamber view with high temporal resolution [4 ± 3 (1-7) ms]. The depth of the sample volume was kept constant in each patient during DSE. A sample volume with a fixed length of 4 mm was used. Both electrocardiogram and phonocardiogram were simultaneously recorded with the pulse-wave Doppler tissue sampling velocity profile and stored on videotape. The peak pulsed wave-Doppler tissue sampling velocity amplitude of ejection phase, early and late diastole were measured off-line using a computer assisted drawing system and the values were expressed in cm/s (Fig 1). Five consecutive beats were analyzed and mean velocity values calculated, in order to minimize the measurement variability determined by respiration. E/A ratio was also calculated. Cardiac cycles with extrasystolic, post-extrasystolic beats or any disturbance of the rhythm were excluded. Recordings and measurements were repeated at baseline, low dose (10 μg/kg/min) and max dobutamine infusion rate.

**Statistical analysis.** Unless specified, data were expressed as mean values ± SD. Comparison of continuous variables was performed with the unpaired Student's *t* test. Comparison of proportions was performed with the chi-square test and the Fisher's exact tests. A $p < 0.05$ was considered

statistically significant. Sensitivity, specificity, predictive value and accuracy were presented with their corresponding 95% confidence interval (CI).

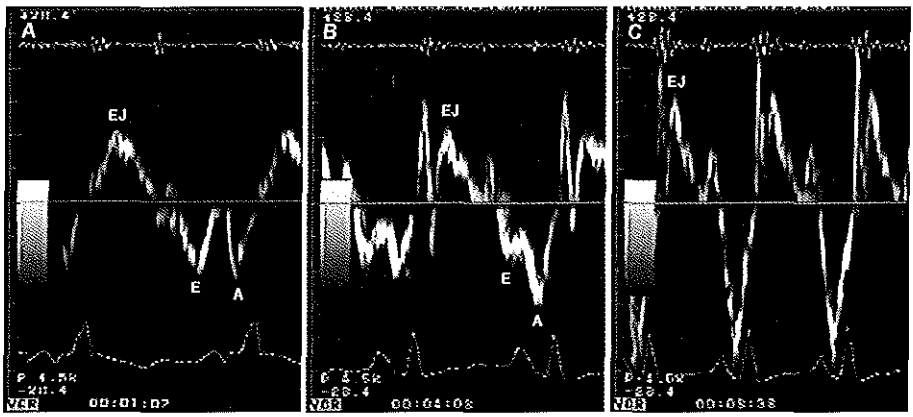


**Fig. 1:** Pulsed wave-Doppler tissue sampling of the right ventricular free wall at rest (panel A), low dose (10 µg/kg/min) (panel B) and peak dobutamine stress (panel C) in subject without right coronary artery narrowing (Group 1). Ejection phase velocity progressively increases from rest to peak dobutamine stress. EJ = ejection phase, E = early diastole, A = late diastole.

## RESULTS

**Patient characteristics (Table I).** There was no significant difference between group 1 and 2 with regard to clinical and angiographic data. Twenty patients (67%) had an old (>3 months) myocardial infarction. Q wave in D3/aVF

**Table I.** Clinical and angiographic data of patients without (group 1) and with (group 2) right coronary artery narrowing.

| | Group 1 (N = 19) | Group 2 (N = 11) |
|---|---|---|
| Age (years) | 58.6 ± 10.7 | 53.6 ± 9.9 |
| Male gender | 16 (84%) | 10 (91%) |
| Previous infarction | 11 (58%) | 9 (82%) |
| Anterior infarction | 8 (42%) | 3 (27%) |
| Posterior infarction | 3 (16%) | 6 (55%) * |
| Left ventricular ejection fraction | 55 ± 9 | 56 ± 10 |
| Left anterior descending coronary artery stenosis | 13 (68%) | 6 (55%) |
| Left circumflex coronary artery stenosis | 8 (42%) | 6 (55%) |
| Antianginal therapy | 18 (95%) | 10 (91%) |
| Beta-blocking agents | 11 (58%) | 6 (54%) |
| * $p < 0.05$. | | |

electrocardiographic leads, which indicates posterior myocardial infarction, was encountered more frequently in group 2 ($p < 0.05$; 6 patients).

**Coronary angiography (Table I).** All patients had RCA dominance. In 19 patients (group 1) no significant narrowing was present in RCA. In this group a significant single vessel stenosis was found in the left anterior descending coronary artery in 9 patients, in the circumflex coronary artery in 4 patients and in both in 4 patients. Two patients had a normal coronary angiogram and were included in group 1. In 11 patients (group 2) a significant narrowing was present in the proximal or medial part of RCA. In this group an additional single vessel stenosis was present in the left anterior descending coronary artery in 1 patients, in the circumflex coronary artery in 1 patients and in both in 5 patients.

**Dobutamine stress echocardiography (Table II).** There was no significant difference between group 1 and group 2 with respect to DSE parameters. Based on increase of wall motion score index from rest to peak do-

**Table II.** Dobutamine stress and hemodynamic data of patients without (group 1) and with (group 2) right coronary artery narrowing.

| | Group 1 (N = 19) | Group 2 (N = 11) |
|---|---|---|
| Resting HR (bpm) | 75 ± 12 | 76 ± 17 |
| Peak dobutamine HR (bpm) | 131 ± 19 | 137 ± 10 |
| Resting SBP (mm Hg) | 130 ± 21 | 128 ± 8 |
| Peak dobutamine SBP (mm Hg) | 139 ± 30 | 131 ± 21 |
| HR x Systolic BP | 9,750 ± 1,944 | 9,728 ± 2,036 |
| Peak HR x Systolic BP | 18,209 ± 3,344 | 17,947 ± 2,857 |
| Angina during the test | 12 (63%) | 3 (27%) |
| ST-segment depression | 8 (42%) | 2 (18%) |
| ST-segment elevation | 1 (5%) | 1 (9%) |
| LV resting wall motion score index | 1.30 ± 0.45 | 1.33 ± 0.33 |
| LV stress wall motion score index | 1.35 ± 0.34 | 1.39 ± 0.33 |
| Left anterior descending coronary artery field ischemia | 11 (58%) | 1 (9%) * |
| Left circumflex coronary artery field ischemia | 6 (32%) | 3 (27%) |
| Right coronary artery field ischemia | 0 (0%) | 4 (36%) * |
| Atropine | 9 (47%) | 5 (45%) |

HR = heart rate (beats/min = bpm), LV = left ventricle, BP = blood pressure, * $p < 0.05$.

butamine stress, ischemia prevailed in group 1 for the left anterior descending coronary artery field and in group 2 for the RCA field ($p < 0.05$).

**Pulse-wave Doppler tissue sampling (Tables III-IV).** A progressive increase of the ejection phase velocity, expressed by >25% increase from 10 μg/kg/min (low dose) to peak dobutamine stress (Figure 1) was predictive of a normal or non-significantly narrowed RCA, while a blunted increase, expressed by <25% increase of velocity (Figure 2) was predictive of a significantly narrowed RCA.

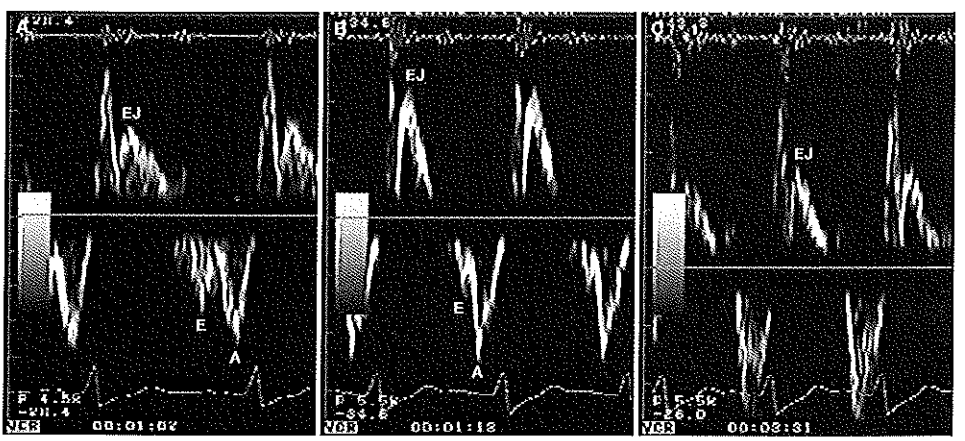


**Fig. 2:** Pulsed wave-Doppler tissue sampling of the right ventricular free wall at rest (panel A), low dose (10 μg/kg/min) (panel B) and peak dobutamine stress (panel C) in subject with right coronary artery narrowing (Group 2). Ejection phase velocity does not increase from low dose to peak dobutamine stress. EJ = ejection phase, E = early diastole, A = late diastole.

**Table III.** Diagnostic accuracy of pulse wave-Doppler tissue sampling for the prediction of right coronary artery narrowing.

| | Sensitivity | Specificity | PPV | NPV | Accuracy |
|---|---|---|---|---|---|
| % | 82 | 78 | 69 | 88 | 79 |
| 95% C.I. | 68-96 | 67-93 | 52-86 | 75-100 | 65-96 |
| C.I. = confidence intervals, NPV = negative predictive value, PPV = positive predictive value. | | | | | |

The diagnostic accuracy of pulse-wave Doppler tissue sampling is shown in table III. In table IV a significant difference appears by comparing the mean

percentages of increase from low dose to peak dobutamine stress of the two groups: +37 % ± 27 (group 1), + 4 % ± 27 (group 2) (p <0.01). The comparison of absolute velocities between the two groups was difficult because of a wide range of RV velocity values for each group and at each dobutamine step.

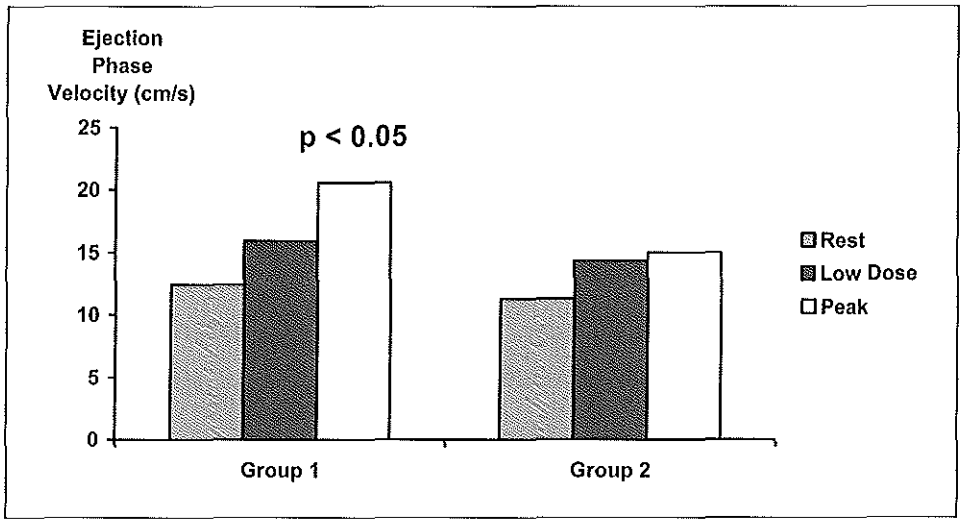


**Fig 3:** Pulsed wave-Doppler tissue sampling of right ventricular free wall during dobutamine stress echocardiography. At peak dobutamine stress, ejection velocity absolute values of group 1 are significantly higher than group 2.

**Table IV.** Pulsed wave-Doppler tissue sampling data of patients without (group 1) and with (group 2) right coronary artery narrowing.

| | Group 1 (N = 19) | Group 2 (N = 11) |
|---|---|---|
| EJ velocity at rest | 12.4 ± 2.2 | 11.3 ± 4.7 |
| EJ velocity at low dose | 15.9 ± 3.8 | 14.3 ± 6.5 |
| EJ velocity at peak stress | 20.6 ± 7.5 | 15 ± 7.2 * |
| %EJ rest-low dose | 37 ± 27% | 4 ± 27% * |
| E velocity at rest | 10.7 ± 2.8 | 10.7 ± 4.9 |
| E velocity at low dose | 11.2 ± 3.3 | 12.7 ± 4.9 |
| E velocity at peak stress (18 patients) | 11.9 ± 3.4 | 12.2 ± 5.3 |
| A velocity at rest | 17.1 ± 4.3 | 13.2 ± 6.4 |
| A velocity at low dose | 20.1 ± 4.7 | 15.9 ± 8.8 |
| A velocity at peak stress (18 patients) | 25.3 ± 7.8 | 23.5 ± 7.8 |
| E/A at rest | 0.6 ± 0.2 | 0.8 ± 0.3 |
| E/A at low dose | 0.6 ± 0.2 | 0.8 ± 0.4 |
| E/A at peak stress (18 patients) | 0.5 ± 0.4 | 0.5 ± 0.2 |

A = late diastole, E = early diastole, EJ = ejection phase, * p < 0.05.

However, a borderline difference was found of the absolute velocity values at peak dobutamine stress between group 1: 20.6 ± 7.5 cm/s and group 2: 15 ± 7.2 cm/s ($p = 0.05$) (table IV) (Figure 3).

E and A wave velocities were not measurable in 12 patients (40%) at peak dobutamine stress, because of the superimposition of both waves. Therefore, diastolic velocities could be measured in 18 patients (60%) at peak dobutamine stress. In spite of this non-significant difference, we noticed a trend to a deeper decrease of E/A ratio during DSE in group 2 (Table IV). The visual assessment of the RV free wall in grey-scale images was of poor quality in 3 patients, while pulse-wave Doppler tissue sampling velocity profile could be recorded in all patients. Therefore, the feasibility of pulse-wave Doppler tissue sampling was 100%, vs 90% of visual assessment.

## DISCUSSION

The main findings of our study were: 1) a high predictive value of a significant RCA stenosis detected by a blunted increase pattern of pulse-wave Doppler tissue sampling ejection phase velocity values of RV free wall, measured at the tricuspid level, during DSE, and 2) a higher feasibility of pulse-wave Doppler tissue sampling than grey-scale imaging for RV free wall motion analysis, because of its higher signal-to-noise ratio.

**The amplification effect of longitudinal ventricular velocity assessment.** By using pulse-wave Doppler tissue sampling at the basal level of RV wall in apical echocardiographic images, the velocity of longitudinal displacement may be considered expression of the longitudinal myocardial contraction. These longitudinal velocities are higher than inward wall motion velocities measured in parasternal views (12). This amplification effect, typical of the longitudinal assessment, is determined by the vectorial sum of the contraction velocity of each myocardial fibre interposed between the base and apex.

**Myocardial mechanisms involved in the present study population.** According to this amplification effect, longitudinal velocities do not increase during any step of DSE in the presence of a large nonviable scarred myocardium. In contrast, viable myocardial fibres interposed between the cardiac base and the apex are likely to increase proportionally the resulting velocity, measured at the base, at any step of DSE. According to the Bowditch phenomenon (13) the increased heart rate may partially counterbalance the hypo-contractile effect deriving from the shortening of diastolic filling time at the highest heart rates, deriving from the Frank-Starling law. Dobutamine inotropic stimulation should further counterbalance this hypo-contractile effect. Therefore, considering the comparable level of heart rate achieved by each group of our patient population, we can assume that group 2, who exhibited a blunted increase of myocardial velocities from low dose to peak dobutamine stress, may had an amount of non-viable myocardium unable to counterbalance the Frank-Starling law. Conversely, group 1 may had a favourable balance between normal fibres and non-viable or ischemic fibres, thus enabling the RV wall to keep its contractile power at peak dobutamine stress. In absence of an accepted gold standard for pulse-wave Doppler tissue sampling or an histological myocardial evaluation, we emphasize the higher prevalence of RCA narrowing, posterior myocardial infarction and RCA field ischemia in the patients (group 2) with blunted increase of pulse-wave Doppler tissue sampling ejection velocities.

**Previous studies.** We can make some assumptions from previous studies that used techniques which were different from pulse-wave Doppler tissue sampling to evaluate RV function. The tricuspid annulus excursion reflects the global function of RV, as shown by Kaul et al. (14) and Wilson et al. (15). The hypothesis of impaired RV function in presence of a significant chronic RCA stenosis, regardless the presence of myocardial infarction, is supported by Fujiwara et al. (16). These authors found reduced RV-ejection fraction at rest by MRI in presence of RCA disease without inferior myocardial

infarction. Our study found similar data during DSE: absolute velocity values were lower in group 2 than in group 1, regardless the presence of a posterior myocardial infarction (17), yet more frequently documented (Table I) in group 2, or the presence of posterior myocardial ischemia. Therefore, a subendocardial fibrosis of the RV free wall is likely to prevent many patients of group 2 from achieving a further increase of ejection velocities at peak dobutamine stress.

**Study limitations.** A blunted increase of velocity at peak stress, as shown by group 2, could also derive from the Frank-Starling law. The Bowditch phenomenon (13) should balance this limitation, as shown by our patients whose velocity patterns were not influenced by the level of heart rate achieved during DSE. Furthermore, the 85% of maximum heart rate, as criterion to stop the test and the absence of any ventricular dysfunction (18) further minimize any relevant interference from the Frank-Starling aw. A second limitation is the cardiac translational movement, further increased by DSE. This movement is mainly influenced by the interventricular interaction in the direction of the ventricular short axis (19). Therefore, by excluding parasternal images, and by using the cardiac apex as a fixed reference point, this limitation could be minimized.

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# CHAPTER 5

# DOPPLER TISSUE IMAGING FOR THE ASSESSMENT OF MYOCARDIAL VIABILITY

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The assessment of myocardial viability has important clinical relevance. Since current acute coronary revascularizations and acute thrombolysis in patients with acute coronary ischemic syndromes, have resulted in recovery of regional and global dyssynergic myocardium, it is of utmost clinical importance to determine myocardial regions which have potential to improve their function (i.e. myocardial viability).

This so-called recovery of function has been studied by several noninvasive cardiologic techniques. Among these are nuclear techniques to evaluate myocardial flow and metabolism and echo Doppler techniques using pharmacological inteventions.

Myocardial viability is defined by reversible myocardial dysfunction which may be caused by either myocardial stunning or myocardial hibernation. Several factors as summarized in Table I may influence recovery of myocardial dysfunction.

**Table I**

**Potential factors that may influence recovery of myocardial dysfunction**

- amount and degree of stunning
- amount and degree of hibernation
- amount and degree of myocardial scar
- presence of coronary collaterals
- overall left ventricular function
- primary myocardial disease (-it is or myopathy)

Myocardial stunning is a transient prolonged post-ischemic dysfunction that may occur after restoration of coronary blood flow. Thus, despite the absence of irreversible damage mechanical dysfunction may persist for longer periods even after coronary intervention procedures such as percutaneous transluminal coronary angioplasty or coronary artery bypass grafting.

Hibernating myocardium is defined as myocardial dysfunction due to a chronic reduction in myocardial blood flow. It has beeen suggested that hibernating

myocardium is caused by a chronic down regulation of contractile cellular function.

A number of studies nowadays is directed towards the question whether restoration of myocardial blood flow by coronary revascularization may induce an improvement in myocardial function. If no recovery of myocardial is present in myocardial dysfunction then these areas are either necrotic or replaced by scar tissue formation.

It is known that in patients with coronary artery disease either chronically or acutely both reversible and irreversible myocardial dysfunction can be present.

The following methods both accepted and investigational have been used for the assessment of myocardial viability (see Table II).

**Table II**

**Methods to determine myocardial viability**

| | |
|---|---|
| Current: | FDG-PET (gold standard) |
| | Tl injection |
| | Tc-qqm sestamibi |
| | Dobutamine stress echocardiography (ischemic and viability) |
| | Dobutamine stress elettrocardiography |
| Investigational: | Low dose dobutamine echocardiography with myocardial contrast |
| | Doppler tissue imaging |
| | Color kinesis |

Tc-qqm sestamibi, $^{201}$Tl both at rest and after stress and recently studies with F-18 Fluorodeoxyglucose (FDG) have been described and there are good correlations between these techniques.

Currently FDG studies using Positron Emission Tomography (PET) are considered to be the gold standard for the assessement of myocardial viability. The same studies have been done with SPECT using a dual isotope technique (Tetrofosmin/FDG). Also Low Dose Dobutamine Echocardiography (LDDE) is proposed as an alternative method to determine residual myocardial viability.

Since at low doses of 5 to 15 μg/kg/min of dobutamine an inotropic effect is seen with moderate increase in heart rate, LDDE seems a good alternative approach for the cardiologist.

The LDDE studies are determined and analyzed by visual assessment of two-dimensional echo (2DE) images. Although reasonable inter- and intra-observer variabilities (between 84% and 92%) have been described for all kinds of dobutamine stress echocardiography respectively there is still need for improvement.

Therefore we propose an alternative approach and report our preliminary experience using Doppler Tissue Imaging (DTI) for measurements of myocardial viability.

## DOPPLER TISSUE IMAGING

For a detailed description of the method we refer to previous manuscripts (1,2). Briefly, Doppler tissue imaging uses pulsed wave Doppler to interrogate low velocity shifts. Doppler tissue imaging differs from standard blood pool Doppler in that high amplitude, low frequency signals form the myocardium are processed and velocities calculated. Thus, high frequencies from the bloodpool are filtered and excluded from the analysis by Doppler tissue imaging.

The myocardial velocities are currently displayed in the 2DE B-mode representation using a color-encoded overlay or as a graphic display of pulsed wave Doppler recordings.

Low frequency shifts corresponding of 2 to 200 mm/sec are encoded in a color scheme analogous to that of standard color Doppler flow imaging.

Doppler tissue imaging may be displayed either as a two dimensional tomogram or in color M-mode of a single spatial dimension over time.

In Table III potential uses of Doppler tissue imaging are reported as modified from Bach and Armstrong (1).

| Table III | |
|---|---|
| **Potential uses of Doppler tissue imaging (DTI)** | |
| • Wall motion analysis (diastolic and systolic) | |
| • Myocardial contractility | |
| • Intravenous contrast echo perfusion | |
| • Ventricular pre-excitation | |
| • Infarct size | ] not yet validated |
| • Myocardial viability | ] not yet validated |

It is clear from this table that myocardial viability might be potentially studied by DTI but that the method has not been clinically validated yet.

## PRELIMINARY THORAXCENTER EXPERIENCE WITH DTI AND MYOCARDIAL VIABILITY

The machine used in our Institution is the Toshiba Powervision. Sutherlandt et al (2) were the first to suggest a potential role for DTI in the assessment of myocardial viability. These authors found preserved systolic velocities on DTI within myocardial regions that appear akinetic on standard B-mode echocardiography. As will be discussed later we were not able to reproduce the finding of these authors. Mainly because we find it hard to observe color changes in a small region of interest.

Using a M-mode display the myocardial velocities are displayed with greater sensitivity. It is seen that we use registration of heart sound in addition to Electrocardiography (ECG) for timing purposes. This is especially important if the myocardial velocities are displayed in a graphic format. Using this approach (graphic display of myocardial pulsed wave Doppler velocities ) we studied right ventricular myocardial velocities in patients with and without a severe stenosis of right coronary artery as the supplying artery (3). We found that pulsed wave DTI myocardial velocities used in conjunction with dobutamine can distinguish between patients with and without a >50% stenosis of the right coronary artery. In normal patients a continuous increase in myocardial velocities is seen whereas in patients with severe RCA stenosis a bi-phasic response is present.

In this respect we were directly confronted with a technical limitation of Doppler tissue imaging. We were not able to reproducibly put our Doppler sample volume on a akinetic area and keep the sample volume at this same place during dobutamine infusion. Therefore, as is shown in Figure 1, we had to put the sample volume first outside the akinetic areas as assessed from 2DE images. So no information can be obtained from the akinetic area. We hypothesized that if no viable tissue was present, and no recovery of myocardial function was obtained after 10 µg/kg/min of dobutamine, DTI myocardial velocities will not change. Conversely, if viable myocardium was seen then myocardial DTI velocities would increase. Figure 1 shows 2DE images before and after low dose dobutamine (left and right side respectively). It is seen that after low dose dobutamine myocardial velocities of the regions first outside the akinetic area increase as is seen from the pulsed Doppler graphic display.

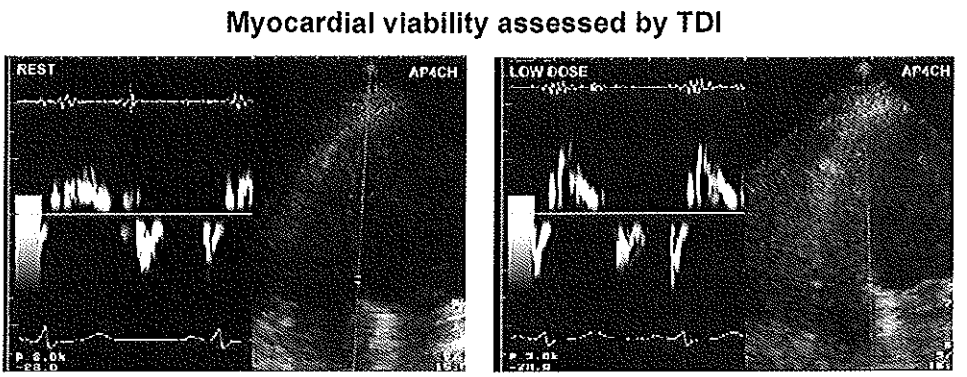


**Fig 1:** Two-dimensional echo from AP4C views before and after LDDE. Sample volume of DTI is placed just outside the dyssynergic region with pulsed Doppler graphic display at the left side of both pictures. Observe an increase in velocities after 10 µg/kg/min dobutamine concordant with viable tissue on 2DE imaging. For further explanation see text.

From the 2 DE analysis in this particular patient the so-called akinetic area shows recovery after LDDE: this analysis however has not excluded an increase of myocardial velocities of the studied region itself. In the first patients studied using this methodology we could show a definite increase in myocardial

velocities in patients with viable myocardium whereas in patients with scar tissue the increase of myocardial velocity was less (See Table VI). Furthermore, a regional analysis of pulsed wave Doppler forms from the myocardium was found to be too time consuming and impractical.

In conclusion: although we show that our proposed method is feasible there are current strong limitations for Doppler tissue imaging inherent to the Doppler technology. Our preliminary results show that this method until now precludes a useful assessment of myocardial viability. Further studies or improvements of Doppler tissue imaging methods are needed to increase our confidence of Doppler tissue imaging in patients myocardial dysfunction for the assessment of viability. A digital analysis system for color analysis on a pixel to pixel format is obligating for Doppler tissue imaging analysis.

**Table VI**

**Problems encountered with DTI for myocardial viability**

- Technical
- Time consuming (no regional pulsed waves Doppler)
- High variability in color analysis
- No algorithms for analysis of color on pixel to pixel formatting

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# CHAPTER 6

# DOPPLER TISSUE VELOCITY SAMPLING IMPROVES DIAGNOSTIC ACCURACY DURING DOBUTAMINE STRESS ECHOCARDIOGRAPHY FOR THE ASSESSMENT OF VIABLE MYOCARDIUM IN PATIENTS WITH SEVERE LEFT VENTRICULAR DYSFUNCTION

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## ABSTRACT

*Background*: Both nuclear imaging with F18-fluorodeoxyglucose [FDG] and dobutamine stress echocardiography [DSE] have been used to identify viable myocardium, although DSE has been demonstrated less sensitive.

*Aim*: To compare the accuracy of Pulsed-wave Doppler tissue sampling [PW-DTS] with DSE for the detection of viable myocardium; using FDG imaging as a reference.

*Methods*: Forty patients with chronic coronary artery disease and LV dysfunction [mean ejection fraction 33±11 %], underwent FDG imaging, DSE and PW-DTS. Evaluation was performed using a 6-segment model.

*Results*: Visual assessment by resting echo was feasible in 230 out of 240 segments [96%]; 177 [77%] segments showed severe dyssynergy at rest. FDG imaging showed viability in 95 [54%] segments while 82 [46%] were nonviable. Ejection [EJ] phase velocity at rest was not significantly different; EJ velocities during low-dose and peak-dose dobutamine however, were significantly higher in viable myocardium [8.6±2.9 vs. 6.0±1.8 and 9.3±3.1 vs. 6.2±2.1 cm/sec]. Using receiver operating characteristic curves the optimal cut-off value for viability assessment was an increase of EJ phase velocity low-dose of 1±0.5 cm/sec, while 0±0.5 cm/sec predicted non-viability. The sensitivity and specificity [95%CI] of PW-DTS and DSE for prediction of viability was respectively 87% [82-92] vs. 75% [67-81] [$p<0.05$] and 52% [44-59] vs. 51% [45-59] [p=NS].

*Conclusions*: Sensitivity of PW-DTS is superior to DSE for the assessment of myocardial viability.


## SUMMARY

Both nuclear testing and dobutamine stress echocardiography are used to assess myocardial viability. Pulsed-wave Doppler tissue sampling during dobutamine stress is a new technique for quantification of wall motion. The agreement between Pulsed-wave Doppler tissue sampling and nuclear scanning for

myocardial viability assessment was superior to that of dobutamine stress echo using the nuclear test as a reference.

## INTRODUCTION

The presence of dysfunctional but viable myocardial in patients with severe LV dysfunction has therapeutic implications since revascularization may improve both the functional status and survival [1]. Among the different techniques to demonstrate myocardial viability, much experience has been gained with nuclear imaging using F18-fluorodeoxyglucose [FDG] or dobutamine stress echocardiography [DSE] and higher sensitivity of FDG imaging has been demonstrated [2]. Moreover, FDG imaging allows semi-quantitative analysis, while DSE relies on subjective visual interpretation of wall motion [3]. Pulsed-wave Doppler tissue sampling [PW-DTS] provides a quantitative parameter of myocardial contraction of the vectorial sum of contraction velocities of myocardial fibres [i.e. longitudinal and equatorial contracting fibres] between the base and apex [4-6]. The importance of measuring longitudinal myocardial contraction was based on the observation that both the endocardial inward motion and the longitudinal contraction contribute equally to the ejection fraction [7].

In the present study we compared the use of PW-TDS with DSE for the identification of myocardial viability in patients with chronic coronary artery disease and severe LV dysfunction, using FDG-SPECT as a reference method [8].

## METHODS

*Patients*: The study population comprised 40 patients [29 males, mean age 56±9 years] with reduced LV function [mean RNV-EF 33±11%] who underwent both DSE/PW-DTS and FDG-SPECT for the evaluation of viable myocardium [Table1].

**Table I.** Clinical characteristics of patients evaluated by PW-TDS and DSE.

| | Number of patients [%]. |
|---|---|
| Previous MI | 26 [65] |
| History of angina pectoris | 31 [78] |
| Beta blocker therapy | 14 [35] |
| ACE-inhibitors | 29 [73] |

Cardiac disease potentially interfering with either cardiac preload or afterload, [e.g. valvular heart diseases, pulmonary or systemic hypertension, cardiovascular shunts] was a criterion for exclusion.

*Resting two-dimensional echocardiography:* All echocardiograms were performed with an ATL HDI 3000 imaging system equipped with a 1.8 MHz transducer using second harmonic imaging to optimise endocardial border visualisation. Standard parasternal long- and short-axis views were obtained as well as apical long-axis 2- and 4-chamber views as described by the American Society of Echocardiography [9]. The LV was divided into six segments, [posterior septum, anterior septum, lateral, inferior, anterior, and posterior]. Each segment was divided into 3 sub-segments; wall motion was scored by the pattern displayed by 2/3 of the sub-segments.

*Pulsed-wave Doppler tissue sampling.* Beta-blockers were not interrupted before testing. PW-DTS was performed with the Toshiba Powervision echocardiographic imaging system, by using a 3.7 MHz probe, with a pulse repetition frequency of 4.5-6.0 KHz. The temporal resolution of PW-DTS was 4±3 ms. A sample volume of 4 $mm^3$ was used. The continuous measurement of velocity of the myocardium close to the mitral annulus was sampled in apical views [posterior septum, anterior septum, lateral, inferior, anterior, and posterior wall] during a minimum of 5 consecutive beats in order to minimise the variability induced by respiration. The depth of the sample volume of every wall was kept constant during DSE to make sure that LV myocardium was sampled close to the mitral annulus.

The Doppler velocity profiles, electrocardiogram and phonocardiogram tracings were simultaneously stored on videotape. All the measurements were performed

off-line using a computer assisted drawing system. The velocity values [cm/s] were obtained on calibrated still frames by manually measuring the distance between the zero baselines and the peak Doppler profile of ejection phase [EJ], early [E] and late diastole [A] in reference to both electrocardiogram and phonocardiogram. The E/A ratio was also calculated. Cardiac cycles with extrasystolic, post-extrasystolic beats or any rhythm disturbance were excluded. Recordings and measurements were made at baseline, low dose [10 μg/kg/min] and peak dobutamine infusion rate.

*Dobutamine stress echocardiography*: Beta-blockers were not interrupted before testing. After baseline echocardiography, dobutamine was infused at a starting dose of 5 μg/kg/min for 5 min, followed by 10 μg/kg/min for 5 min [low-dose stage]. Dobutamine was then increased by 10 μg/kg/min every 3 minutes up to a maximum dose of 40 μg/kg/min. Atropine [1-2 mg] was added at the end of the last stage if the target heart rate [85% of the maximal predicted heart rate] had not been achieved. Images were acquired continuously and recorded on tape at the end of every dose-step. In addition the baseline, low-dose, peak stress, and recovery images [standard apical and short-axis views] were displayed in a cineloop format. End points for interruption of the test were: 1) achievement of target heart rate; 2) maximal dose of both dobutamine and atropine; 3) extensive new wall motion abnormalities; 4) horizontal or downsloping ST-segment depression [0.2 mV 80 ms after the J-point compared with the baseline]; 5) severe angina; 6) symptomatic reduction in systolic blood pressure > 40 mm Hg from baseline; 7) hypertension [blood pressure >240/120 mm Hg]; 8) significant arrhythmia's or 9) any serious side effect regarded as being due to dobutamine infusion.

*Echocardiographic analysis:* The LV was divided into six segments, [posterior septum, anterior septum, lateral, inferior, anterior, and posterior]. Each segment was divided into 3 sub-segments and visually scored by 2 experienced reviewers [R.R and D.P., blinded to the FDG-SPECT data] for both systolic wall thickening and inward wall motion. Wall motion was scored by the pattern

displayed by 2/3 of the sub-segments. A 5-point scoring system [1 = normokinesis; 2 = mild hypokinesis; 3 = severe hypokinesis; 4 = akinesis and 5 = dyskinesis] was used. Segments with normal wall motion or mild hypokinesia were considered normal and viability was assessed only in the severely dysfunctional segments [severe hypokinesia, a- or dyskinesia]; four types of wall motion responses were observed during the infusion of dobutamine: 1) biphasic pattern: improvement of wall motion during low-dose with worsening at high-dose; 2) worsening: deterioration of wall motion without initial improvement; 3) sustained improvement: improvement of wall motion at low- or high-dose dobutamine; 4) no change: unchanged wall motion. Severely dysfunctional segments exhibiting a biphasic response, worsening or sustained improvement were considered viable, whereas the severely dysfunctional segments with unchanged wall motion were considered scar tissue. The inter- and intra-observer concordance of resting wall motion score were respectively 94% and 97%, whereas the inter- and intra-observer concordance for the response of wall motion during dobutamine infusion were 92% and 94% respectively.

*FDG-SPECT imaging*: Patients received an intravenous dose of 600 MBq $^{99m}$technetium-tetrofosmin to evaluate resting regional perfusion. To enhance cardiac FDG uptake, the patients received 500 mg Acipimox [Byk, The Netherlands] orally, followed by a carbohydrate-enriched meal. Acipimox is a potent nicotinic acid derivative that reduces plasma levels of free fatty acids, thereby stimulating cardiac glucose [and FDG] uptake. This meal stimulated endogenous insulin release, thereby further promoting cardiac glucose [and FDG] uptake. Several studies have shown that this approach yields an excellent image quality, comparable to that obtained with hyperinsulinemic glucose clamping [10,11]. FDG [185 MBq] was injected 60 min after the meal. A 45-min period after FDG injection was allowed for myocardial FDG uptake, followed by the dual-isotope simultaneous acquisition SPECT. Cardiac medication was not discontinued for the SPECT study.

Data acquisition was performed with a triple-head gamma camera system [Picker Prism 3000 XP, Cleveland, OH, USA] equipped with 511 keV collimators. The energies were centred on the 140 keV photon peak of $^{99m}$technetium-tetrofosmin with a 15% window and on the 511 keV photon peak of FDG with a 15% window. Imaging was performed over 360° [120 sectors of 3°] with a total imaging time of 32 min. Data were stored in a 64x64, 16-bit matrix. The raw scintigraphic data were reconstructed by filtered back projection using a Butterworth filter [cut-off frequency at 0.17 cycle/pixel, of order 3.5]. No attenuation correction was employed. Further reconstruction yielded standard long- and short-axis projections perpendicular to the heart-axis. Reconstructed slices were 8 mm in all projections. The perfusion and FDG short-axis slices were adjusted to peak myocardial activity [100%]. The myocardium was divided into six segments [matching the echocardiographic segments, including anterior, lateral, posterior, inferior, posterior septum and anterior septum]. Segments were divided into four categories [assessed visual with the assistance of normalised tracer activity], showing normal tracer uptake [>75% activity], mildly reduced tracer uptake [50-75% activity], severely reduced tracer uptake [<50% activity] or absent tracer uptake.

The dysfunctional segments [identified by resting echocardiography] were divided into viable and nonviable segments. Segments with normal perfusion, mildly reduced perfusion and FDG uptake, or severely reduced/absent perfusion with increased FDG uptake [mismatch] were classified viable, while segments demonstrating severely/absent perfusion with concordantly reduced FDG uptake were classified nonviable.

*Statistical analysis*. Unless specified, data were expressed as mean values ± SD. Comparison of continuous variables was performed with the Student's *t*-test. Comparison of proportions was performed with the chi-square test and the Fisher's exact tests. Sensitivity and specificity were presented with their corresponding 95% confidence interval [CI]. Kappa value was also calculated.

To assess the optimal cut-off point of PW-DTS assessed EJ velocity at low dose and at peak dose dobutamine for the detection of myocardial viability, we used receiver operator's characteristics [ROC] curve. In theses curves, the sensitivity vs. specificity of a test was plotted, in which the sensitivity is a fraction of positive classification for all patients who satisfy the viability criteria of FDG-SPECT and specificity is the fraction of all negative classifications for all patients who satisfy the non-viability criteria of FDG-SPECT. A p-value< 0.05 was considered significantly.

## RESULTS

*Baseline characteristics*. Visual assessment by resting echo was feasible in 230 out of 240 segments [96%]. One hundred seventy seven [77%] segments showed severe dyssynergy at rest; severe hypokinesia in 115 [65%]; akinesis in 61 [34%]; and dyskenesis in 1 [0.6%]. Per patient the mean number of dysfunctional segments was 4.4±2.5. During dobutamine infusion PW-TDS could be assessed in 227 / 240 [95%] segments and wall motion patterns could be scored in 230 / 240 [96%]. The analysis of FDG-SPECT was feasible in all 240 segments.

*FDG-SPECT*: In 177 severely dyssynergic segments viability was present in 95 [54%]; normal perfusion in 57 [32%]; mildly reduction in perfusion and FDG uptake in 20 [11%]; mismatch in 18 [10%]. Non-viability was present in 82 segments [46%] [Figure 1].

*PW-DTS*. The feasibility of the anterior wall, anterior septum, posterior, inferior, lateral, posterior septum was 85%, 90%, 93%, 100%, 100%, and 100% respectively. The analysis of PW-DTS velocity profile showed significant morphological variations for each wall and each dobutamine step. Velocity patterns assessed at rest, low dose and at peak dobutamine are presented in Table II.

**Table II.** Pulsed Doppler mean ejection phase velocities (cm/sec ± Standard Deviation) and E/A ratio's of each left ventricular wall during dobutamine stress echocardiography. (1) Viable myocardium, as assessed by FDG-SPECT, reveals higher ejection phase velocities than (2) nonviable myocardium both at low dose and peak dobutamine. No significant differences are shown by rest ejection phase velocities and by E/A ratio.

| | EJ rest (1) | EJ ld (1) | EJ peak (1) | EJ rest (2) | EJ ld (2) | EJ peak (2) |
|---|---|---|---|---|---|---|
| PS | 5.8 ± 1.7 | 7.8 ± 2.6 | 9.8 ± 3.2* | 5.4 ± 2.2 | 7.0 ± 3.3 | 7.4 ± 3.0 |
| L | 6.0 ± 1.6 | 8.6 ± 2.4* | 9.6 ± 3.2* | 4.1 ± 1.5 | 4.5 ± 1.8 | 4.6 ± 1.7 |
| I | 6.8 ± 1.6 | 8.3 ± 2.0* | 9.1 ± 3.0 * | 4.9 ± 2.1 | 6.2 ± 3.2 | 7.1 ± 3.2 |
| A | 6.2 ± 1.8 | 8.3 ± 2.8* | 9.1 ± 2.8* | 4.8 ± 1.7 | 6.5 ± 2.4 | 5.5 ± 3.3 |
| AS | 6.3 ± 1.6 | 8.2 ± 2.4* | 9.4 ± 2.9* | 4.8 ± 2.3 | 6.2 ± 2.8 | 6.2 ± 3.0 |
| P | 6.4 ± 1.9 | 8.6 ± 2.9* | 9.3 ± 3.1* | 4.5 ± 1.5 | 6.0 ± 1.8 | 6.2 ± 2.1 |
| Total | 6.4 ± 1.9 | 8.6 ± 2.9* | 9.3 ± 3.1* | 4.5 ± 1.5 | 6.0 ± 1.8 | 6.2 ± 2.1 |

| | E/A rest (1) | E/A ld (1) | E/A peak (1) | E/A rest (2) | E/A ld (2) | E/A peak (2) |
|---|---|---|---|---|---|---|
| PS | 0.6 ± 0.2 | 0.6 ± 0.2 | 0.4 ± 0.2 | 0.9 ± 0.2 | 0.7 ± 0.3 | 0.6 ± 0.3 |
| L | 0.5 ± 0.2 | 0.4 ± 0.2 | 0.4 ± 0.4 | 0.6 ± 0.2 | 0.6 ± 0.3 | 0.4 ± 0.3 |
| I | 0.6 ± 0.2 | 0.4 ± 0.3 | 0.3 ± 0.2 | 0.8 ± 0.3 | 0.7 ± 0.4 | 0.3 ± 0.2 |
| A | 0.7 ± 0.2 | 0.7 ± 0.2 | 0.4 ± 0.3 | 0.8 ± 0.2 | 0.5 ± 0.3 | 0.4 ± 0.3 |
| AS | 0.9 ± 0.2 | 0.7 ± 0.2 | 0.3 ± 0.4 | 0.7 ± 0.2 | 0.7 ± 0.2 | 0.3 ± 0.2 |
| P | 0.8 ± 0.2 | 0.7 ± 0.3 | 0.4 ± 0.2 | 0.8 ± 0.3 | 0.8 ± 0.4 | 0.3 ± 0.4 |
| Total | 0.5 ± 0.2 | 0.5 ± 0.2 | 0.4 ± 0.4 | 0.8 ± 0.3 | 0.8 ± 0.3 | 0.6 ± 0.3 |

A = anterior wall, A = late diastole, AS = anterior septum, E = early diastole, EJ = ejection phase, I = inferior wall, L = lateral wall, ld = low dose, P = posterior wall, PS = posterior septum, (1) viable segments, (2) non-viable segments, * $p < 0.05$.

For each segment PW-DTS recognised 4 patterns of contraction [Figure 2]. E/A ratio was not feasible in 15 patients [38%] at peak stress, because of superimposition between A and E waves, thus limiting the feasibility of PW-DTS diastolic evaluation at peak stress to 62%.

*DSE.* The 177 severely dyssynergic segments exhibited four different patterns of wall thickening. [Figure 3]. Ninety-seven segments [55%] were considered nonviable.

*PW-DTS vs. FDG-SPECT.* Improvement of ejection phase velocities at low dose and peak stress dobutamine for viability assessment were classified in two patterns with the highest sensitivity and specificity based on ROC curves using FDG-SPECT as a reference. Viability by PW-TDS at low-dose corresponded

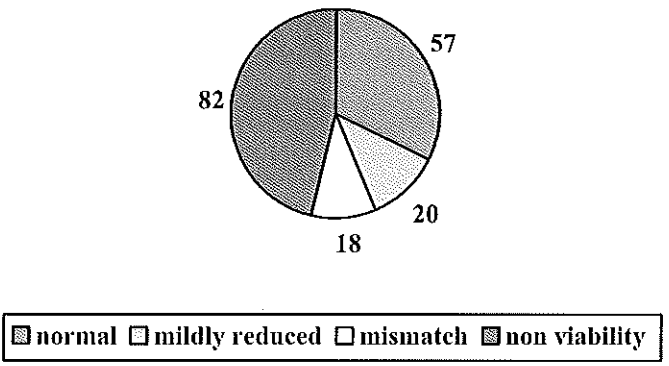


**Figure 1**. Pie-chart showing FDG-SPECT patterns of 177 severely dyssynergic segments for viability: normal perfusion and FDG uptake n = 57 (32%), mildly reduced perfusion and FDG uptake n = 20 (11%), mismatch n = 18 (10%); and for nonviability: n = 82 (46%).

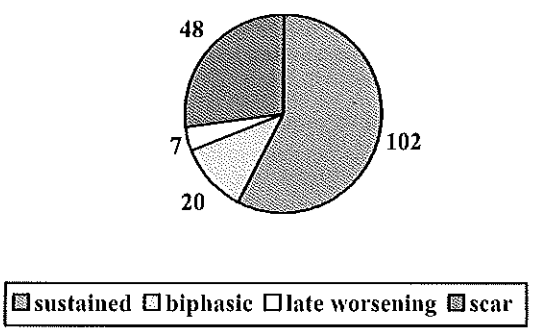


**Figure 2**. Pie-chart showing PW-TDS patterns of 177 severely dyssynergic segments: sustained improvement n = 102 (58%), biphasic n = 20 (11%), late worsening n = 7 (4%), no change n = 48 (27%).

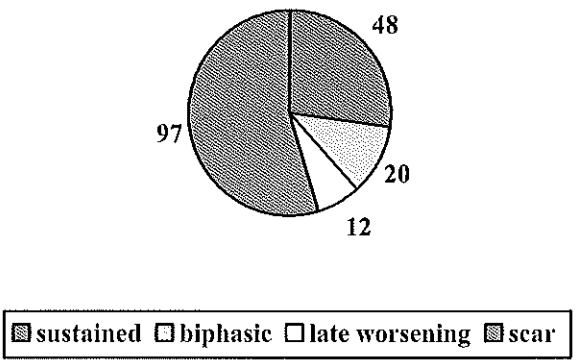


**Figure 3.** Pie-chart showing DSE patterns of 177 severely dyssynergic segments: sustained improvement n = 48 (27%), biphasic n = 20 (11%), late worsening n = 12 (7%), no change n = 97 (55%).

with an improvement of velocity of 1±0.5 cm/sec [n = 129] [73%]. Non-viability corresponded with no improvement [0±0.5 cm/sec] [n = 48] [27%]. PW-TDS had a sensitivity of 87% [82-92], specificity of 52% [44-59] for the prediction of viable myocardium.

Viability by PW-TDS at peak-dose corresponded with an improvement of velocity of 0±0.5 cm/sec with a sensitivity of 64% [58-71], a specificity of 62% [56-69]. However, these data added no diagnostic value to PW PW-DTS for the assessment of myocardial viability [p=NS].

*Agreement between PW-DTS and DSE vs. FDG-SPECT.* Mean EJ velocity values increased at low dose dobutamine more in viable than non-viable walls [Table III]. This increase, 1±0.5 cm/sec, compared to 0±0.5 cm/sec, exhibited an incremental value to DSE for the diagnosis of myocardial viability. The sensitivity of DSE respectively PW-DTS was 75/87% [p <0.05], specificity was 51/52% [p = NS] [Table III].

**Table III.** Diagnostic accuracy for detection of myocardial viability in severely dyssynergic segments: (1) DSE versus FDG-SPECT, (2) PW-TDS versus FDG-SPECT. PW-TDS shows an increased sensitivity ($p < 0.05$) to DSE to detect myocardial viability. Data are presented as percentages with 95% confidence intervals.

| Sensitivity | Specificity | PPV | NPV | Accuracy |
|---|---|---|---|---|
| | | **(1) DSE versus FDG-SPECT** | | |
| 75 (67-81) | 51(45-59) | 72 (65-79) | 54 (47-60) | 66 (58-73) |
| | | **(2) PW-TDS versus FDG-SPECT** | | |
| 87 (82-92)* | 52 (44-59) | 76 (62-82) | 69 (62-75) | 74 (67-80) |
| NPV = negative predictive value, PPV = positive predictive value, * $p < 0.05$. | | | | |

E/A ratio showed a regional variation. However, E/A ratio changes from rest to low dose failed to predict myocardial viability.

## DISCUSSION

In patients with ischemic LV dysfunction and myocardial contractile reserve, coronary revascularization improves both functional capacity and prognosis of survival [1]. The most cost-effective imaging techniques to detect reversible contractile function currently are stress echocardiography and nuclear perfusion/metabolism imaging. Echocardiography has the advantage of widespread availability but subjective evaluation remains a limitation [3]. Doppler tissue imaging provides quantitative data and therefore merits clinical evaluation for testing patients for viability. The PW-TDS allows sampling of selected segments and we used this for measuring the velocities of six myocardial segments. We correlated subjective wall motion scores during DSE and quantitative data of PW-DTS with FDG-SPECT. This method has comparable accuracy for viability detection to positron emission tomography and was used as a reference [8].

The main finding of the present study is a higher sensitivity of PW-DTS than DSE for myocardial viability detection when FDG-SPECT is used as a

reference. This finding is explained by the amplification effect of basal assessment by PW-DTS, able to detect even small amounts of viable myocardium disseminated between base and apex. However, PW-DTS may overestimate the presence of myocardial viability. In segments with scar tissue increased contraction velocity during low-dose dobutamine may occur due to a tethering effect of adjacent viable segments. Most of these observations are made in akinetic segments in the intraventricular septum. A possible way to avoid this would be a multi-sampling approach, in additional areas between the base and the apex or by using parasternal views [the latter allows assessing a limited number of segments]. On the opposite, an underestimation may be related to a lack of contractile function in severely dyssynergic areas, with preserved epicardial metabolic activity. These findings are consistent with higher myocardial integrity required for an inotropic response than for a metabolic uptake. This was also shown by PET imaging were areas with a mismatch pattern of flow/metabolism by PET failed to improve after revascularization [1].

*Potential advantages of using the long axis.* Cumulative velocities obtained in apical views by PW-DTS, in contrast to the equatorial velocities, represent the vectorial sum of contraction velocities of myocardial fibres between the base and apex. The importance of the longitudinal contraction for the evaluation of the LV function was emphasised by Gibson et al. [12] using M-mode at the level of the mitral annulus in apical views. It was shown that longitudinal contraction contributes to half of the LV ejection fraction and adds prognostic information for late cardiac event [7]. Also diastolic PW-DTS parameters are better investigated by the longitudinal approach [13,14]. Finally the use of apical views excludes virtually any global cardiac displacement, as the apex acts as a fixed reference point and the displacement of the cardiac base toward the apex as the result of only myocardial fibres contraction [15].

*Respiratory effect on LV function.* Respiration affects more right than left ventricular dynamics. Garcia et al. [13] showed by averaging a sequence of 5

beats, usually encompassing a normal respiratory cycle, a minimal effect on LV dynamics. In our study we also used the average of 5 consecutive beats.

*Dobutamine infusion protocol.* We used a low-dose dobutamine [5 and 10 μg/kg/min, 5-min step] infusion protocol. As shown in a previous study, in the "classic" low-dose stepwise protocol starting with 10-μg/kg/min for 3-min, sufficient dobutamine plasma concentrations might not be achieved to evaluate improved wall thickening in all patients [16]. In all patients a sufficient plasma dobutamine concentration to evaluate improved wall thickening [80-90 ng/ml] was achieved after a 6-min. infusion period. We therefore assessed improved wall thickening after 10-min. dobutamine infusion.

*Comparison with previous Doppler tissue studies.* So far, few reports indicate the potential of Doppler tissue imaging [DTI] and more particularly PW-TDS, to detect myocardial viability [6]. Gorcsan et al. [17] sampled velocity profile by colour M-mode during dobutamine in apical 4-chamber view close to the mitral annulus. They demonstrated an increased sensitive for myocardial viability, compared to the same approach in parasternal view. Moreover, even other traditional viability parameters were less sensitive than the basal longitudinal approach. Recently, the longitudinal approach using PW-DTS was also used to detect myocardial ischemia in the animal model [18]. After induction of ischemia in pigs it was shown that myocardial contraction velocity was reduced using a single sample of PW-DTS in apical views.

In our study peak EJ velocity of nonviable myocardium reproduced velocity values of abnormal myocardium found by Katz et al [19] and Yamada et al [20]. Most of our EJ velocity values remained below the cut-off of 12 cm/sec as reported by Yamada et al [20] as typical of normal contracting myocardium.

The severity of resting myocardial dyssnergyy in our study may explain the low magnitude of velocity increase under dobutamine, while in normal myocardium a higher and earlier increase of EJ velocity was reported by Gorcsan et al [17].

*Study limitations*. Due to time limitations of the standard DSE protocol, especially at peak stress, we rejected a 16-segment approach. We were also not able to measure the equatorial contraction, due the Doppler angular dependence. Recent advances, e.g. anatomical M-mode, show potential for overcoming this latter limitation [21].

*In conclusion*: In patients with severe LV dysfunction, longitudinal PW-DTS provides quantitative information and was complementary to DSE for the assessment of myocardial viability.

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# CHAPTER 7

# DOBUTAMINE STRESS ECHOCARDIOGRAPHY AND TECHNETIUM-99M-TETROFOSMIN/FLUORINE 18-FLUORODEOXYGLUCOSE SINGLE-PHOTON EMISSION COMPUTED TOMOGRAPHY AND INFLUENCE OF RESTING EJECTION FRACTION TO ASSESS MYOCARDIAL VIABILITY IN PATIENTS WITH SEVERE LEFT VENTRICULAR DYSFUNCTION AND HEALED MYOCARDIAL INFARCTION

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## ABSTRACT

**Background:** Viable myocardium in patients with severe left ventricular (LV) dysfunction predicts improved outcome and survival after revascularization.

**Aim:** To compare two different techniques: dobutamine-atropine stress echocardiography (DSE) and dual-isotope simultaneous acquisition ($^{99m}$Tc-tetrofosmin/fluorine 18-fluorodeoxyglucose (FDG)) single photon emission computed tomography (DISA-SPECT) for assessment of viable myocardium.

**Methods**: One hundred ten patients (mean age 55±9 years) with LV dysfunction (mean LV-ejection fraction 27±13%) underwent both DISA-SPECT and DSE. A 16-segment scoring model was adopted for both techniques. Four types of wall motion during DSE were assessed: 1) biphasic: improvement at low dose (10 μg/kg/min) with worsening at high dose; 2) worsening: deterioration without initial improvement; 3) sustained: persisted or late improvement and 4) no change. Viability criteria were biphasic, worsening and sustained improvement by DSE. Viability criteria by DISA-SPECT were normal perfusion and metabolism (normal) or concordantly mildly reduced perfusion and metabolism (subendocardial scar) or severely reduced perfusion and increased metabolism (mismatch). Myocardium was considered non-viable by DSE in case of unchanged wall motion, or moderate reduction or absence of both $^{99m}$Tc-tetrofosmin perfusion and FDG uptake by DISA-SPECT.

**Results**: Of 1756/1760 analyzable left ventricular segments, 1373 (78%) had severe wall motion abnormalities at baseline (severe hypokinesia, akinesia, or dyskinesia). Out of these abnormal segments, 282 (21%) were considered viable during DSE: 63 (5%) with biphasic response, 47 (3%) with ischemia and 172 (13%) with sustained improvement, while 1091 (79%) were considered nonviable. By DISA-SPECT, 396 (29%) segments were considered viable: 312 (23%) with matched perfusion/metabolism and 84 (6%) with mismatch, while 977 segments (71%) were considered nonviable. Both techniques showed

agreement for viability in 201 segments and 896 were concordantly classified as non-viable. Disagreement was present in 276 segments of which 195 (71%) were non-viable by DSE and viable by DISA-SPECT. The overall agreement between the two techniques was 81%, kappa 0.46, in a subgroup of patients with an ejection fraction <25% 78%, kappa 0.39.

**Conclusions**: DSE and DISA-SPECT showed a good agreement for the assessment of viable myocardium not influenced by resting ejection fraction. However, DSE underestimated the amount of viable tissue as compared to DISA-SPECT.

## INTRODUCTION

Non-invasive assessment of viable myocardium helps to determine the optimal treatment in patients with chronic ischemic left ventricular dysfunction: medical therapy, coronary revascularization or heart transplantation. In the presence of viable myocardium, revascularization may improve LV function and prognosis (1,2). Both nuclear imaging and dobutamine-atropine stress echocardiography (DSE) are available to assess myocardial viability (3-5).

DSE is a relatively new developed technique to assess viability (3,4). The hallmark for viability is the improvement of systolic wall thickening and motion of a dysfunctional segment during low-dose dobutamine infusion. Many studies have determined the value of low-dose dobutamine echocardiography for the prediction of functional recovery after revascularization (6). More recently, a combination of low- and high-dose dobutamine echocardiography appeared more accurate to assess myocardial viability (7). This was related to the induction of ischemia during high-dose dobutamine infusion.

Currently, nuclear imaging with F-18 fluorodeoxyglucose (FDG) and positron emission tomography (PET) remains the reference method to detect viable myocardium (8). In the PET studies, regional FDG uptake is compared with regional perfusion. It appeared that dysfunctional segments with either normal

perfusion and FDG uptake or decreased perfusion with (relatively) increased FDG uptake (perfusion-FDG mismatch) have a high likelihood of functional recovery after revascularization. In contrast, dysfunctional segments with concordantly reduced perfusion and FDG uptake (perfusion-FDG match) do not improve in function after revascularization (9). However, PET imaging is currently not able to meet the increasing demand for viability studies, due to its limited availability (10). Therefore, various centres have recently explored the use of single photon emission computed tomography (SPECT) to evaluate cardiac FDG uptake (11-14). Besides the widespread availability, SPECT imaging allows simultaneous acquisition of perfusion and cardiac FDG uptake. The dual-isotope simultaneous acquisition protocol shortens imaging time and enhances patient throughput.

While combined perfusion-FDG imaging with either PET or SPECT provides information on viability (or resting ischemia), DSE provides information on both viability and stress-induced ischemia. It is unknown how these two approaches compare. Accordingly, we have performed a head-to-head comparison between FDG SPECT and DSE in patients with chronic ischemic left ventricular dysfunction.

## METHODS

**Patient selection:** We prospectively enrolled 110 patients (mean age: 55± 9 years, 79 men). Inclusion criteria were: 1) stable coronary artery disease, (i.e. no recent myocardial infarction, unstable angina or overt heart failure), 2) a resting left ventricular ejection fraction ≤30% assessed by radionuclide ventriculography, 3) presence of 2 or more adjacent severely dysfunctional segments on resting echocardiography, 4) no primary cardiomyopathy. The local medical ethics committee approved the study protocol.

**DSE:** All echocardiograms were performed with an ATL HDI 3000 imaging system equipped with a 1.8 MHz transducer using second harmonic

imaging to optimize endocardial border detection. Beta blockers were not interrupted before testing. After baseline echocardiography, dobutamine was infused at a starting dose of 5 μg/kg/min for 5 min, followed by 10 μg/kg/min for 5 min (low-dose stage). Dobutamine was then increased by 10 μg/kg/min every 3 minutes up to a maximum dose of 40 μg/kg/min. Atropine (1-2 mg) was added at the end of the last stage if the target heart rate had not been achieved. Images were acquired continuously and recorded on tape at the end of every dose-step. In addition the baseline, low-dose, peak stress, and recovery images (standard apical and short-axis views) were displayed in a cineloop format. End-points for interruption of the test were: 1) achievement of target heart rate (85% of the maximal predicted heart rate); 2) maximal dose of both dobutamine and atropine; 3) extensive new wall motion abnormalities; 4) horizontal or downsloping ST-segment depression ≥0.2 mV 80 ms after the J-point compared with the baseline; 5) severe angina; 6) symptomatic reduction in systolic blood pressure > 40 mm Hg from baseline; 7) hypertension (blood pressure >240/120 mm Hg); 8) significant arrhythmia's or 9) any serious side effect regarded as being due to dobutamine infusion.

**Echocardiographic analysis:** The left ventricle was divided into 16 segments (according to the American Society of Echocardiography, (15) and visually scored by 2 experienced reviewers (D.P., R.R., blinded to the SPECT data) for both systolic wall thickening and inward wall motion. A 5-point scoring system (1 = normokinesis; 2 = mild hypokinesis; 3 = severe hypokinesis; 4 = akinesis and 5 = dyskinesis) was used. Segments with normal wall motion or mild hypokinesia were considered normal and viability was assessed only in the severely dysfunctional segments (severe hypokinesia, a- or dyskinesia). Four types of wall motion responses were observed during the infusion of dobutamine: 1) biphasic pattern: improvement of wall motion during low-dose with worsening at high-dose; 2) worsening: deterioration of wall motion without initial improvement; 3) sustained improvement: improvement of wall motion at

low- or high-dose dobutamine; 4) no change: unchanged wall motion. Severely dysfunctional segments exhibiting a biphasic response, worsening or sustained improvement were considered viable, whereas the severely dysfunctional segments with unchanged wall motion were considered scar tissue. Segments with akinesia at rest, which became dyskinetic during stress were not considered ischemic. This is considered to be a mechanical phenomenon (16) The inter- and intra-observer concordance of resting wall motion score were respectively 94% and 97%, whereas the inter- and intra-observer concordance for the response of wall motion during dobutamine infusion were 92% and 94% respectively.

**Dual-isotope simultaneous acquisition SPECT:** Following an overnight fast, the patients received an intravenous dose of 600 Mbq technetium-99m tetrofosmin to evaluate resting regional perfusion. To enhance cardiac FDG uptake, the patients received 500 mg Acipimox (Byk, the Netherlands) orally, followed by a carbohydrate- and protein-enriched meal (providing 70 g carbohydrate, 41 g protein and 21 g fat for a total of 639 calories). Acipimox is nicotinic acid derivative that reduces plasma levels of free fatty acids, thereby stimulating cardiac glucose (and FDG) uptake. This small meal stimulated endogenous insulin release, thereby further promoting cardiac glucose (and FDG) uptake. Several studies have shown that this approach yields an excellent image quality, comparable to that obtained with hyperinsulinemic glucose clamping (17). FDG (185 Mbq) was injected 60 min after the meal. A 45 min period after FDG injection was allowed for myocardial FDG uptake, followed by the dual-isotope simultaneous acquisition SPECT. Cardiac medication was continued during the SPECT study.

Data acquisition was performed with a triple-head gamma camera system (Picker Prism 3000 XP, Cleveland, OH, USA) equipped with 511 keV collimators. The energies were centered on the 140 keV photon peak of technetium-99m tetrofosmin with a 15% window and on the 511 keV photon peak of FDG with a 15% window. Imaging was performed over 360° (120 sectors of 3°) with a total imaging time of 32 min. Data were stored in a 64x64,

16-bit matrix. From the raw scintigraphic data 6-mm thick (1 pixel) transaxial slices were reconstructed by filtered back projection using a Butterworth filter (cut-off frequency at 0.17 cycle/pixel, of order 3.5). Slices were not corrected for attenuation. Further reconstruction yielded long- and short-axis projections perpendicular to the heart-axis.

**SPECT analysis:** For the interpretation of the SPECT images, the technetium-99m tetrofosmin and the FDG short- and long-axis slices were displayed side-by-side. The left ventricle was divided into 16 segments (6 basal (anterior, anterolateral, inferolateral, inferior, inferoseptal, anteroseptal), 6 distal and 4 apical segments, corresponding to the echocardiographic segments (see above). The segmental tetrofosmin and FDG uptake was scored by consensus of 2 experienced observers (blinded to the echo data) using a four-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.

**Radionuclide ventriculography:** Radionuclide ventriculography was performed at rest with the patient in supine position after administration of 740 Mbq of technetium-99m. Images were acquired with a small filed of view gamma camera (Orbiter, Siemens Corp.) oriented in the 45° left anterior oblique position with a 5° to 10° caudal tilt. The left ventricular ejection fraction was calculated by an automated technique.

**Statistical analysis:** Unless specified, data were expressed as mean value ± standard deviation or percentage ± confidence interval (CI). Comparison of dichotomous variables was performed by contingency tables, from which correlation and kappa-values with standard errors were calculated. A p-value of $<0.05$ was considered significant.

## RESULTS

Mean LV ejection fraction assessed by radionuclide ventriculography was 27±13%. Patient characteristics are presented in Table I.

**Table I.** Characteristics of 110 patients

| | Number of patients (%) |
|---|---|
| LV ejection fraction 25-30% | 78 (71) |
| LV ejection fraction <25% | 32 (29) |
| Angina pectoris | 93 (86) |
| **Class I** | 1 (1) |
| **Class II** | 20 (19) |
| **Class III** | 71 (66) |
| **Class IV** | 1 (1) |
| Diabetes mellitus | 14 (13) |
| Medication | |
| **ACE-inhibitors** | 80 (73) |
| **Beta blockers** | 58 (54) |
| **Calcium antagonists** | 46 (43) |
| **Nitrates** | 48 (44) |
| **Diuretics** | 56 (52) |
| **Coronary angiography** | |
| **1-vessel disease** | 33 (30) |
| **2-vessel disease** | 37 (34) |
| **3-vessel disease** | 40 (36) |

ACE-inhibitors= angiotensin converting enzyme inhibitors.

**DSE.** During DSE heart rate increased from 66±9 to 129±14 beats/min ($p < 0.01$). Blood pressure increased from 113±19/66±18 to 130±25/71±14 mmHg ($p < 0.01$). Test end-point was target heart rate in 105 (95%) patients. The test was interrupted in five patients at peak stress because of side effects. Three patients experienced severe and symptomatic hypotension (decrease systolic blood pressure >40 mmHg) and two patients developed sustained ventricular tachycardia (> 10 complexes). There were no fatal complications or myocardial infarctions. Adequate echographic visualization was achieved in 1756/1760 (99%) LV segments. Of 1756 ventricular segments, 1373 (78%) had severe abnormal wall motion at baseline (including 823 severely hypokinetic segments, 517 akinetic and 33 dyskinetic segments). Wall motion assessed during DSE yielded 4 different patterns: 63 (5%) biphasic, 47 (3%) worsening, 172 (13%)

sustained improvement and 1091 (79%) no change (table II). The prevalence of viable myocardial segments, according to DSE, was 282/1373 (21%), while 1091 (79%) were considered nonviable.

**Table II.** Agreement for each pattern of wall motion during DSE for assessment of viability.

| Echo pattern | N | Scan viable (%) | Scan nonviable (%) |
|---|---|---|---|
| Biphasic | 63 | 53 (86) | 10 (14) |
| Sustained | 172 | 145 (84) | 27 (16) |
| Ischemic | 47 | 32 (68) | 15 (32) |
| Scar | 1091 | 195 (18) | 896 (82) |

**$^{99m}$Tc-tetrofosmin/FDG SPECT.** Feasibility of $^{99m}$Tc-tetrofosmin/FDG SPECT was 100%. Of the 1373 severely dysfunctional segments 396/1373 (29%) were classified viable according to the scan findings: 190 (14%) exhibited normal FDG uptake and $^{99m}$Tc-tetrofosmin perfusion in, 122 (9%) had a mild-moderate reduction in both perfusion and metabolism and 84 (6%) had a mismatch pattern. Conversely, 977 (71%) segments exhibited no viability, as defined by concordantly severely reduced or absent perfusion and metabolism.

**Comparison of the two techniques**: The wall motion responses during DSE and the corresponding DISA-SPECT patterns are presented in figure 1. While segments with a biphasic response showed the highest incidence of viability assessed by scan (53/63, 84%), the segments with no change during DSE revealed the highest incidence of nonviability by scan (925/1091, 85%). The segments with sustained improvement and worsening on DSE had an intermediate incidence of viability by scan of 84 and 68% respectively. Hence, the agreement between the two techniques was 80%, with a kappa value of 0.46±0.03 (table II). This concordance was not significantly different for segments with severe hypokinesia at rest vs segments with a or dyskinesia at rest.

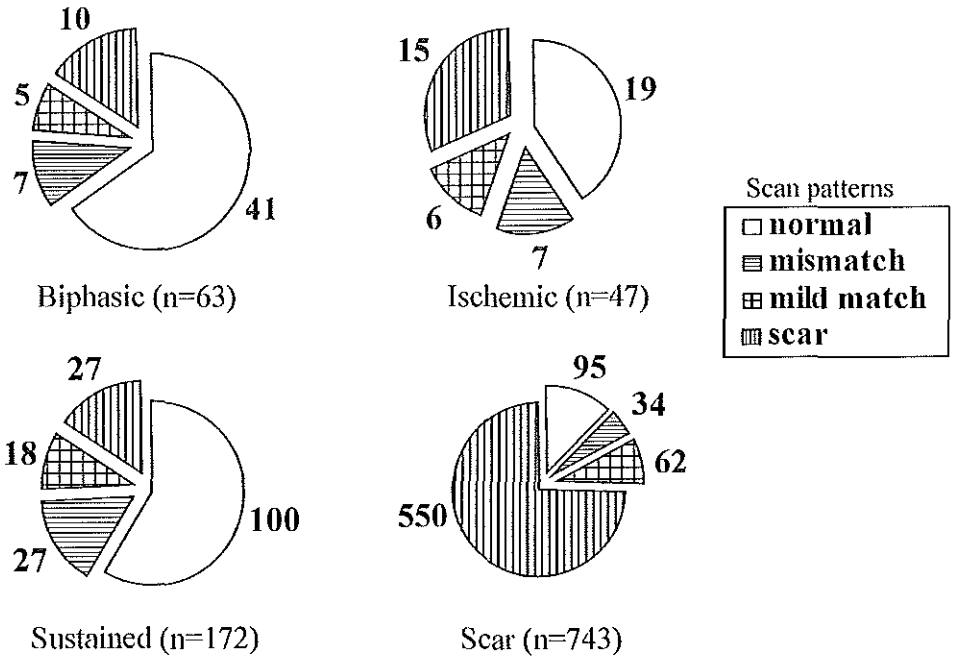


**Fig. 1**: Correlation between DSE patterns of wall motion and simultaneous myocardial flow/metabolism assessed by DISA-SPECT. DSE wall motion patterns were described as: biphasic: improvement of wall motion during "low-dose" dobutamine with worsening at peak. Ischemic: deterioration of wall motion without initial improvement. Sustained: improvement of wall motion at low or high dose dobutamine. Scar: no change. Scan patterns were described as: Normal: normal perfusion and metabolism. Mild match: concordantly mildly reduced perfusion and metabolism (subendocardial scar). Mismatch: severely reduced perfusion and increased metabolism. Scar: moderately reduced to absent perfusion and FDG uptake.

Agreement of a subgroup 32 patients with a LVEF <25% was slightly lower 78%, kappa 0.39±0.04 than those with a higher LVEF (Table III). Disagreement was present in 276 segments of which 195 (71%) were non-viable by DSE and viable by DISA-SPECT.

**Table III.** Agreement by DSE and scan for assessment of viability in relation to resting ejection fraction assessed by radionuclide ventriculography.

| | N | Agreement (%) | Kappa ± SEM |
|---|---|---|---|
| All patients | 110 | 80 | 0.46±0.03 |
| Ejection fraction ≥25% | 78 | 81 | 0.46±0.03 |
| Ejection fraction <25% | 32 | 78 | 0.39±0.04 |

The relation between rest myocardial perfusion, assessed by $^{99m}$Tc-tetrofosmin, and wall motion pattern during DSE is presented in Table IV. There was a significant reduced perfusion at rest in segments with a scar pattern. Segments with a sustained improvement and an ischemic response showed a normal or mildly reduced perfusion in respectively 78 and 70%.

**Table IV.** Relation between myocardial perfusion, assessed by $^{99m}$Tc-tetrofosmin and wall motion pattern during DSE.

| DSE pattern | No. | Normal perfusion (%) | Mildly reduced perfusion (%) | Severe reduced perfusion (%) |
|---|---|---|---|---|
| Biphasic | 63 | 56 | 19 | 25 |
| Ischemic | 47 | 54 | 16 | 30 |
| Sustained | 172 | 62 | 16 | 22 |
| Scar | 1091 | 19 | 12 | 69 |

## DISCUSSION

The present study addresses a head-to-head comparison in patients with severe LV dysfunction between patterns of wall motion during DSE and simultaneous resting myocardial flow/metabolism assessed by DISA-SPECT for the detection of viable myocardium. There is a good correlation of the two imaging techniques for detection of myocardial viability on segmental basis, uninfluenced by resting ejection fraction. These data are in agreement with previous reports correlating low dose DSE with thallium-201($^{201}$Tl)/FDG SPECT (6).

**Nuclear imaging techniques.** The reference method to detect viable myocardium remains FDG PET (8,9). FDG uptake within hypoperfused segments predicted functional improvement after revascularization with the highest accuracy (8,9). To overcome limitations to FDG PET routine clinical use, due to restricted availability, high costs and complex technology, an alternative technique has been recently developed, able to image both FDG uptake and myocardial perfusion by SPECT (11-13). FDG uptake may be studied by special gamma cameras equipped with special 511 keV collimators,

obtaining either planar imaging or SPECT imaging (13). This approach has been validated for prediction of functional recovery after revascularization in patients with LV dysfunction. The sensitivity and specificity of this method for prediction of recovery of function was respectively 85% and 86%, comparable to FDG PET (6). However, so far, myocardial perfusion and metabolic uptake by SPECT required separate acquisitions, resulting in a misalignment between flow and metabolic imaging. This was overcome by the use of $^{99m}$Tc-MIBI or $^{99m}$Tc-tetrofosmin, both $^{99m}$Tc-agents, allowing dual-isotope simultaneous acquisition (13). The simultaneous acquisition of both perfusion and metabolism, as in the present study, may improve accuracy for detection of viable myocardium. The diagnostic accuracy may be further increased by the use of a nicotinic acid derivative (acipimox) (17). By the reduction of circulating free fatty acid levels and the stimulation of glycogen synthetase activity the glucose and subsequently the FDG uptake of the heart is increased. This simple orally taking drug offers a practical advantage over the previous hyperinsulinemic glucose clamping method (18).

**DSE patterns.** DSE has become a promising imaging modality to assess viable myocardium (3,4). A complete test, compared to only low dose, is more accurate to predict left ventricular functional recovery after revascularization. This was ascribed to the ability of full dose dobutamine to recognize more accurately the biphasic and ischemic response, which have the best prognosis for recovery of function after revascularization (7). These ischemic responses may be missed if only a low dose dobutamine protocol was performed.

**Correlation DSE patterns and scan, what do they mean?** The pathological substrate of each pattern is a subject of discussion. A biphasic response is considered the best marker of myocardial viability (3,4). After an improvement of wall motion at low dose, a decrease at peak dobutamine indicates a limited coronary flow reserve. In this study this response had the highest percentage of viable tissue assessed by tetrofosmin/FDG SPECT, 86%. This is in agreement with the study of Afridi et al (7). In a group of 34 patients,

12 showed predominantly a biphasic response during DSE. In this group wall motion score improved after revascularization significantly at rest, low and peak-dose dobutamine. This improvement of contractile response after revascularization during DSE may also have additional prognostic value. Further studies are needed to clarify this issue.

In the ischemic segments, only worsening during stress, there was a moderate correlation between the resting myocardial flow and metabolism, 68% of these segments showed viability by tetrofosmin/FDG SPECT. Coronary flow reserve and collateral flow is probably so limited that initial improvement of wall thickening in these segments is impossible. This can occur irrespective of resting myocardial flow and metabolism as shown in our study.

Sustained improvement is a pattern with a good agreement for nuclear assessed viability. This pattern should indicate viable epicardial myocardium, able to compensate the subendocardial scar, with preserved coronary flow reserve. Unlike the biphasic pattern, after a hypercontractile response at low dose, at peak stress there is no worsening. However, if we describe hibernating myocardium as a reduction of coronary flow reserve in dyssynergic segments, it is difficult to include this pattern in hibernation, as the coronary flow reserve is able to meet the increased metabolic requirement at peak stress. This probably explains to low prognostic value for improvement of function of segments with a sustained improvement during DSE after revascularization as shown by the studies of Afridi et al (3,7).

The last pattern of no wall motion change represents a transmural scar and we observed a significant reduction of both myocardial flow and FDG uptake in 82% of these segments. However, 18% segments with this pattern exhibited FDG uptake. These data comply with previous studies demonstrating that segments, akinetic at DSE, can be viable at FDG-PET, and exhibit improvement of contractile function after revascularization (17).

Coronary flow assessed by tetrofosmin perfusion at rest is not discriminative for a DSE pattern, with the exception of a scar. A scar pattern

during DSE exhibited a normal or mildly reduced perfusion at rest in only 31%. In segments with a biphasic, ischemic and sustained improvement a normal or mildly reduced perfusion was present in 75, 70, and 78% respectively. However, this resting flow pattern is not related with coronary flow reserve which is the limiting factor in both ischemic and biphasic patterns.

**Major findings.** We found a high correlation between DISA-SPECT and DSE, irrespective of resting ejection fraction and wall motion pattern by echo, even if the two techniques assess different aspects of myocardial function. Another finding of our study is that DISA-SPECT, compared to previous results by using thallium-imaging (6), has a better discrimination for nonviable segments. This superiority of DISA-SPECT may be explained by the fact that FDG uptake is based on membrane metabolic function. This performance renders DISA-SPECT quite similar to FDG-PET in detecting viable myocardium.

**Disagreement between the two techniques.** We found a higher prevalence of viability by nuclear imaging, compared to DSE. This may be related to the degree of myocyte damage, in which the functional integrity required for contractile response is lost, while the metabolic activity for membrane function is preserved. The agreement between DSE and DISA-SPECT of about 80% probably results from the fact that these two techniques assess different myocardial functions. This may suggest a complementary use of both.

**Study limitations.** There were two major limitations. Firstly, DSE interpretation was, subjective. Although there was a high inter and intraobserver agreement this potential disadvantage may reduced by the introduction of quantitative techniques like Doppler tissue imaging (19). A second limitation of the present protocol of DISA-SPECT was the performance under resting conditions. For a complete reconstruction of the viability profile of each myocardial segment a stress technique may be required, thus allowing assessment of flow/metabolic ischemia, to match with the dobutamine ischemia.

Unfortunately, we did not have the opportunity to compare our results with the improvement of left ventricular function after revascularization; however, this was not goal of the present study.

## CONCLUSIONS

There is a good correlation between myocardial flow/metabolism assessed by DISA-SPECT and myocardial viability assessed by DSE irrespective of resting ejection fraction. This suggests that these two techniques share a potential for an accurate prediction of functional improvement after revascularization.

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# CHAPTER 8

# SAFETY AND UTILITY OF ATROPINE ADDITION DURING DOBUTAMINE STRESS ECHOCARDIOGRAPHY FOR THE ASSESSMENT OF VIABLE MYOCARDIUM IN PATIENTS WITH SEVERE LEFT VENTRICULAR DYSFUNCTION

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## ABSTRACT

Objective: To assess the feasibility, safety and side effects of atropine addition to dobutamine stress echocardiography (DASE) for the detection of viable myocardium in patients with left ventricular (LV) dysfunction [ejection fraction (EF) ≤35%] prior to coronary revascularization.

Background: The assessment of viable and/or ischemic myocardium has high prognostic value for improvement of function and survival after coronary revascularization. The addition of atropine to dobutamine during echocardiographic testing for the presence of viable myocardium is not common practice. Consequently, no data exist on safety and additional diagnostic value of this practice.

Methods: Two hundred patients with LVEF ≤35% were studied.

Results: Test end-point were: target heart rate in 164 (82%), severe angina in 18 (9%), maximum dobutamine-atropine dose in 6 (3%), severe ST-segment changes in 5 (2%), cardiac arrhythmias in 4 (2%), and hypotension in 3 (1%) of the patients. Viability could be assessed echocardiographically in 105/200 (53%) by a bi-phasic response (improvement of wall motion at low dose dobutamine and worsening at high dose) or ischemia in 93 and sustained or late improvement in 12 patients. In 36/105 (34%) patients ischemic myocardium could only be assessed after the addition of atropine. Cardiac arrhythmias occurred in 11/200 (6%) and hypotension (decrease of systolic blood pressure >30 mmHg) in 21/200 (11%). Neither the use of atropine nor the induction of ischemia were associated with an increased incidence of cardiac arrhythmias or hypotension.

Conclusions: In a large group of patients with severe LV dysfunction DASE is feasible in 186/200 (94%), safe and atropine addition was necessary in 34% to assess myocardial viability. Hypotension and cardiac arrhythmias were the most frequent occurring side effects, but were not related to the induction of ischemia and addition of atropine.

## INTRODUCTION

Dobutamine-atropine stress echocardiography (DASE) is commonly employed to assess the location, extent and severity of coronary artery disease (1). DASE is particularly useful in patients who cannot exercise because of non-cardiac disease, and when ECG abnormalities preclude the diagnosis of ischemia. Dobutamine is a relatively selective β1-adrenoceptor agonist with weak α and β2-adrenoceptor stimulating properties. At infusion rates of 5-10 μg/kg/minute, dobutamine elicits primarily a positive inotropic response, while significant positive chronotropic effects are apparent when more than 20 μg/kg/minute is infused (2). During DASE, atropine is mostly used to increase heart rate when the chronotropic response to dobutamine is inadequate to induce ischemia (3-5).

The safety of DASE for ischemia detection has been extensively evaluated. The most frequent side effects are hypotension and arrhythmia's (3-10). Hypotension occurs more often in the absence of chronic beta-adrenoceptor therapy (2). Cardiac arrhythmias occur in about 3% of patients and are related to the presence of extensive resting wall motion abnormalities and a history of atrial or ventricular arrhythmia's (8).

Recently, DASE has been used to evaluate the extent of viable myocardium in patients with severe left ventricular dysfunction (11,12). When stunned, hibernating, or ischemic myocardium is demonstrated, aggressive anti-ischemic therapy, and/or coronary revascularization may improve cardiac function and survival, providing an alternative to heart transplantation (13). Two characteristic echocardiographic patterns have a high diagnostic value for viable myocardium: 1) a bi-phasic response to dobutamine infusion, with initial improvement in wall motion at low doses, followed by worsening at higher infusion rates and 2) an ischemic response (14). In order to make a correct decision for revascularization in these high risk patients both factors are important. We believe that a complete DASE testing may provide additional

information, especially regarding worsening of wall motion at peak stress with or without initial improvement at low-dose dobutamine. However, recently Rahimtoola (15) and Nagueh (16), expressed their concern that DASE may induce cardiac arrhythmias or myocardial infarction in patients with extensive rest wall motion abnormalities. The principal purpose of this study was 1) assess the utility of addition of atropine to high dose dobutamine for the detection of myocardial viability and 2) to evaluate the feasibility and safety of DASE in patients with a reduced left ventricular function, prior to coronary revascularization.

We hypothesized that use of atropine is feasible, safe and has incremental diagnostic value in severe ischemic cardiomyopathy.

## METHODS

DASE was attempted in 201 qualifying patients during the period 1995-1997. All patients had undergone coronary angiography within the preceding six weeks, and were selected to undergo coronary revascularization. All were studied for detection of jeopardized myocardium and had a resting LVEF of ≤35% as assessed by radionuclide ventriculography or cineventriculography. Adequate echocardiographic images could not be obtained in one (0.5%) patient. Data from the remaining 200 patients are reported here.

DASE: Beta-blocker medication was not discontinued for the study. A resting two-dimensional transthoracic echocardiographic examination, including standard apical and parasternal views of the left ventricle was performed and recorded on quad screen format (n=80) or as consecutive standard views (n=120) on video tape. A resting 12-lead ECG was obtained. Dobutamine was administered intravenously by infusion pump at 5 μg/kg/minute and increased to 10 μg/kg/minute after 5 minutes (low dose stage). The infusion rate was then increased by 10 μg/kg/minute every 3 minutes to a maximum of 40 μg/kg/minute (high dose stage), and continued for 6 minutes. If signs and symptoms of ischemia were absent during the high dose stage, and a target heart

rate [(220-age) X 0.85 in men, and (200-age) X 0.85 in women] was not achieved, atropine was administered iv in 0.25 mg increments, to a maximum of 2 mg, while the dobutamine infusion was continued. During the test, the 12-lead ECG was monitored continuously and recorded each minute. Blood pressure was measured non-invasively at rest and at each stage of the protocol. The two-dimensional echocardiogram was monitored continuously and recorded during the last minute of each stage and during recovery. The recovery phase was considered complete, when heart rate had returned to within 10 bpm of baseline.

The criteria for stopping the test were: a symptomatic decline in systolic blood pressure of more than 30 mmHg from the resting value or a systolic blood pressure of less than 90 mmHg; significant cardiac arrhythmias; severe anginal chest pain; horizontal or downsloping electrocardiographic ST depression of ≥0.2 mV measured 80 ms after the J point; ST-segment elevation of ≥0.2 mV in the absence of Q waves; and severe new echocardiographic wall motion abnormalities in multiple locations.

Off-line assessment of echocardiographic images was performed by two independent investigators. The intra and inter-observer agreement of the interpretation of the echocardiographic images was respectively 92 and 90%. The left ventricular wall was divided into 16 segments (17) and wall motion subjectively scored on a five-point scale: 1 = normal; 2 = mildly hypokinetic; 3 = severely hypokinetic; 4 = akinetic, and 5 = dyskinetic. Viable myocardium was considered to be present in segments exhibiting severe dysfunction at rest (severe hypokinesia, akinesia, or dyskinesia) plus either of the following: 1) improvement at low dose and worsening at high dose (bi-phasic response); 2) continuous or late improvement; 3) worsening of movement without initial improvement, with the exception of akinesia becoming dyskinesia which was considered to be a mechanical phenomena. Severely dyssynergic segments without change of wall motion during DASE were considered as non-viable or scar. For each patient, a wall motion score index (total score divided by the number of assessable segments) was calculated at rest, at the end of the 10

μg/kg/minute stage, and during peak stress based on the standard 16 segment model.

Statistical analysis: The study population (with LVEF ≤35%) was divided in two sub-groups according to their ejection fraction. Chi-square analysis was performed to evaluate differences in the use of atropine, the occurrence of angina, ST-segment changes, NWMA, hypotension and cardiac arrhythmias during DASE between patients with LVEF ≤25% and those with LVEF >25%. Reported are odds ratio's (OR) with corresponding 95% confidence intervals (CI).

Haemodynamic variables (heart rate, systolic and diastolic blood pressure) are described as mean ± standard deviation (SD). Differences in haemodynamic measurements at rest, low-dose (10 μg/kg/min) and peak-dose dobutamine infusion between patients with and without viable myocardium were evaluated by Student's t-tests. Differences were considered significant at the 0.017 probability level (thus applying Bonferroni's correction for 3 repeated comparisons).

## RESULTS

*Demographics.* The study group had the following characteristics: male, 188 (94%); mean age 63 years, range 34 to 78; previous myocardial infarction, 188 (94%); typical angina pectoris, 134 (67%); diabetes mellitus requiring drug therapy, 16 (8%). Eighty patients (40%) were being treated with angiotensin converting enzyme inhibitors, and 22 (11%) were taking β-adrenoceptor blocking agents. LVEF was ≤25% in 96 patients (48%), and between 26 and 35% in 104 (52%). All patients had angiographically significant coronary artery stenosis (>50% narrowing of the luminal diameter). Single vessel coronary artery disease was present in 24 patients (12%); two-vessel disease in 64 patients (32%), and three-vessel disease in 112 patients (56%).

*Feasibility of DASE.* In 13 patients the test was non-diagnostic either because it was stopped prematurely because of side effects (sustained ventricular tachycardia (≥10 complexes) [n=3], atrial fibrillation [n=1], severe, symptomatic hypotension [n=3]), or because the target heart rate was not achieved despite maximal dobutamine and atropine doses [n=6]. The overall feasibility of the test was 187/201 (93)%. The number of patients at dobutamine stages during stress test is presented in table 1.

**Table 1:** Hemodynamic characteristics of 200 patients during dobutamine-atropine stress echocardiography. Data presented as mean ± SD.

| Dobutamine µg/kg/min | rest | 5 | 10 | 20 | 30 | 40 | 40 + atropine |
|---|---|---|---|---|---|---|---|
| N | 200 | 200 | 200 | 182 | 124 | 111 | 64 |
| Heart rate (bpm) | 76±13 | 76±13 | 89±17 | 101±18 | 113±19 | 125±26 | 135±16 |
| SBP (mmHg) | 124±22 | 125±22 | 125±23 | 126±24 | 124±24 | 124±25 | 121±22 |
| DBP (mmHg) | 74±14 | 67±14 | 67±14 | 65±14 | 65±13 | 66±13 | 67±13 |

n.= number of patients studied; bpm= beats per minute; SBP= systolic blood pressure; and DBP= diastolic blood pressure.

In the remaining 187 patients the test endpoint was: the target heart rate (n=164, 82%); angina pectoris (n=18, 9%); electrocardiographic evidence of severe ischemia (n=5, 2.5%). Stress induced ischemia developed in 105 patients (52%), manifest as bi-phasic response or new or worsening wall motion abnormalities in 93 patients (46%), and ST segment changes in 81 patients (40%). The mean wall motion score at rest was 2.24, range 1.60-3.5. Stress induced ischemia was more frequent in patients with LVEF ≤25%. In 36/105 patients ischemia could only be assessed during the addition of atropine on top of dobutamine. During the recovery phase no persistent new wall motion abnormalities were detected. Echocardiographically detected viable myocardium was present in 105 patients (52%); sustained or late improvement in 12 and bi-phasic response or ischemia in 93 patients.

*Hypotension.* Hypotension occurred in 31% of patients during DASE. In 40 patients (20%) the decrease of systolic blood pressure was 10-30 mmHg and in 21 patients (11%) >30 mmHg. The test had was stopped in only 3 patients (1.5%) because of severe dizziness, in all other patients the decrease of bloodpressure occurred at the end of the test. The occurrence of hypotension was not correlated with stress induced ischemia (OR 0.9, 95% CI 0.5 to 1.9), diabetes mellitus (OR 2.1, 95% CI 0.7 to 6.0), absence of beta blockers (OR 1.3, 95%CI 0.3 to 4.8) or LVEF ≤25% ( OR 1.8, 95% CI 1.1 to 9.5).

*Cardiac arrhythmias.* Cardiac arrhythmias occurred in 11 patients (5%); supraventricular tachycardia in 2 (1%); nonsustained ventricular tachycardia (< 10 complexes) in 5 (2.5%); sustained ventricular tachycardia (≥ 10 complexes) in 3 (1.5%); and atrial fibrillation in 1 (0.5%). Arrhythmia's were not more frequent in patients with LVEF ≤25% (OR 0.9, 95% CI 0.8 to 2.8) or when myocardial ischemia was induced by DASE (OR 0.9, 95% CI 0.3 to 3.4)

*Atropine.* Atropine was added in 64 patients (32%) of which 36 showed myocardial ischemia and was administered more frequently to patients with LVEF ≤25% (OR 2.3, 95% CI 1.3 to 4.3) (Table 2).

**Table 2:** Clinical and dobutamine-atropine stress test characteristics of patients with severe left ventricular dysfunction (EF ≤25%).

| | O.R | 95% CI |
|---|---|---|
| Atropine | 2.3 | 1.3-4.3 |
| ST segment ↑↓ | 1.9 | 1.1-3.4 |
| NWMA | 1.8 | 1.0-3.2 |
| Hypotension | 1.8 | 0.7-4.6 |
| Arrhythmia's | 0.9 | 0.8-2.8 |
| Diabetes mellitus | 0.9 | 0.4-1.9 |
| Beta blockers | 0.8 | 0.3-1.9 |

Atropine = atropine addition on top of maximum dose dobutamine, up to 2.0 mg i.v.; NWMA = echocardiographic detected new wall motion abnormalities; Hypotension = decrease of systolic blood pressure > 30 mmHg compared to rest.

Patients on beta blocker therapy did not require atropine more frequently (OR 0.8, 95% CI 0.3 to 1.9). There was no association between atropine administration and the induction of cardiac arrhythmias (OR 0.7, 95% CI 0.2 to

2.9) or the occurrence of hypotension (decrease bloodpressure >30 mmHG) (OR 1.8, 95% 0.94-3.4) (Figure 1), although the latter relationship approached statistical significance.

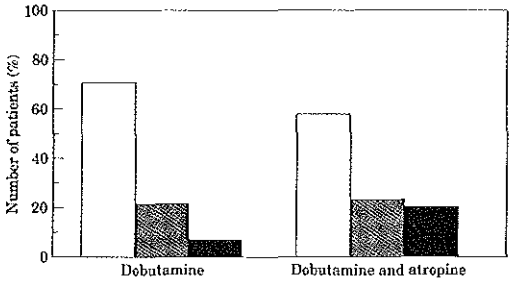


**Figure 1:** The percentage of patients with hypotension with or without additional atropine administration. Mild hypotension= decrease of systolic blood pressure of 10-30 mmHg and severe hypotension= decrease of systolic blood pressure >30 mmHg during DASE. There was no significant increase of mild or severe hypotension after atropine addition.

*Blood pressure response to low-dose dobutamine.* Haemodynamic changes during DASE are presented in Table 1. In patients with viable myocardium both systolic and diastolic blood pressure were significantly higher during low dose dobutamine infusion, than in patients without myocardium at risk ($p< 0.05$) (Table 3). This difference was no longer apparent at peak dobutamine infusion rates and may reflect improved myocardial function at low dobutamine infusion rates in patients with viable myocardium.

*Recovery.* No persistent wall motion abnormalities were detected at the end of the recovery phase. There were no deaths or myocardial infarctions.

**Table 3:** Hemodynamic changes during DASE in patients with and without echocardiographically detected viable myocardium.

| Dobutamine | rest | rest | p | Low | low | p | peak | peak | p |
|---|---|---|---|---|---|---|---|---|---|
| Viable | no | yes | | No | yes | | no | yes | |
| n | 98 | 102 | | 98 | 102 | | 28 | 36 | |
| Heart rate (bpm) | 76±13 | 76±13 | 0.8 | 91±18 | 87±17 | 0.3 | 138±13 | 131±19 | 0.06 |
| SBP (mmHg) | 126±22 | 121±22 | 0.08 | 122±22 | 132±24 | 0.03 | 120±20 | 118±23 | 0.8 |
| DBP (mmHg) | 73±14 | 75±13 | 0.3 | 65±14 | 71±14 | 0.01 | 65±11 | 68±14 | 0.4 |

n= number of patients studied; bpm= beats per minute; SBP= systolic blood pressure; DBP= diastolic blood pressure; viable= echocardiographically detected improved wall motion with or without worsening at peak stress or new wall motion abnormalities; p = difference between viable and non viable group; low= low dose dobutamine (10μg/kg/min); peak= 40μg/kg/min with addition of atropine; and ns = not significant.

## DISCUSSION

Our results show that the addition of atropine was necessary in 36 patients to peak dobutamine infusion for the assessment of myocardial ischemia in 200 patients with severe LV dysfunction during stress echocardiography. So atropine addition improves the accuracy of stress echocardiography for ischemia assessment in 34%. DASE can be safely used to detect the presence of viable myocardium in patients with coronary artery disease and severe LV dysfunction. The presence of viable myocardium was inferred if wall motion improved with low dose dobutamine infusion, or if new wall motion abnormalities developed at any point during DASE.

It was necessary to administer atropine to 41% of the entire study group in order to reach the target heart rate. Atropine was required more frequently in the patients with more severe LV dysfunction (EF ≤25%), although beta blockers were not used more frequently in this subgroup. The addition of atropine did not induce cardiac arrhythmias, although there was a tendency for hypotension (a decrease of systolic blood pressure of >30 mmHg compared to the resting value) to occur more frequently after atropine administration (OR 1.8, 95% CI 0.94 to 3.3).

*Comparison with previous studies.* DASE is commonly used for the detection and evaluation of coronary artery disease (14,18). In patients with severe LV dysfunction it can detect the presence of viable myocardium (improvement of wall motion at low dose followed by worsening at high dose, ischemia, or late or sustained improvement) which influences prognosis and therapy (12,14,19). The recent study of Williams et al (19) evaluating the prognostic value of viable and/or ischemic myocardium by DASE in patients with severe LV dysfunction, showed a high cardiac event rate during 16±8 months of follow-up of 43 vs 8% in patients with viability and/or ischemia. The cardiac event rate was not different in patients with viable or ischemic myocardium. Especially for the ischemic response high dose of dobutamine often in combination with atropine is frequently necessary. Safety of DASE with

regard to cardiac arrhythmias was however not assessed. There is the concern that serious cardiac arrhythmias or infarction might be more frequent in patients with a history of severe left ventricular dysfunction (8). In our study, side effects caused the test to be stopped prematurely in only 6% of patients. These results compare favorably with pooled data from the literature evaluating patients with proven or suspected coronary artery disease (Table 4), where a failure rate of 16% was reported.

**Table 4:** Overview of dobutamine-atropine stress echocardiography data for analysis of proven or suspected coronary artery disease.

| Author | year | n | Atro-pine | Feasibility | arrhythmia's | | Hypo-tension | mmHg |
|---|---|---|---|---|---|---|---|---|
| Mertes | 1993 | 1118 | no | 737/1118 | 86 | AF/shVT | 36 | 16-84 |
| Marwick | 1993 | 217 | no | 152/217 | 6 | shVT/SVT | 36 | >20 |
| Poldermans | 1994 | 650 | yes | 633/650 | 24 | AF/shVT/ susVT/VF | 34 | >20 |
| Picano | 1994 | 2949 | yes | 2608/2949 | 178 | Ventricular tachyarrhy/SVT | 62 | >30 |
| Pingitore | 1996 | 360 | yes | 323/360 | 23 | Ventricular tachyarrhy/AF | 3 | >30 |
| Ling* | 1996 | 1171 | yes | | 240 | SVT/AF/shVT | | |
| Anthopoulos | 1996 | 120 | no | 108/120 | 2 | AF | 8 | >20 |
| Total | | 6595 | | 4562(84%) | 559(8%) | | 179(3%) | |

n= total number of patients; *= the study of Ling et al was only evaluated for the presence of cardiac arrhythmias; atropine= addition of atropine in sub-maximal cases; AF= atrial fibrillation or atrial flutter; shVT= short ventricular tachycardia (3-10 complexes); susVT= sustained ventricular tachycardia (>10 complexes); ventrtachyarrhy= complex ventricular tachyarrhythmias; and hypotension= fall of systolic blood pressure compared to rest value (mmHg)

Our comparative success may reflect increasing experience with DASE. For example, one of the earliest studies, by Mertes et al (6), reported a feasibility of only 66%, whereas more recent publications report success rates of 85-90% (2,9).

*Atropine use in patients with severe LV dysfunction.* Atropine was needed more frequently in patients with LVEF ≤25%. One explanation for the increased use of atropine in patients with severe LV dysfunction is decreased beta-adrenergic responsiveness and/or reduced baroreflex sensitivity in patients with stress induced ischemia (2). In a previous study of 360 patients who were not taking beta blockers, we observed a decreased chronotropic response to

dobutamine in patients with acutely induced myocardial ischemia. In the present study, patients with more advanced LV dysfunction (EF ≤25%) developed stress induced ischemia significantly more frequently. This reduced responsiveness to beta-adrenergic stimulation can be overcome by the addition of atropine, which potentiates the effect of β-adrenergic stimulation by blockade of vagal efferents to the heart.

*Side effects.* Hypotension, occurring in 11% of patients, was the most frequently observed side effect. However, it was usually asymptomatic, occurring at the end of the test and necessitated interruption of the test in only 3 cases (1.5%). The supine testing position may explain why hypotension was generally well tolerated. In our experience, stopping the dobutamine infusion and elevating the legs is a simple and effective treatment for hypotension once the test is complete. The occurrence of hypotension was unrelated to the presence or extent of stress induced ischemia, and beta blocker medication was not protective. Hypotension was not more frequent in patients with an EF of ≤25%, compared to those with a EF of 26 to 35% (OR 1.8, 95%CI 0.7 to 4.6). However, compared to pooled data from the literature, hypotension has occurred much more frequently in our patients with LV dysfunction (11% vs 3%). Impaired cardiac function probably explains the high incidence of hypotension in our study (Table 4). Presumably, in patients with significant LV dysfunction dobutamine causes a decrease in systemic vascular resistance that is not matched by a corresponding increase in cardiac output. Stress-induced ischemia does not explain the inadequate cardiac response, because we noted no association between hypotension and echocardiographic or electrocardiographic evidence of ischemia.

Cardiac arrhythmias were the second most frequent side effect observed during DASE. In contrast to hypotension, when cardiac arrhythmias occur the test is often stopped. In our patients with severe LV dysfunction cardiac

arrhythmias occurred at a similar frequency as in pooled data from the literature. Conversely, we consider multifocal ventricular ectopic beats to be more benign.

In contrast to our previous study (8) we found no correlation between the extent of resting wall motion abnormalities and cardiac arrhythmias. This may simply reflect the relative inhomogeneity of the population of patients with significant LV dysfunction. This confirms the findings of Cornel et al (13), who evaluated a smaller group of patients with less severe ventricular dysfunction.

The most widely used antidote for stress induced side effects is intravenous administration of a beta blocker. However, if coronary-spasm is suspected, one should restrain from beta blocker administration, as an unopposed $\alpha$-adrenergic vasoconstriction may aggravate coronary spasm. In these cases and in patients with severe asthma intravenous nitroglycerine or short acting calcium antagonists should be used first.

*Blood pressure response to low dose dobutamine.* Besides improved wall motion, patients with viable myocardium had higher systolic and diastolic blood pressure at low dobutamine infusion rates, compared to patients without this contractile reserve. Presumably the systolic improvement represents transiently improved function of stunned or hibernating myocardium in response to low doses of dobutamine. This initial difference was not apparent at high doses of dobutamine, perhaps indicating inadequate oxygen delivery (i.e. a bi-phasic response).

*Safety.* During the recovery phase no persistent new wall motion abnormalities were observed, indicating that neither prolonged ischemia and/or infarction resulted from DASE. However, special care should be taken in performing a DASE in patients with advanced LV dysfunction as the appearance of new wall motion abnormalities and/or ECG abnormalities, which are a test end-point may be difficult to assess due to pre-existing abnormalities.

*Study limitations.* In the population studied, consisting of a selected group of two hundred patients all awaiting elective coronary revascularization and high male proportion (94%), angina pectoris occurred frequently as all

patients were scheduled for elective coronary revascularization. The presence of viable myocardium was inferred from echocardiographic analysis of wall motion patterns only. The ultimate proof is improved function after revascularization, both echocardiographically and clinically. Such follow-up was not performed in this study.

In conclusion, in patients with more advanced LV dysfunction atropine addition improved diagnostic accuracy of DASE for viability with 34%. The addition of atropine is safe and does not increase the incidence of cardiac arrhythmias or hypotension.

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# CHAPTER 9

# EJECTION FRACTION RESPONSES TO DOBUTAMINE INFUSION PREDICTS FUNCTIONAL RECOVERY AFTER CORONARY REVASCULARIZATION IN PATIENTS WITH LEFT VENTRICULAR DYSFUNCTION

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## ABSTRACT

Quantification of dysfunctional, but viable myocardium has high prognostic value for improvement of left ventricle (LV) function after coronary artery bypass surgery (CABG). Dobutamine stress echocardiography (DSE) can assess viable myocardium by segmental wall motion changes during stress. However, analysis of wall motion is subjective with only moderate interinstitutional agreement (70%) and frequently overestimates functional improvement after CABG. Analysis of ejection fraction (EF) responses during DSE is more objective and allows a more precise quantification of global contractile reserve. The aim of the study was to compare the prognostic value of EF responses and segmental wall motion changes, during DSE for the prediction of improvement of LV function after CABG. Forty patients underwent a DSE prior to CABG. EF responses were assessed at rest, low dose dobutamine and at peak stress using the bi-plane discs method. Wall motion was scored using a 16-segment 5-point model. Resting radionuclide ventriculography (RNV-LVEF), performed before and 8±2 months after CABG was used as an independent reference. Five patients were excluded because of perioperative infarction or poor echo images. In 11/35 patients RNV-LVEF improved >5%. Improvement of EF during dobutamine predicted RNV-LVEF recovery after CABG significantly better than segmental wall motion changes, 72% vs. 53%, p=0.03. A biphasic-EF response (i.e. improvement of ≥10% at low dose and subsequent worsening at peak stress) had the highest predictive value (80%) for late functional recovery. In conclusion, EF response to dobutamine was superior to segmental wall motion changes in the prediction of RNV-LVEF improvement after CABG.


## INTRODUCTION

In patients with severe left ventricular (LV) dysfunction the presence of myocardial viability has important therapeutic and prognostic implications. It predicts functional improvement and long-term outcome after coronary revascularization (CABG).[1-3] Dobutamine stress echocardiography (DSE) is

frequently used to assess the presence of myocardial viability. An improved contraction and or ischemic change during dobutamine of dysfunctional segments characterizes viability. The test is highly feasible and safe, even in patients with poor LV function.[4] However, segmental wall motion assessment during DSE is subjective with moderate interinstitutional agreement (70%) and frequently overestimates the recovery of LV function after CABG.[1,5,6] In contrast, analysis of ejection fraction (EF) response to dobutamine infusion is less subjective and allows a more precise quantification of global contractile reserve.

The aim of the study was to compare the prognostic value of EF responses and segmental wall motion changes, during dobutamine infusion, in predicting recovery of LV function after CABG using resting radionuclide ventriculography (RNV) as an independent reference.

## METHODS

**Patients:** Patients with a resting EF <40% scheduled for coronary artery bypass grafting (CABG) were enrolled in the study. Diabetes mellitus requiring treatment was present in six patients and twenty-eight used angiotensin converting enzyme inhibitors. Exclusion criteria were unstable angina, recent myocardial infarction (<6 months), and valvular disease including significant mitral valve regurgitation.

**Study protocol:** Each patient underwent a DSE and a resting RNV one to two weeks before CABG. A second resting RNV was performed after CABG. LV function recovery was defined as RNV-LVEF improvement of ≥5% after CABG. Patients were divided in two groups on the basis of LV function change after CABG.

**Dobutamine stress echocardiography:** Beta-blocker medication was not discontinued for the study. Dobutamine was administered intravenously by infusion pump at 5 μg/kg/min and increased to 10 μg/kg/min after 5 min (low

dose stage). The infusion rate was then increased by 10 μg/kg/min every 3-min to a maximum of 40 μg/kg/min (high dose stage), and continued for 6 min. If signs and symptoms of ischemia were absent during the high dose stage, and a target heart rate [(220-age) × 0.85 in men, and (200-age) ×0.85 in women)] was not achieved, atropine was administrated intravenously in 0.25 mg increments per minute, to a maximum of 2 mg, while the dobutamine infusion was continued. The ECG was continuously monitored. Blood pressure was measured at end of each stage. The two-dimensional echocardiogram was continuously monitored and recorded during the last minute of each stage and during recovery.

**Wall motion analysis:** LV wall motion was recorded in 3 planes and divided into 16 segments as recommended by the American Society of Echocardiography.[7] Two experienced investigators (G.R., D.P.) performed subjective off-line assessment of wall-motion using a five-point scale: 1 indicated normal; 2, mildly hypokinetic; 3, severely hypokinetic; 4, akinetic, and 5, dyskinetic. For each patient a wall motion score index (WMSI) (total score divided by the number of analyzable segments) was calculated at rest, low dose (10 μg/kg/min), and at peak stress. Wall motion patterns are presented in Table I.

**TABLE I.** Description of segmental wall motion patterns and ejection fraction patterns during low-high-dose dobutamine stress echocardiography

| | Responses | Viable |
|---|---|---|
| Biphasic | Improvement at low-dose and worsening at peak stress | Yes |
| Sustained | Continuous improvement during stress | Yes |
| Ischemic | Only worsening during stress | Yes |
| Scar | No change during stress. For wall motion analysis including akinesia becoming dyskinesia, which is considered to be a mechanical phenomenon. | No |

**EF analysis:** End-diastolic and end-systolic volumes and EF were assessed off-line by two-dimensional biplane discs method at rest, low dose and peak stress.

The biplane discs method measures LV volume using a modification of Simpson's rule described by Schiller et al.[7,8] Two-chamber and four-chamber apical views were recorded. The endocardial borders of these views were digitally traced at end-diastole and end-systole and volumes and ejection fraction were calculated. EF was assessed during five consecutive heartbeats and the average value was calculated. Investigators were blinded to the results obtained by RNV-LVEF. Both wall motion changes and EF changes during dobutamine infusion were classified into four different patterns of contractile response (Table I).

**Variability analysis:** Intra- and interobserver variability of the echo data was assessed in a sub-group of 15 patients. Variability of EF calculation was expressed as 2 standard deviations of the difference of the two readings. EF was obtained at rest, low dose and peak dobutamine stress in two different blind evaluations 30 days apart for intraobserver variability and by two different observers (G.R., R.R) for interobserver variability. Intraobserver variability of EF calculation was 3.3% (mean difference 0.2±1.7%) and interobserver variability was 5.3% (mean difference 0.4±2.6%). The inter- and intra-observer agreement for wall motion interpretation during low-high DSE was respectively 92% and 88%.

**Resting radionuclide ventriculography:** LVEF was assessed by radionuclide ventriculography (RNV) before and 8±2 months after CABG and used as an independent reference. RNV-LVEF was performed at rest with the patient in the supine position after intravenous administration of 740 MBq of $^{99m}$Technetium. Images were acquired in a small field of view gamma camera (Orbiter, Siemens Corp., Erlangen, Germany), oriented in the 45° left anterior oblique view by an automated technique. Recovery of resting RNV-LVEF was considered as the "gold standard" for the assessment of myocardial viability and was defined as an improvement of resting RNV-LVEF >5% after CABG. This criterion has been applied in many other viability studies because it is higher than inter-observer

and intra-observer variability of the technique in patients with left ventricular dysfunction.[9]

**Statistical analysis:** EF responses and wall motion score changes were calculated at rest, low-dose and peak dose dobutamine. Data are presented by mean value ± SD. Patients were divided into two groups based on presence or absence of an improvement of resting RNV-LVEF of >5% after CABG. Data of the two groups were compared and differences were evaluated by paired Student *t*-tests, and by two-way analyses of variance (ANOVA) with repeated measures for the dobutamine dose-steps. A p-value <0.05 was considered significant.

## RESULTS

**Study population:** Forty patients were enrolled in the study. All patients presented with heart failure symptoms with mean NYHA class of 3.1±0.5. Eight patients presented also with angina pectoris. All patients were studied more than six months after myocardial infarction and were stable during the entire study period. Five patients were excluded: three of them because of inadequate two-dimensional images to perform measurements by biplane discs method, and two because of a non-fatal myocardial infarction during CABG. The remaining 35 patients (29 males, mean age 59±11 years) represented the study population. Coronary angiography was performed in all patients; the mean number of affected vessels was 2.9±0.2. The resting RNV-LVEF and echo-EF were respectively 33.7±9.7% (range 38-15%) and 33.6±12.3% (range 39-14%) (p=0.97). Resting RNV-LVEF was repeated 8±2 moths after CABG. Patients were divided in two groups on the basis of the response of LV function after CABG. RNV-LVEF improved >5% in 11 patients (group A) whereas in 24 patients EF remained unchanged or worsened (group B). Baseline characteristics of the two groups were similar (table II).

**TABLE II.** Baseline characteristics of patients according to left ventricular function improvement after CABG

| | Improvement (n=11) (group A) | No improvement (n=24 ) (group B) | p value |
|---|---|---|---|
| Age (years) | 58.8±12.0 | 58.8±10.3 | 1.00 |
| Female gender | 18% (2/11) | 17% (4/24) | 0.73 |
| Previous anterior MI | 46% (5/11) | 46% (11/24) | 1.0 |
| Previous inferior MI | 27% (3/11) | 29% (7/24) | 0.78 |
| Both anterior and inferior MI | 27% (3/11) | 25% (6/24) | 0.77 |
| Diabetes mellitus | 18% (2/11) | 17% (4/24) | 0.73 |
| Beta-blocker therapy | 18% (2/11) | 17% (4/24) | 0.73 |
| NYHA class | 3.1±0.4 | 3.0±0.5 | 0.56 |
| Angina Pectoris | 18% (2/11) | 25% (6/24) | 0.98 |
| Number affected vessels | 3.0±0 | 2.96±0.2 | 0.51 |
| End-diastolic volume by echo (ml) | 173.9±61.8 ml | 187.6±60.8 | 0.54 |
| Rest pre CABG EF by RNV | 33.5±13.2% | 33.8±8.1% | 0.93 |
| Rest pre CABG EF by echo | 33.4±11.7% | 33.8±12.7% | 0.92 |
| Rest pre CABG WMSI | 2.31±0.77 | 2.31±0.67 | 1.00 |

CABG = coronary artery bypass grafting; MI = myocardial infarction; EF = ejection fraction; RNV = radionuclide ventriculography; WMSI = wall motion score index.

During DSE, EF improvement from rest to low dose was statistically higher in-group A than in-group B (p=0.01), whereas WMSI improvement was higher in group A but not significantly different from group B (p=0.06)(table III).

**TABLE III.** Comparison of different variables according to left ventricular function improvement after CABG

| | Improvement (n=11) (group A) | No improvement (n=24) (group B) | p value |
|---|---|---|---|
| EF improvement at low dose dobutamine | +12.2±5.3 | +5.6±7.6 | 0.01 |
| Number of improving segments at low dose dobutamine. | 6.8±3.1 | 4.7±2.8 | 0.06 |
| WMSI improvement at low dose dobutamine | -0.42±0.18 | -0.29±0.19 | 0.06 |
| EF worsening at peak stress (ischemia) | -4.2±7.3 | -0.11±8.3 | 0.17 |
| Number of worsening segments at peak stress | 3.3±3.3 | 2.3±2.4 | 0.30 |

CABG = coronary artery bypass grafting; EF = ejection fraction; WMSI = wall motion score index.

At peak stress group A showed higher reduction of EF (ischemia), but the difference was not statistically significant (p=0.17) (table III) (figure 1).

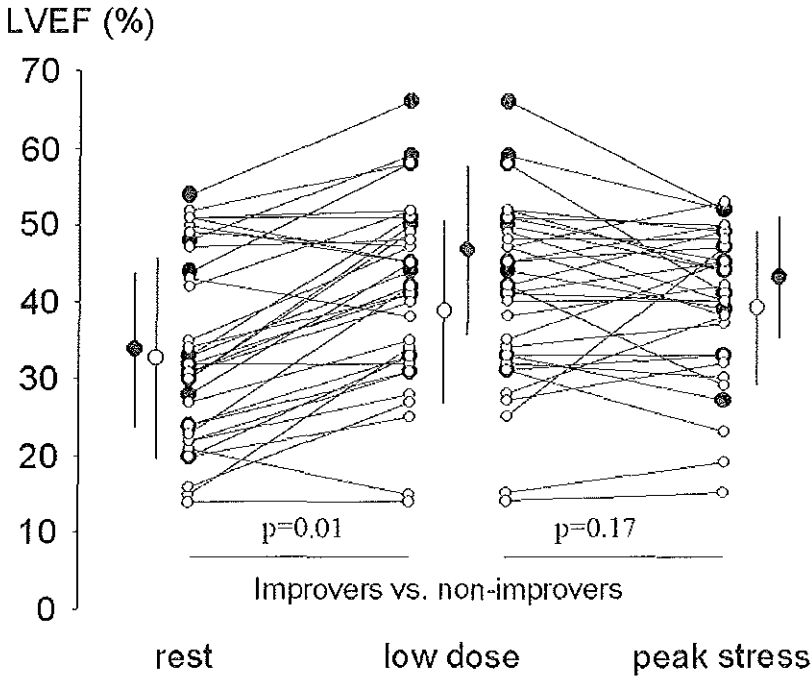


**Fig 1.** Scatter plots showing the individual EF responses from rest to low-dose dobutamine and from low-dose dobutamine to peak stress. The solid rounds represent group A (improvement of RNV-EF after revascularization) and open rounds represent group B (non-improvement).

Analysis of EF changes showed that the positive predictive value for LV function recovery after CABG was proportional to the degree of EF improvement at low dose DSE, whereas negative predictive value was inversely related. Analysis of the four different patterns of contractile response showed that biphasic response (viability plus ischemia) had the best positive predictive value for LV function improvement after revascularization. A decrease of EF of ≥5% from low dose to peak stress increased the positive predictive value for resting RNV-LVEF improvement after CABG for every degree of EF improvement at low dose dobutamine. Moreover, resting RNV-LVEF recovery

after revascularization was significantly higher in patients with a biphasic response when compared to patients with the three other predefined patterns of response (respectively +8.5±10.2% vs. -0.96±5.7%; p=0.002).

Mean predictive value for resting RNV-LVEF improvement after CABG was significantly higher when viability and ischemia were assessed by EF changes than by segmental wall motion changes (72% vs. 53%; p=0.03). EF improvement at low dose of ≥10% and worsening at peak stress of ≥5% (biphasic response) had the best predictive value (80%) for LV function improvement after CABG (table IV).

**TABLE IV.** Predictive value of ejection fraction response and segmental wall motion response to dobutamine infusion for left ventricular function recovery after CABG

| Improvement At low dose | Worsening at peak | Positive PV | Negative PV | Overall PV | Mean overall PV | |
|---|---|---|---|---|---|---|
| EF ≥5% | no | 40%(10/25) | 90% (9/10) | 54% (19/35) | | |
| EF ≥5% | EF ≥5% | 58% (7/12) | 87% (20/23) | 77% (27/35) | | |
| EF ≥10% | no | 60% (9/15) | 85% (17/20) | 74% (26/35) | **72%** (25.2/35) | |
| **EF ≥10%** | **EF ≥5%** | **70%** (7/10) | **84%** (21/25) | **80%** (28/35) * | | |
| EF ≥10% | EF ≥10% | 75% (3/4) | 74% (23/31) | 74% (26/35) | | **P=0.03** |
| ≥2 segments | no | 31% (9/29) | 66% (4/6) | 37% (13/35) | | |
| ≥2 segments | ≥2 segments | 35% (6/17) | 61% (11/18) | 48% (17/35) | | |
| ≥4 segments | no | 32% (7/22) | 69% (9/13) | 46% (16/35) | **53%** (18.8/3) | |
| ≥4 segments | ≥2 segments | 43% (6/14) | 76% (16/21) | 63% (22/35) | | |
| **≥4 segments** | **≥4 segments** | **56%** (5/9) | **81%** (21/26) | **74%** (26/35) * | | |

* Best predictive value among EF response and segmental wall motion response to dobutamine (both in patients with a biphasic response). CABG = coronary artery bypass grafting; PV = predictive value.

## DISCUSSION

Dysfunctional, but viable myocardium is a clinical situation in which impaired LV function at rest is reversible after revascularization. Before recommending revascularization an estimate of the extent of myocardial viability is important to determine the expected improvement of LV recovery and patient long-term

outcome, since the risk of perioperative complications and mortality is considerable.[3,10,11] The most commonly used tests for diagnosing myocardial viability are DSE, thallium or sestamibi single-photon emission computed tomography (SPECT) and positron emission tomography (PET).[12] Using DSE, the common criteria to identify viability are improved wall thickening in at least two adjacent abnormal segments of LV at low dose dobutamine infusion.[13] However, the improvement of LV function after CABG is frequently less than expected.[1,14] Therefore, we evaluated whether EF changes during DSE could provide a better marker of myocardial viability.

**Ejection fraction improvement at low dose.** Late functional improvement of LV function after CABG was related to the degree of EF improvement at low dose dobutamine ($p=0.01$). An EF improvement $\geq 10\%$ was predictive for postoperative functional recovery in 60% of patients, whereas an EF improvement $<5\%$ was predictive for absence of postoperative functional recovery in 90% of patients. These data suggest that the degree of EF improvement at low dose DSE reflect the extent of hibernating myocardium.

**Biphasic response.** Recent studies demonstrated that a biphasic response during DSE is the best predictive echocardiographic pattern for recovery of function after revascularization.[14,15] Sustained improvement, although a marker of residual viability, is a poor predictor. This may be related to the absence of ischemia at peak stress, indicating the absence of a critical stenosis. We analyzed different patterns of response to DSE using EF changes as a test result rather than segmental wall motion changes. The presence of a biphasic response (EF increasing at low dose $\geq 10\%$ and EF decreasing at peak $\geq 5\%$) had the highest predictive value (80%) for post-operative LV function recovery (table 4). Moreover, resting LVEF recovery after revascularization was significantly

higher in patients with a biphasic response when compared to patients that presented one of the other three predefined patterns (p=0.002).

**Ejection fraction compared to wall motion.** Mean predictive value for functional recovery after CABG was significantly higher when viability was assessed by EF responses than by segmental wall motion changes during dobutamine infusion (72% vs. 53%; p=0.03) (table 4). In the patients with post-CABG improvement of RNV-LVEF WMSI improvement at low dose dobutamine was higher but not significantly different from group B (p=0.06). This was probably because of the small sample size, whereas EF improvement at low dose dobutamine was higher in group A and significantly different from group B (p=0.01) (table 3).

**Rationale for use of ejection fraction changes.** EF changes during DSE allow a global quantitative assessment of viability less subjective than segmental wall motion score. EF calculation does not needs dedicated echo readers and is an easy method common to cardiological community at large. On the other side EF, as an index of global function, does not provide information on the segmental nature of the myocardial dysfunction and is influenced by heart rate, preload and afterload. Being a ratio, it offers no information on absolute LV volumes. However, patients evaluated for viability have diffuse coronary disease and global LV dysfunction: 97% (36/37) of our patients had extensive coronary disease ("three vessel disease") and almost all the segments were hypo-akinetic (mean rest WMSI=2.31±0.71). For this reason LV-function recovery results from global function improvement rather than wall motion improvement of few segments.

**Quantification of the extent of viable myocardium:** A strong correlation between the number of dysfunctional segments with contractile reserve during DSE and the improvement of LVEF after revascularization has been found

recently.[16,17] The extension of dysfunctional but viable myocardium predicts a better prognosis and allows risk stratification of patients with LV dysfunction referred for bypass surgery.

Wall motion score provides the number of improving segments but roughly and subjectively quantify the amount of improvement of each segment. In most of segments the improvement is of one grade only (100% of our patients) even using a five-point scale. Moreover most of the centers base the classification of DSE on change in wall motion (improvement or not) rather than absolute wall motion score.[10,] This method has a lower variability but does not take into account the degree of wall motion improvement of each segment. Probably, EF responses can better quantify the amount of global improvement of LV function at low dose dobutamine. This can explain the higher predictive value of EF changes for LV function recovery after CABG.

**Study limitations.** The number of patients in our study was relatively small and follow-up coronary angiography was not performed. However, all infarct zones underwent adequate revascularization as shown by surgical reports (39/40 patients received at least 3 grafts), and two patients that presented perioperative infarction were excluded from the analysis. Therefore, we can assume that the revascularization was complete in all patients.

During DSE we used a two-dimensional acquisition method to calculate LVEF that is known to have high inter-observer and intra-observer variability. However the results of the study suggest to use EF responses during a single DSE and not to use EF absolute values for prediction of LV function recovery. Therefore we were interested only in intraobserver variability that is known to be lower than interobserver variability.[18] A previous study showed that intraobserver variability for 2-D Simpson's method in our laboratory was 3.5%.[18] In this study intraobserver variability, expressed as 2 standard deviation of the two different readings, was 3.3%. This value was more than twice lower

of the main EF change cut-off value suggested by the results of the study (improvement of ≥10% at low dose DSE).

**Conclusions and clinical implications.** In patients with LV dysfunction, EF response to dobutamine infusion has an high prognostic value in predicting LV function recovery after CABG, superior to traditional wall motion score evaluation. The degree of EF improvement at low dose dobutamine reflects the extent of hibernating myocardium. EF worsening at peak stress is a marker of ischemia. EF improvement of ≥10% at low dose together with EF worsening of ≥5% at peak stress (biphasic response) identifies 80% of patients who will benefit from revascularization.

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# CHAPTER 10

# EARLY RECOVERY OF WALL MOTION ABNORMALITIES AFTER RECANALIZATION OF CHRONIC TOTALLY OCCLUDED CORONARY ARTERIES: A DOBUTAMINE-ATROPINE ECHOCARDIOGRAPHIC PROSPECTIVE SINGLE CENTER EXPERIENCE

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## ABSTRACT

**Background.** Patients with symptomatic myocardial ischemia due to a chronic totally occluded coronary (TOC) artery are usually referred for coronary artery bypass surgery. As in recent years guidewire technology has improved considerably, percutaneous coronary angioplasty became a useful technique in opening chronic TOC arteries. We evaluated the early functional results of successful percutaneous recanalization by performing dobutamine stress echocardiography (DSE).

**Methods.** Fifteen patients with a chronic TOC artery who underwent a successful recanalization were prospectively studied. Each patient had a DSE within 24 h before and 48 h after the procedure. Wall motion was scored according to a 16 segments/5 points model. A clinical and angiographic follow-up of 6 months was obtained.

**Results.** The wall motion score index at rest improved from 1.26 ± 0.23 pre- to 1.22 ± 0.21 post-procedure ($p < 0.05$). Of those 10 segments that improved at rest, 7 were collateral-recipients and 3 were collateral-donors. The number of ischemic segments decreased from 46 pre- to 4 post-procedure ($p < 0.0001$). Wall motion score index at peak stress improved from 1.34 ± 0.20 pre- to 1.15 ± 0.12 post-procedure ($p < 0.05$). DSE was positive for ischemia in 15 patients pre- and 2 patients post-procedure ($p < 0.0001$). Angina was present in 12 patients pre- and in 2 patients after recanalization ($p < 0.0001$). Two patients (13%) had angiographic reocclusion and 5 (33%) restenosis after 6 months of follow-up.

**Conclusions.** Successful percutaneous recanalization of chronic TOC artery results in an early improvement of both clinical status and resting or stress-induced wall motion abnormalities, as detected by DSE.


## INTRODUCTION

Angina pectoris is usually related to a significant stenosis of one or more coronary arteries (1). Progression of a stenosis may lead to chronic total occlusion of the vessel, also in the absence of myocardial infarction (2). Patients

with a chronic totally occluded coronary (TOC) artery may experience exertional angina, possibly due to an inverted shunt of coronary flow from the occluded segment(s) through collaterals to the non-occluded segments in times of increased blood flow requirements (3). Therapeutic options are limited, as medical treatment is not always sufficient and coronary angioplasty is associated with both a high failure rate (4) and a high restenosis or reocclusion rate. Therefore, patients with significant symptoms are routinely referred for coronary bypass surgery (5). However, various recent improvements in guidewire technology have considerably increased the success rates of percutaneous attempts at recanalization (6-8). The efficacy of successful recanalization has been proven in the late follow-up by exercise test (9) and early after the procedure by cardiac pacing (10,11). Dobutamine stress echocardiography (DSE), an established technique for the detection of myocardial ischemia (12), has not been used to test the effects of recanalization of TOC artery early after a successful procedure. Therefore, we performed DSE to investigate whether a successful procedure results in an early reduction of myocardial ischemia in patients who underwent guidewire percutaneous recanalization of a chronic TOC artery.

## METHODS

**Patient population:** Patients were prospectively included according to presence of angina pectoris and/or objective signs of ischemia in relation to a chronic TOC artery. An attempt was made to recanalize the target occlusion, for which various guidewire technologies were used. This included the use of the excimer laser guide wire (Spectranetics Corp., Colorado Springs, CO) in case of a failed attempt by using conventional guide wires. An informed consent was obtained from all patients, according to the guidelines of the Medical Ethics Committee of the University Hospital Rotterdam.

**Angiographic data:** A TOC artery was considered chronic if more than 4 weeks of angiographically proven duration (4) elapsed between the diagnostic

coronary angiography and the date of the attempt at recanalization. For each patient the echocardiographic 16 segments model (13) was assigned to each coronary field and when collaterals were found, the corresponding echocardiographic segments were divided in either collateral-donors or collateral-recipients.

**Dobutamine stress echocardiography:** Dobutamine was administered: 10 μg/kg/min for 3 minutes, increasing by 10 μg/kg/min every 3 minutes to a maximum of 40 μg/kg/min. In submaximal non-diagnostic DSE, atropine was added: 0.25 mg repeated to a maximum of 1.0 mg in 4 minutes. Criteria for a positive DSE were stress-induced new or worsened wall motion abnormalities. Additional criteria were: ST-segment elevation = 0.1 mV after the J point in patients without prior myocardial infarction and horizontal or downsloping ST-segment depression = 0.1 mV 80 ms after the J point and angina. Pre-test criteria for interruption of DSE were: achieved 85 % of the maximal for sex and age predicted target heart rate, achieved maximal dose of both dobutamine and atropine, new significant wall motion abnormalities, horizontal or downsloping ST-segment depression >0.2 mV 80 ms after the J point compared with the baseline, ST-segment elevation >0.1 mV 80 ms after the J point in patients without prior myocardial infarction, severe angina, symptomatic reduction in systolic blood pressure >40 mm Hg from baseline, hypertension (blood pressure >240/120 mm Hg), significant cardiac tachyarrhythmias and any serious side effect attributed to dobutamine infusion, such as e.g. headache, dizziness or a symptomatic vagal activation (12).

**Echocardiographic imaging:** The left ventricle was divided in 16 segments (13) and visually assessed for both systolic wall thickening and inward wall motion. Each segment was graded on a 5-point scoring system (1 = normo- or hyperkinesis; 2 = mild hypokinesis; 3 = severe hypokinesis; 4 = akinesis and 5 = dyskinesis ) by an experienced observer blinded to both pre- and post-procedural data. The scoring was repeated by the same observer and in case of

intra-observer disagreement the judgment of a second observer was obtained. Ischemia was defined as a deterioration in score at any stage of the test in one or more segments, unless an akinetic segment at rest and low dose dobutamine became dyskinetic at peak stress (14). Wall motion score index was defined as the sum of the scores of the individual segments divided by the total number of segments. The medication used during the two DSE was not significantly different. The beta-blocking agents were withdrawn 3 days before the first DSE and not reintroduced before the second DSE.

**The angioplasty procedure:** The attempt at recanalization was performed typically using either the Choice PT wire (Scimed, Minneapolis, MN), Terumo Crosswire (Terumo, Japan) or the Prima laser wire (Spectranetics Corp., CO). The technique of the laser wire procedure has been extensively described elsewhere (6,7,15). After successful crossing of the occlusion by the guidewire, angioplasty was performed either by balloon angioplasty, or a combination of excimer laser coronary angioplasty (ELCA) using the Spectranetics 1.4 mm or 1.7 mm Vitesse-C rapid exchange coronary catheters with adjunctive balloon angioplasty. Routinely, one or more intracoronary stents were implanted to obtain an optimal procedural result. Following a successful angioplasty, patients were kept on a heparin infusion for 24 hours, maintaining the activated prothrombin time (APTT) between 60 and 90 seconds.

**Follow-up study**: All patients underwent a 6 months clinical and angiographic follow-up. Functional classification was performed according to the Canadian Cardiovascular Society. Restenosis was defined as >50% diameter stenosis at the treated coronary site, relative to the baseline value before the procedure, as determined by on-line quantitative angiographic analysis.

**Statistical analysis:** Unless specified, values were expressed as mean ± SD. Comparison of variables was performed with two-tailed Student's t test for continuous variables and chi-square test for discrete variables. Differences of $p \leq 0.05$ were considered significant.

## RESULTS

**Protocol compliance:** Of 34 consecutive patients with a chronic TOC artery and a DSE before the procedure, 22 (65%) patients were successfully recanalized. Of these, 2 patients were excluded due to poor echocardiographic image quality and 5 for no adherence to the protocol. Therefore, 15 patients fulfilled the study protocol, by undergoing two DSE: before (<24h) and after (<48h) successful recanalization. The pre-test baseline characteristics are given in Table I and confirm that the patient population is representative of current clinical practice with coronary angioplasty.

TABLE I. Pre-test baseline characteristics of the patient population.

| Subject | Age | Sex | AP (CCS) | Prior MI | Hypertension | Smoke | Diabetes | Hypercholesterolemia | FamHx |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 48 | F | 3 | 0 | + | 0 | + | 0 | 0 |
| 2 | 71 | F | 3 | + | + | 0 | 0 | 0 | 0 |
| 3 | 39 | M | 2 | + | 0 | + | 0 | + | + |
| 4 | 57 | M | 3 | + | 0 | + | 0 | 0 | + |
| 5 | 69 | M | 3 | 0 | + | 0 | 0 | 0 | 0 |
| 6 | 62 | M | 3 | 0 | 0 | 0 | 0 | 0 | + |
| 7 | 36 | M | 2 | 0 | 0 | + | 0 | + | 0 |
| 8 | 67 | M | 3 | + | 0 | 0 | 0 | + | 0 |
| 9 | 54 | M | 3 | 0 | 0 | + | 0 | + | 0 |
| 10 | 67 | F | 3 | + | 0 | 0 | 0 | 0 | 0 |
| 11 | 67 | F | 3 | + | + | 0 | 0 | + | 0 |
| 12 | 62 | M | 3 | + | + | + | 0 | 0 | 0 |
| 13 | 45 | M | 2 | + | 0 | 0 | 0 | + | + |
| 14 | 58 | M | 2 | 0 | + | 0 | 0 | 0 | 0 |
| 15 | 50 | M | 4 | + | 0 | + | 0 | 0 | 0 |
| Mean ± SD | 56 ± 11 | | 2.8 | | | | | | |
| Total | | 11 M | | 9 MI | 6 | 6 | 1 | 6 | 4 |

AP = angina pectoris; CCS = Canadian Classification; F = female; FamHx = family history, M = male; MI = myocardial infarct.

**Angiographic data:** The angiographic data are given in Table II. The TOC artery was right coronary artery (RCA) in 7 patients (47%), left anterior descending coronary artery (LAD) in 7 (47%) and left circumflex coronary artery (LCX) in one patient (6%).

**Dobutamine stress echocardiography:** The hemodynamic data of DSE pre- and post-procedure are given in Table III. As shown, there

was no significant difference between the pre- and post-procedural data. Wall motion score index (Table IV) at rest improved from 1.26 ± 0.23 pre- to 1.22 ± 0.21

**TABLE II.** Angiographic and pre- and post-procedure clinical data.

| Subject | Occluded vessel | Collateral-donor vessel (s) | Angina | | ST-T | |
|---|---|---|---|---|---|---|
| | | | Pre | Post | Pre | Post |
| 1 | RCA | LAD | + | 0 | 0 | + |
| 2 | RCA | LAD | + | + | 0 | 0 |
| 3 | RCA | LAD, LCX | 0 | 0 | 0 | 0 |
| 4 | RCA | LAD | 0 | 0 | 0 | 0 |
| 5 | RCA | LAD, RCA | + | 0 | + | 0 |
| 6 | RCA | LAD, LCX | + | 0 | 0 | 0 |
| 7 | RCA | LAD | + | 0 | 0 | 0 |
| 8 | LAD | RCA | + | 0 | 0 | 0 |
| 9 | LAD | RCA | + | 0 | 0 | 0 |
| 10 | LAD | LCX, RCA | + | 0 | 0 | + |
| 11 | LAD | LCX, RCA | + | 0 | + | + |
| 12 | LAD | LCX, RCA | 0 | 0 | + | 0 |
| 13 | LAD | RCA | + | + | + | + |
| 14 | LAD | RCA | + | 0 | + | 0 |
| 15 | LCX | LAD | + | 0 | 0 | + |
| Total | 48 | | 12 | 2* | 5 | 5 |

LAD = left anterior descending coronary artery; LCX = circumflex coronary artery; Post = post-procedure; Pre = pre-procedure; RCA = right coronary artery, * = $p < 0.0001$ pre- vs post-procedure.

**TABLE IV.** Wall motion analysis pre- and post-procedure.

| Subject | WMA resting segments | | Ischemic segments | | Resting WMSI | | Stress WMSI | |
|---|---|---|---|---|---|---|---|---|
| | Pre | Post | Pre | Post | Pre | Post | Pre | Post |
| 1 | 0 | 0 | 1 | 0 | 1.00 | 1.00 | 1.13 | 1.00 |
| 2 | 3 | 1 | 3 | 1 | 1.19 | 1.06 | 1.19 | 1.06 |
| 3 | 5 | 5 | 1 | 0 | 1.31 | 1.31 | 1.25 | 1.19 |
| 4 | 3 | 3 | 2 | 0 | 1.31 | 1.31 | 1.19 | 1.13 |
| 5 | 2 | 0 | 2 | 0 | 1.13 | 1.00 | 1.13 | 1.00 |
| 6 | 3 | 3 | 6 | 0 | 1.31 | 1.31 | 1.50 | 1.25 |
| 7 | 0 | 0 | 5 | 0 | 1.00 | 1.00 | 1.38 | 1.00 |
| 8 | 8 | 7 | 1 | 0 | 1.75 | 1.69 | 1.81 | 1.25 |
| 9 | 7 | 7 | 5 | 0 | 1.50 | 1.50 | 1.38 | 1.31 |
| 10 | 0 | 0 | 1 | 0 | 1.00 | 1.00 | 1.06 | 1.00 |
| 11 | 4 | 4 | 7 | 0 | 1.25 | 1.25 | 1.56 | 1.25 |
| 12 | 4 | 3 | 4 | 0 | 1.25 | 1.19 | 1.50 | 1.13 |
| 13 | 4 | 4 | 5 | 3 | 1.25 | 1.25 | 1.31 | 1.25 |
| 14 | 0 | 0 | 2 | 0 | 1.00 | 1.00 | 1.31 | 1.19 |
| 15 | 6 | 2 | 1 | 0 | 1.63 | 1.38 | 1.38 | 1.31 |
| Sum and means (±SD) | 49 | 39 | 46 | 4* | 1.26 ± 0.23 | 1.22 ± 0.21* | 1.34 ± 0.20 | 1.15 ± 0.12* |

Post = post-procedure; Pre = pre-procedure; WMA = wall motion abnormalities; WMSI = wall motion score index; * = $p < 0.05$ pre- vs post-procedure.

**TABLE III.** Hemodynamic data at rest and peak dobutamine pre- (1) and post- (2) procedure.

| (1) Pre-procedure | | | | | | |
|---|---|---|---|---|---|---|
| Subject | HR rest | HR peak | SBP rest | SBP peak | DP rest | DP peak |
| 1 | 64 | 116 | 140 | 125 | 8,960 | 14,500 |
| 2 | 80 | 133 | 92 | 86 | 7,360 | 11,438 |
| 3 | 75 | 135 | 147 | 163 | 11,025 | 22,005 |
| 4 | 90 | 143 | 153 | 153 | 13,770 | 21,879 |
| 5 | 61 | 105 | 142 | 124 | 8,662 | 13,020 |
| 6 | 71 | 120 | 110 | 115 | 7,810 | 13,800 |
| 7 | 74 | 117 | 145 | 180 | 10730 | 21,060 |
| 8 | 70 | 130 | 163 | 144 | 11,410 | 18,720 |
| 9 | 70 | 138 | 112 | 107 | 7,840 | 14,766 |
| 10 | 60 | 115 | 130 | 130 | 7,800 | 14,950 |
| 11 | 74 | 142 | 137 | 103 | 10,138 | 14,626 |
| 12 | 70 | 132 | 98 | 100 | 6,860 | 13,200 |
| 13 | 60 | 132 | 135 | 135 | 8,100 | 17,820 |
| 14 | 59 | 91 | 145 | 151 | 8.555 | 13.741 |
| 15 | 50 | 126 | 110 | 125 | 5,500 | 15,750 |
| Mean ± SD: | 68 ± 10 | 125 ± 14 | 130 ± 21 | 129 ± 25 | 8,968 ± 2100 | 16,085 ± 3,392 |

DP = double (heart rate • systolic blood pressure) product in beats.mm Hg/min; HR = heart rate in beats/min; SBP = systolic blood pressure in mm Hg.

| (2) Post-procedure | | | | | |
|---|---|---|---|---|---|
| HR rest | HR peak | SBP rest | SBP peak | DP rest | DP peak |
| 80 | 127 | 90 | 66 | 7,200 | 8,382 |
| 90 | 130 | 86 | 80 | 7,740 | 10,400 |
| 85 | 130 | 110 | 100 | 9,350 | 13,100 |
| 80 | 137 | 132 | 162 | 10,560 | 22,194 |
| 62 | 121 | 141 | 107 | 8,742 | 12,947 |
| 70 | 120 | 120 | 120 | 8,400 | 14,400 |
| 80 | 133 | 125 | 150 | 10,000 | 19,950 |
| 76 | 131 | 126 | 109 | 9,576 | 14,279 |
| 74 | 144 | 137 | 131 | 10,138 | 18,864 |
| 72 | 113 | 111 | 86 | 7,992 | 9,718 |
| 88 | 115 | 115 | 95 | 10,120 | 10,925 |
| 77 | 158 | 112 | 129 | 8,624 | 20,382 |
| 84 | 142 | 120 | 120 | 10,080 | 17,040 |
| 70 | 118 | 126 | 110 | 8.820 | 12.980 |
| 50 | 117 | 108 | 125 | 5,400 | 14,625 |
| 76±10 | 130 ± 13 | 117 ±15 | 113 ± 26 | 8,849± 1,380 | 14,679 ± 4,185 |

after the procedure ($p < 0.05$). Of 10 segments (in 5 patients) that improved at rest, 7 were collateral-recipients and 3 were collateral-donors. DSE was positive for ischemia in 15 patients pre- and in 2 patients post-procedure ($p < 0.0001$). The number of ischemic segments decreased from 46 pre- to 4 post-procedure ($p < 0.0001$). Wall motion score index at peak stress improved from 1.34 ± 0.20

pre- to 1.15 ± 0.12 post-procedure ($p < 0.05$). Angina was experienced during DSE by 12 patients pre- and 2 patients post-procedure ($p < 0.0001$) (Table II).

**Follow-up data:** A 6 months clinical and angiographic follow-up was available for all patients. No major cardiac events such as death, myocardial infarction, coronary bypass surgery, repeated PTCA or hospital admission for unstable angina occurred in this patient group. At six month follow-up four patients (27%) were in stable angina, while angiographycally two patients had a reocclusion (13%) and five (33%) had restenosis.

## DISCUSSION

Shortly after the introduction of coronary angioplasty by Andreas Gruentzig in 1977, this technique was attempted in patients with chronic TOC arteries. Successive investigators reported on the relatively low procedural success rates and high restenosis rates following successful percutaneous recanalization (16-18). However, the long-term clinical improvement (19,20), the increased resting left ventricular function and the reduction of exercise-induced ischemic symptoms in the late follow-up of patients after successful recanalization (7), supported the continuing effort in developing more effective technologies for percutaneous treatment of chronic TOC arteries. Typical examples of improved technology are the introduction of hydrophilic coated guide wires and the excimer laser guide wire.

Thus far, no study documented the early functional impact of a successful percutaneous recanalization of a chronic TOC artery, in terms of resting regional left ventricular function and stress-induced myocardial ischemia. Obviously, a successful revascularization procedure should result in a reduction of myocardial ischemia. We used DSE, an established technique for the detection of myocardial ischemia, 24 h before and within 48 h after a successful revascularization to evaluate the immediate functional outcome of the procedure. As a main result of our study, we found a significant improvement of stress-induced wall motion abnormalities. Therefore, DSE is helpful to document

objectively the early functional outcome of a successful procedure. Besides, we also detected a significant improvement of resting wall motion abnormalities, involving 7 segments of the collateral-recipient coronary artery and 3 segments of the collateral-donor. These result suggests the presence of dysfunctional but viable myocardium, which improves early after revascularization, consistently with previous studies documenting an immediate functional recovery after revascularization (21). Viable myocardium is also present in some collateral-donor segments (although supplied by a non-diseased coronary artery) possibly through a stealing effect resulting in repetitive stunning. The immediate increase of both coronary flow and flow reserve after revascularization, involving both collateral-recipient and collateral-donor segments, parallel with the angiographic disappearance of collaterals, may be the vascular substrate of the early functional recovery detected in our patients (22).

Although not aim of the present study, a reocclusion rate of 13% and a restenosis rate of 33% at six-month follow-up angiography appear significantly better than previously reported rates of the literature. The consequent use of intracoronary stents to stabilize the angioplasty results could be responsible for this favorable outcome.

## STUDY LIMITATIONS

A possible limitation of the present study is the inclusion of patients after a successful revascularization only. However, the focus of this study was not the evaluation of the success rate of percutaneous revascularization in chronic TOC arteries, but the effectiveness of DSE to document the early functional and clinical impact of a successful revascularization. We feel that the demonstration of improvement of myocardial function early after a revascularization of chronic TOC artery is important, and may support further efforts to improve non-surgical techniques for revascularization of TOC arteries.

## CONCLUSIONS

In patients with symptoms and/or signs of myocardial ischemia dependent from a chronic TOC artery, DSE performed before and within 48 hours after a successful percutaneous recanalization documents a significant improvement of both clinical status and resting or stress-induced wall motion abnormalities.

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# CHAPTER 11

# CARDIAC EVALUATION USING DOBUTAMINE-ATROPINE STRESS ECHOCARDIOGRAPHY IN HYPOTENSION-PRONE AND HYPOTENSION-RESISTANT HEMODIALYSIS PATIENTS

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## ABSTRACT

Cardiac evaluation using dobutamine-atropine stress echocardiography in hypotension-prone [HP] and hypotension-resistant [HR] hemodialysis patients.

*Background:* Hypotension during hemodialysis occurs frequently but the precise mechanism remains unclear. In this study the presence of myocardial ischemia and myocardial contractile reserve during infusions of the beta-adrenergic receptor agonist dobutamine were assessed by means of stress echocardiography [DSE] in hypotension-prone [HP] and hypotension-resistant [HR] hemodialysis patients.

*Methods:* Eighteen HP patients [age 53±6 years] were compared with 18 HR patients [age 53±3 years], matched with respect to duration of hemodialysis, and cardiovascular history. New wall abnormalities during dobutamine stress reflect the presence of myocardial ischemia, whereas the increase in stroke index and cardiac index reflects myocardial contractile reserve.

*Results:* Wall motion score at rest [1.42±0.53 versus 1.44±0.57] and dobutamine-induced new wall motion abnormalities [4 versus 3 patients] between HP and HR patients were similar, but responses of cardiac index, stroke index and systolic blood pressure to dobutamine between the two groups were different. Notwithstanding a similar cardiac index at rest [2.4±1.1 L/min/$m^2$ in HP and 2.8±1.2 L/min/$m^2$ in HR patients], were dobutamine-induced increments in cardiac index considerably smaller in the former [0.8±1.3 l/min/$m^2$] than in the latter patients [2.3±1.6 l/min/$m^2$, p=0.002], predominantly because of a progressive decrease in stroke index in the HP patients.

*Conclusion*: Impaired myocardial contractile reserve rather than ischemia is predominant in HP patients. This impaired myocardial contractile reserve may play a role in the development of hemodialysis-induced hypotension.

## INTRODUCTION

Hypotension during hemodialysis occurs in approximately 30% of patients [1]. The pathophysiology of hemodialysis-induced hypotension is multifactorial, ranging from primarily patient related factors such as underlying coronary artery disease, diastolic and systolic dysfunction [2], to more hemodialysis related factors such as speed and amount of ultrafiltration and used dialysate [3].

Atherosclerosis occurs frequently in patients with renal insufficiency. Cardiovascular disease is reported to cause about 50% of deaths among patients with end-stage renal failure [2]. Factors causally related to this high frequency of coronary artery disease are hypertension, hypertriglyceridemia, and hypercholesterolemia [4]. More recently, hyperhomocysteinemia, endothelial dysfunction and increased oxidant stress have been identified as additional cardiovascular risk factors [5].

Assessment of left ventricular function and presence of coronary artery disease can be performed by dobutamine-atropine stress echocardiography [DSE]. At low infusion rates [10 µg/kg/min] dobutamine predominantly exerts an inotropic effect, whereas at higher infusion rates the chronotropic effect prevails. Hence with the lower infusion rates of dobutamine information about myocardial contractile reserve, whereas with higher infusion rates information about the presence of ischemia is obtainable. Ischemia is detected by DSE as new wall motion abnormalities. The accuracy of DSE for diagnosing coronary artery disease has been confirmed in a large number of patients, including patients with end stage renal disease with significant coronary artery disease as diagnosed by coronary angiography [6-8].

The aim of the present study was to investigate whether HP and HR hemodialysis patients differ with respect to the presence of coronary artery disease and myocardial contractile reserve as assessed by DSE.

## METHODS

*Patients*:

Eighteen HP dialysis patients were studied. Hypotension prone was defined as: 1) symptoms of hypotension [dizziness and syncope] during hemodialysis during at least one third of dialysis sessions for more than one year in combination with a reduction in systolic blood pressure by at least 25% and/or a systolic blood pressure below 100 mmHg; 2) requirement of intravenous inotropic pressor agents and/or fluid infusion to avoid hypotension.

Relevant clinical characteristics of the patients are given in Table 1. Eighteen HR dialysis patients served as a control group. These patients were matched with the HP group with respect to age, gender, cardiovascular history and symptoms, presence of diabetes mellitus, and duration of hemodialysis [Table 1].

**Table 1**: Clinical characteristics of HR and HP hemodialysis patients.

| | HR | HP | p-value |
|---|---|---|---|
| Number | 18 | 18 | n.s. |
| Age [mean] | 53±6 | 53±3 | n.s. |
| Sex [M /F] | 15/3 | 10/8 | n.s. |
| BSA [$m^2$] | 1.73 | 1.76 | n.s. |
| Duration of hemodialysis [yrs] | 3.1±2.1 | 3.5±1.9 | n.s. |
| Hematocrit [L/L] | 0.31±0.06 | 0.32±0.05 | n.s. |
| History of myocardial infarction | 14 | 8 | n.s. |
| Angina pectoris [n] | 8 | 10 | n.s. |
| Diabetes mellitus [n] | 2 | 1 | n.s |
| ACE-inhibitors [n] | 9 | 5 | n.s. |
| Norepinephrine [pg/ml] | 429±209 | 381±174 | n.s. |
| Atrial natriuretic peptide [pg/ml] | 817±491 | 809±429 | n.s. |
| Beta blocker treatment [n] | 12 | 6 | 0.04 |
| Rest wall motion score | 1.42±0.56 | 1.40±0.52 | Ns |

BSA= body surface area. n.s.: not significant.

Beta-blockers were more frequently used by the HR than by the HP patients. All subjects were dialyzed three times weekly using a bicarbonate containing dialysate and artificial kidneys with biocompatible membranes [Gambrane, Hemophane or Polysulphone]. All patients were informed about the aim and procedures of the study. If they consented verbally to participate, an appointment to perform a DSE was made. In each patient the DSE was performed one day before a hemodialysis

session. If patients were using beta-blockers or other antihypertensive medications this treatment was discontinued on the day DSE was performed. The local Ethics Committee approved the study protocol.

*Central venous pressure measurement [CVP]:*

This was performed in 9 of the HP and in 8 of the HR patients. For this purpose a small catheter with a length of 12 and a diameter of 0.6 mm was inserted in the internal jugular vein using the Seldinger technique. CVP was measured just prior the DSE for a period of 5 minutes and values were averaged. Via the same catheter a blood sample was taken for measurement of the concentrations of atrial natriuretic peptide [ANP] and norepinephrine [NOR] in plasma.

*Dobutamine-atropine stress echocardiography:*

DSE was performed as previously described [9]. In short, after a two-dimensional resting echocardiographic examination, dobutamine was infused intravenously. Dobutamine infusion was started at 5μg/kg/min for 5 minutes followed by 10μg/kg/min for 5 minutes. After this "low dose" stage, the dobutamine infusion was increased every 3 minutes by 10 μg/kg/min to a maximum of 40 μg/kg/min unless a test end-point was reached. Test end-points were achievement of a target heart rate [maximum heart rate adjusted for age and gender], signs of myocardial ischemia and side effects. If one of the test end-points was not achieved, despite the maximal dobutamine infusion rate, atropine was added to a maximum of 2 mg intravenously. Blood pressure and heart rate were measured at baseline and at the end of every dose step by a semi-automatic oscillometric blood pressure monitor [Accutorr 2, Datascope, Datascope Corp. CA, USA]. Echocardiographic images were recorded from standard parasternal long and short-axis and apical two- and four-chamber views. Images were monitored continuously and recorded at the end of each dose step. The echocardiographic images were analyzed off-line, for the presence of wall motion abnormalities and to obtain values of stroke volume. Two

experienced investigators [DP, RR] performed analyses, unaware of the clinical condition of the patients.

Wall motion analysis: The left ventricular wall was divided into 16-segments, and wall motion was scored by using a five-point scale with values indicating: 1, normal; 2, mild hypokinetic; 3, severe hypokinetic; 4, akinetic, and 5, dyskinetic. For each patient a wall motion score index [total score divided by the number of segments] was calculated at rest, at low dose dobutamine infusion, and at peak dose dobutamine infusion. Reduction of wall thickening and new wall motion abnormalities [NWMA's], with exception of the transition of akinesia to dyskinesia, during the stress test is considered to be hallmark of ischemia. The transition of akinesia to dyskinesia does not reflect ischemia, but is a mechanically induced phenomenon [10].

Stroke volume: Stroke volume was measured at rest, at low dose, and at peak dose dobutamine by means of the bi-plane discs method. The volume of the left ventricle was calculated from the apical two- and four-chamber views using a modification of Simpson's rule [11]. The principle of Simpson's rule is to divide the left ventricle into slices of known thickness. The volume of the ventricle is then equal to the sum of the volume of the slices. Two-chamber and four-chamber apical views were recorded and stored. The endocardial borders of these views were digitally traced at end-diastole and end-systole. Each projection was divided in 20 sections along the long axis. Then the volumes were computed. Stroke volume was calculated as the difference between end-diastolic and end-systolic volume. The stroke volume as determined by the two investigators was averaged. Cardiac output was calculated as stroke volume times heart rate.

Pulse-wave Doppler. Pulse-wave Doppler studies were recorded from the apical four-chamber view, with the Doppler sampler positioned just within the inflow portion of the left ventricle, midway between the annular margins of the mitral valve. Mitral velocity profiles were digitized from the modal velocity of the

Doppler tracings. The peak E [early rapid ventricular filling] and peak A [atrial assisted filling] wave velocities were computed to calculate the E/A velocity ratio. Pulse-wave Doppler signals were only measured at rest.

*Analytical methods*: Blood samples for determination of ANP was collected in chilled tubes containing EDTA and aprotinin. Samples for measurement of catecholamines were collected in chilled heparinized tubes containing gluthatione. All samples were immediately centrifuged at 4o,and plasma was stored at –80°C. ANP was measured by a radioimmunoassay using a commercially available kit [Nichols Institute, Wijchen, The Netherlands]. Plasma NOR was measured with fluorometric detection after HPLC separation.

*Statistical analysis*:

Hemodynamic variables are expressed as mean ± SD. Cardiac output and stroke volume are expressed per body surface area. Total peripheral vascular resistance was calculated as mean arterial pressure divided by cardiac index. Differences in discrete variables between HR and HP groups were analyzed by chi-square tests. Furthermore, a 2-way analysis of variance was applied to evaluated changes in hemodynamic variables with increasing dobutamine dose (repeated measures) as well as differences in response between HR and HP groups. For all tests a p-value $< 0.05$ was considered to be statistically significant.

## RESULTS

The relevant clinical characteristics of the two groups of patients are given in Table 1. The two groups did not differ with respect to age, gender, duration of hemodialysis, cardiovascular history or cardiovascular disease, presence of diabetes mellitus, and rest wall motion score [Table 1]. Adequate 2-D image recordings at rest and during stress were obtained in all patients. Wall motion abnormalities at rest were present in 11 of the patients of the HP and 11 of the patients of the HR group.

In both groups the target heart rate was reached in 89% of patients. The frequency of the occurrence of NWMA's between the two groups did not differ [Table 2].

**Table 2**: Results of dobutamine stress echocardiography in HP and HR hemodialysis patients.

| | HR | HP | p-value |
|---|---|---|---|
| Patients with rest wall motion abnormalities [n] | 11 | 11 | n.s. |
| E/A velocity ratio | 0.81±0.31 | 0.79±0.20 | 0.86 |
| ***Test end-points*** | | | |
| Target heart rate | 16 | 16 | 0.3 |
| Severe angina | 1 | 1 | 0.7 |
| Side effects | 1 | 1 | 0.7 |
| Atropine addition | 9 | 5 | 0.2 |
| NWMA's | 4 | 3 | 1.0 |
| Hypotension during DSE | 2 | 4 | 0.4 |
| Angina during DSE | 4 | 3 | 0.7 |
| ST changes during DSE | 7 | 6 | 1.0 |

NWMA's: New wall motion abnormalities; DSE: dobutamine stress echocardiography; Hypotension during DSE: reduction of systolic blood pressure > 40 mmHg during test.

In 9 HP and 8 HR patients, CVP, plasma ANP and NOR and E/A ratio's were measured as well. CVP values were not low in any of the patients and values between the two groups did not differ. Due to chronic renal failure plasma ANP values were increased, but values between the HP and HR groups were not different. Values of plasma NOR were normal and did not differ between the two groups [Table 1].

E/A ratios were only measured at rest. The ratio was below 1.0 in 7 of the 9 HP patients and in 5 of the 8 HR patients [p = 0.06].

The resting values of blood pressure, heart rate, stroke index, cardiac index and total peripheral vascular resistance for the two groups are given in Table 3. Most likely related to the use of beta-blockers, heart rate was lower and stroke volume was higher in the HR group, but resting cardiac output between the two groups did not differ. The responses of these hemodynamic variables to dobutamine for

the two groups are summarized in Table 3, whereas the hemodynamic responses of individual patients are depicted in Fig. 1 A-D.

**Table 3:** hemodynamic characteristics of HP and HR patients during dobutamine stress echocardiography.

| | Rest HP | Rest HR | Low HP | Low HR | Peak HP | Peak HR | $P_1$ | $P_2$ |
|---|---|---|---|---|---|---|---|---|
| Heart rate [bpm] | 76±13 | 69±12 | 92±22 | 81±18 | 126±17 | 130±19 | <0.0001 | 0.021 |
| SBP [mmHg] | 135±28 | 147±22 | 137±34 | 150±31 | 127±39 | 153±37 | 0.627 | 0.152 |
| MAP [mmHg] | 94±15 | 106±16 | 97±20 | 104±19 | 89±25 | 108±26 | 0.761 | 0.089 |
| DBP [mmHg] | 73±13 | 85±14 | 76±18 | 81±14 | 71±20 | 85±23 | 0.820 | 0.103 |
| TPRI (u) | 2.28±0.05 | 2.26±0.05 | 2.24±0.01 | 1.91±0.06 | 1.75±0.06 | 1.36±0.05 | <0.0001 | 0.124 |
| SI [ml/m$^2$] | 59±19 | 71±16 | 54±18 | 75±21 | 46±21 | 68±23 | <0.0001 | 0.081 |
| CI [l/min/m$^2$] | 2.4±1.1 | 2.8±1.2 | 2.8±1.7 | 3.4±1.8 | 3.2±2.6 | 5.1±3.3 | <0.0001 | 0.001 |

$P_{1=}$ difference during dobutamine infusion (rest-low-peak); $P_2$: difference in response between HP and HR patients during respectively low and peak dobutamine stress.

In response to dobutamine, stroke index decreased in the HP group, whereas it did not change in the HR group. Due to these different responses in stroke index, the increase in cardiac index was considerably lower [p<0.0001] in the HP group. Systolic blood pressure tended to increase in the HR and to decrease in the HP group, but there was no significant difference between the two groups [p=0.627].

**Fig. 1A-D:** Hemodynamic responses of individual patients during dobutamine stress echocardiography. The dotted lines represent patients with beta blocker therapy.

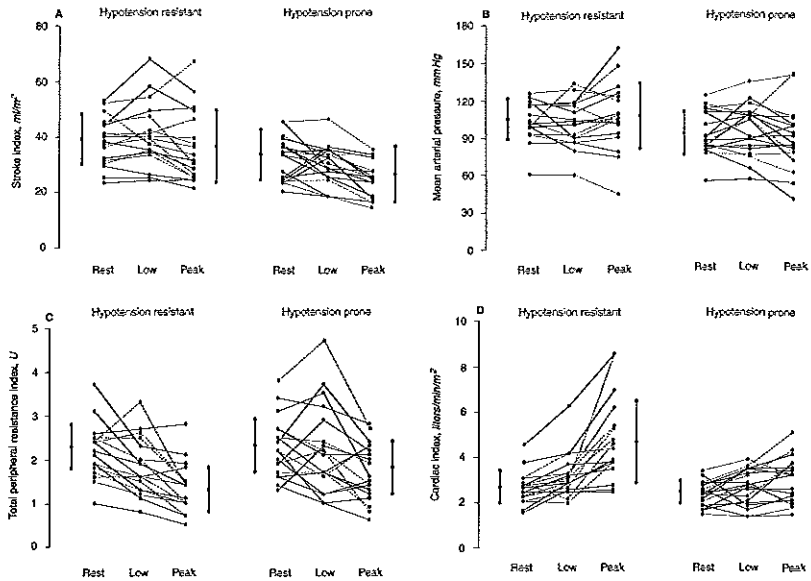


**Fig 1A-D. (Continued)**

## DISCUSSION

In this study DSE was applied to evaluate cardiac contractile reserve and the presence of myocardial ischemia in HP and HR hemodialysis patients. Due to high incidence of previous myocardial infarction, wall motion abnormalities at rest were present in a large proportion of both HP and HR patients. Dobutamine-induced ischemia, as defined by new wall motion abnormalities, was observed in only 3 of the HR and 4 of the HP patients, but compared to the HR patients, myocardial contractile reserve [increase in stroke index in response to dobutamine] was impaired in a considerable larger proportion of the HP than HR patients. As a consequence of this reduced myocardial contractile reserve the dobutamine-induced maximal increase in cardiac index was much lower in the HP patients.

Volume status is among one of the most important determinants for allowing stroke index and cardiac index to increase in response to increasing doses of

dobutamine. To ascertain that patients were studied in a volume-repleted state, DSE was always performed one day before the next hemodialysis session. Central venous pressure just prior to the DSE was measured in about 50% of the patients. In these patients central venous pressure was relatively high, further confirming that the patients were indeed not volume-depleted.

Left ventricular hypertrophy and uremic myocardial fibrosis are commonly present in hemodialysis patients [2,4,12,13]. These abnormalities impair ventricular relaxation and hence diastolic filling, resulting in a decrease in cardiac output. At this time we can not rule out that these abnormalities were more advanced in the HP patients. A greater E/A velocity ratio in HP than in HR patients, as a reflection of diastolic dysfunction, has been reported previously [14]. In the present study no difference in the E/A velocity ratio, although abnormal in almost all patients, between the two groups could be detected.

Dysfunction of cardiac beta-adrenergic receptors could also explain the diminished myocardial responsiveness to dobutamine in the HP patients. High circulating levels of norepinephrine and epinephrine have been reported in patients susceptible to development of hypotension during hemodialysis[15,16]. This high sympatho-adrenergic state was associated with a down-regulation of platelet alpha $_2$- and lymphocyte beta $_2$ -adrenoceptors, as well as a decreased intracellular cAMP generation after isoproterenol stimulation[17]. In the present study no difference in plasma concentrations of norepinephrine between HP and HR patients was present. Is should be stressed that the concentrations of norepinephrine were not measured during the hemodialysis sessions but only under baseline conditions.

Since antihypertensive therapy may adversely affect the development and course of hemodialysis-induced hypotension we were not surprised to see that blood pressure lowering agents were more frequently used by the HR than by the HP patients. Especially the difference in the use of beta-blockers between the two groups was notable. Because of the possibility of the occurrence of beta-blocker withdrawal phenomena these agents were only discontinued on the day the DSE

was performed. When considering the individual responses of stroke index and cardiac index to dobutamine it seems unlikely that the unequal use of beta-blockers provides an explanation for the difference in hemodynamic responses between the two groups.

When translating the results of DSE to the clinical situation, we want to suggest that the inability of cardiac index to increase in response to sympathetic stress can play a key role in the pathogenesis of hemodialysis-induced hypotension. If the hemodialysis-induced activation of the sympathetic nervous system does not lead to an appropriate rise in cardiac output to maintain blood pressure, further sympathetic discharge is likely to occur. Eventually, due to exhaustion, the autonomic nervous system is no longer capable to maintain this high level of sympathetic tone and blood pressure will fall. The cause of hemodialysis-induced hypotension in this situation is not primarily a consequence of failure of the autonomic nervous system, but the consequence of diminished myocardial responsiveness or myocardial contractile reserve (Fig. 2). This hypothesis fits well with the observations of Zocalli et al. showing that tachycardia and not bradycardia is the predominant hemodynamic response to hypotension during hemodialyis[18].

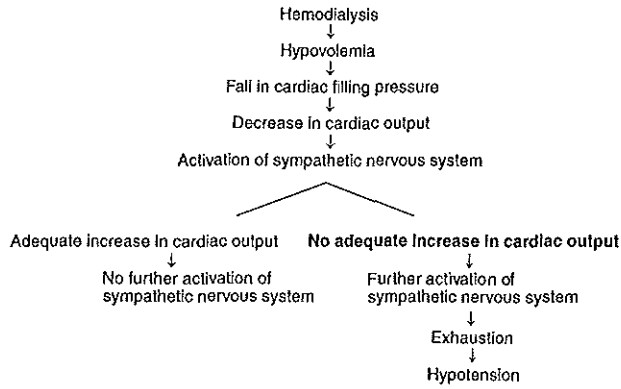


Fig. 2. Scheme of proposed pathophysiological mechanism of hemodialysis-induced hypotension.

**Fig 2.** Scheme of proposed pathophysiological mechanism of hemodialysis-induced hypotension

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## SUMMARY AND CONCLUSIONS

**Summary.**

The main finding of the present thesis is that a quantitative approach of echocardiography is feasible and highly accurate to detect left and right ventricular dysfunction. Moreover, we demonstrated that this approach might be applied to the technically demanding setting of dobutamine stress echocardiography. We found evidence that the traditional qualitative evaluation of stress echocardiography may be improved.

The following list of findings summarizes the major results of the present thesis.

**Chapter 1:** We found that both a reasonable echocardiographic image quality and severe wall motion abnormalities appeared the strongest predictors of echocardiographic assessement reproducibility and that new standardized guidelines should emphasize this finding.

**Chapters 2 and 3:** The evaluation of stress tests results, even by optimizing the echocardiographic recording and scoring, remains subjective. This is the major limitation of the test. To overcome this limitation we started the quantitative evaluation of ventricular function by using Doppler tissue imaging, and particularly its color-independent application: pulsed wave Doppler tissue sampling. We showed that pulsed wave Doppler tissue sampling is able to quantitate left and right ventricular function.

**Chapter 4:** Pulsed wave Doppler tissue sampling systolic velocities exhibited by the right ventricle during dobutamine stress echocardiography showed a depressed pattern in the case of right ventricular dysfunction, correlated to either a prior posterior myocardial infarction or right coronary artery stenosis. We considered this pattern expression of a resting dysfunctional myocardium with jeopardized viable component that improved wall motion at low-dose dobutamine while worsening at peak-dose, possibly expressing right ventricular ischemia. This pattern resembles the biphasic pattern of myocardial viability reported in the literature.

**Chapter 5-6:** We demonstrated that during dobutamine infusion, an increase of myocardial systolic velocities by pulsed wave Doppler tissue sampling from rest to low-dose predicts myocardial viability more accurately than stress echo. Absolute systolic velocities at peak-dose test were similarly higher in viable than nonviable segments. We used as a reference standard for myocardial viability either traditional wall motion scoring by dobutamine stress echocardiography or $^{99m}$Technetium-tetrofosmin-$^{18}$F-fluorodeoxyglucose-single photon emission computed tomography (FDG-SPECT).

**Chapter 7:** We were able to correlate successfully dobutamine stress echocardiography to FDG-SPECT to detect myocardial viability, thanks to an analogous scoring model for myocardial contraction, perfusion and membrane uptake.

**Chapter 8:** We proved that a full dobutamine-atropine dose is safe, feasible and accurate for myocardial viability detection in patients with severe left ventricular dysfunction.

**Chapter 9:** We found that ejection fraction increase at low-dose stress testing, with subsequent worsening at peak, quantitatively predicts functional recovery, defined as functional recovery after coronary revascularization. Also in this case a biphasic pattern appears the best predictor of myocardial viability. Left ventricle functional improvement after revascularization is proportional to the degree of ejection fraction improvement at low-dose dobutamine and it is linearly related to the number of viable segments.

**Chapter 10:** We succeeded in detecting a functional improvement of either left ventricular resting performance or stress-induced myocardial ischemia by performing dobutamine stress echocardiography immediately after percutaneous transluminal coronary angioplasty in chronic totally occluded coronary arteries.

**Chapter 11:** The absence of contractile reserve during low-dose dobutamine performed in end-stage renal failure patients before hemodialysis was able to predict hypotension occurring during hemodialysis. Therefore, the absence of left ventricular functional reserve, as induced by dobutamine, may play a critical

role in the phatophysiology of patients with end-stage renal failure and possibly stratifies a higher risk group.

**Future perspectives of quantitative assessment of ventricular function.**

At the present cardiac imaging is one of the fastest growing areas of cardiology and there is justification of the many efforts that are converging to develop new techniques for quantification of echocardiography. It is difficult at the present to predict which technological trend will ultimately prevail. Apart pulsed wave Doppler tissue sampling, many other noninvasive approaches are trying to extract quantitative functional informations from the myocardium, for example: acoustic quantification/color kinesis, anatomical M-mode, strain imaging, grey-scale videodensitometry, tracking of the speckle pattern, contrast echocardiography, computerized tomography, positron emission tomography, magnetic resonance imaging, etc. It is out of the goal of the present thesis to discuss each one of these new techniques.

**Conclusions.**

The present thesis is a demonstration that the old dream of quantifying ventricular function is feasible and probably close to be achieved in a near future. At least one (or more) of the many techniques presently under investigation will ultimately reach this goal. Among many new methods, we focused on pulsed wave Doppler tissue sampling as applied to dobutamine stress echocardiography, technique that is both relatively cheap and largely available. We considered also some new aspects of nuclear imaging, technique, which is sharing with echocardiography relatively large availability. We demonstrated that both echocardiography and nuclear imaging can be optimized to study ventricular function by improving both the scoring model and by adding quantitative data. We selected pulsed wave Doppler tissue sampling because it is a very simple technique, not sofware demanding, neither requiring complex modifications of the echocardiographic system. However, the application of color Doppler tissue imaging demands further sofware developments to be introduced in the clinical arena and its clinical value must be validated versus

other quantitative approaches. If in the future an other quantitative technique will be available, we will recognize to Doppler tissue imaging the merit of having greatly contributed to the understanding of the pathophysiolgy of ventricular function in many different clinical settings.

## SAMENVATTING EN CONCLUSIES

De belangrijkste conclusie van dit proefschrift is dat een kwantitatieve echocardiografische analyse praktisch uitvoerbaar is. Deze kwantitatieve analyse is beter dan de tot nu toe gebruikte subjectieve analyse voor het opsporen van afwijkingen aan zowel de linker als rechter ventrikel. Dit onderzoek kan gebeuren zowel in rust als tijdens dobutamine belasting.
De belangrijkste gegevens van het proefschrift worden in de volgende hoofdstukken besproken.

**Hoofdstuk 1**: De variatie in interpretatie tussen beoordelaars van echocardiografisch onderzoek, door subjectieve interpretatie, kan worden verminderd wanneer gebruik wordt gemaakt van kwalitatief goede echobeelden en gestandaardiseerde richtlijnen voor het beoordelen van wandbewegingen.

**Hoofdstukken 2 en 3:** De variatie in interpretatie van echocardiografisch onderzoek kan verder worden verminderd door gebruik te maken van een kwantitatieve meting. Hierbij wordt de snelheid van contractie van de hartkamer gemetenn met behulp van de pulsed wave Doppler techniek en als een absoluut getal weergegeven. Deze snelheid wordt bepaald door hartspiervezels die zowel in de longitunale en equitoriale vlak verlopen. Door de snelheid van contractie in een bepaald gebied van de hart te bepalen tijdens verschillende stadia van "dobutamine stress echografie", kan de functie als een absolute waarde worden weergegeven.

**Hoofdstuk 4:** Afwijkingen van contractie van de rechterkamer kunnen met de zogenaamde pulsed wave Doppler sampling methode worden opgespoord. Een verminderde contractie snelheid is aanwezig bij patiënten met een infarct van de rechterkamer. Ook kan ischemie van de rechterkamer worden vastgesteld met deze methode. Tijdens dobutamine stress echografie treedt tijdens een lage dosis

dobutamine een snellere contractie op van de ventrikelwand, in de aanwezigheid van corornair afwijkingen treedt tijdens hogere doseringen dobutamine zuurstof tekort op, zich uitend in een verminderde contractie snelheid. De aanvankelijke verbeterde contractie gevolgd door een verslechtering bij hogere belasting lijkt sterk op het bifasische wandbewegingspatroon wat gecorreleerd is aan myocardvitaliteit.

**Hoofdstukken 5 en 6**: Dysfunctioneel maar vitaal myocard weefsel kan met behulp van een dobutamine stress echografie test worden opgespoord. Segmenten vertonen een verbeterde contractie tijdens lage dosis dobutamine eventuweel gevolgd door een verminderde contractie tijdens piek stress. De gevoeligheid voor het opsporen van vitaal hartspierweefsel is minder dan een nucleaire test. Wanneer echter tijdens dobutamine stress echografie de contractie van wandbeweging in het basale gedeelte van het hart wordt gemeten met de pulsed wave Doppler sampling methode verbetert de gevoeligheid wanneer de nucleaire methode als "gouden standaard" wordt beschouwd.

**Hoofdstuk 7**: Vitaal myocardspierweefsel kan worden aangetoond met nucleaire technieken, waarbij perfusie en metabolisme worden bepaald van de hartspiercel. Recent is aangetoond dat dobutamine stress echografie eveneens vitaal myocardspierweefsel kan aantonen. In een vergelijkend onderzoek waarbij beide testen werden uitgevoerd werd een hoge mate van overeenkomst tussen beide methoden gevonden niet beïnvloed door de uitgang ejectie fractie van de patiënt.

**Hoofdstuk 8**: Dobutamine stress echocardiografie heeft verschillende bijwerkingen zoals hypotensie en ritme stoornissen. In een grote groep van patiënten met een verminderde linker ventrikel functie werd aangetoond dat ten opzichte van patiënten met een "normale" ejectie fractie hypotensie significant vaker optreedt tijdens dobutamine stress echocardiografie. De bijwerking

herstelt snel na het stoppen van het onderzoek. Hartritmestoornissen treden in gelijke mate op ten opzichte van de "normale" populatie.

**Hoofdstuk 9:** De aanwezigheid van vitaal myocardspierweefsel kan worden aangetoond door een verbeterde contractie van dysfunctionele segmenten tijdens lage dosis dobutamine. De ejectie fractie vertoond ook een verbetering in de aanwezigheid van vitaal myocardspierweefsel. Wanneer patiënten voor een coronair revascularizatie werden geëvalueerd met behulp van linker ventrikel ejectie fractie dan bleek de toename van ejectie fractie tijdens lage dosis dobutamine en de verdere verslechtering tijdens piek stress de beste voorspelling te geven voor herstel van functie na revascularizatie.

**Hoofdstuk 10:** Dobutamine stress echocardiografie kan worden gebruikt voor zowel het herstel van dysfunctionele segmenten als de aanwezigheid van ischemie tijdens dobutamine stress na een revascularizatie methode. Bij patiënten behandeld door laeser therapie kan het herstel van coronair doorgankelijkheid worden geobjectiveerd.

**Hoofdstuk 11**: Hypotensie treedt frequent op bij patiënten met nierinsufficiëntie die behandeld worden door middel van hemodialyse. De oorzaak hiervoor is onbekend. In een studie werden patiënten met en zonder dialyse geïnduceerde hypotensie vergeleken door middel van dobutamine stress echocardiografie. Patiënten met dialyse geïnduceerde hypotensie hadden een verminderde contractiele reserve tijdens lage dosis dobutamine. Deze contractiele reserve werd gemeten als een toename van het slagvolume. Tevens werd gevonden dat stress geïnduceerde ischemie evenveel voorkwam in beide groepen.

**Toekomst verwachtingen van kwantitatieve bepalingen van ventrikel functie:**

In de huidige cardiologische praktijk neemt beeldvorming door echografie een steeds belangrijker plaats in. Verschillende technieken worden toegepast om de uitslag van het echo onderzoek te kwantificeren. Welke techniek uiteindelijk de beste zal zijn is moeilijk te voorspellen. Naast pulsed wave Doppler sampling wordt gebruik gemaakt van acoustic quantification/colour kinesis, anatomic M-mode, strain imaging, gray-scale videodensiometrie, tracking of the speckle pattern, contrast echocardiografie, computer tomografie, positron emissie tomografie, magnetische resonantie afbeelding, enz. Het valt buiten het kader van dit proefschrift om al deze verschillende technieken te bespreken.

**Conclusies:** Dit proefschrift toont aan dat het (bijna) mogelijk is de ventrikel functie kwantitatief te beoordelen. Dit proefschrift heeft zich vooral geconcentreerd op pulsed wave Doppler sampling tijdens dobutamine stress echocardiografie, een methode die wijdverspreid aanwezig is en niet duur. Tevens werden nieuwe ontwikkelingen van nucleaire geneeskunde besproken, die eveneens op veel plaatsen aanwezig is. Beide methoden kunnen door een kwantitatieve beoordeling de ventriculaire functie nog beter beoordelen. De in dit proefschrift bescreven pulsed wave Doppler sampling methode is relatief simpel en maakt uitgebreide aanpassingen aan het echoapperaat niet nodig. De introductie van colour Doppler weefsel afbeelding daarentegen zal eerst nog verdere technische ontwikkelingen vergen en gevalideerd moeten worden in de praktijk. Indien pulsed wave Doppler sampling in de toekomst niet de methode van keus wordt heeft het wel bijgedragen aan de ontwikkeling en begrip over toepassingen en ontwikkelingen betreffende kwantificatie van ventrikel functie, dat voorheen niet mogelijk was.

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## CURRICULUM VITAE

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Rambaldi Riccardo was born in Vigarano M. (Ferrara) at 15 july 1956.

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**Clinical experience and scientific activity:**

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- Permanent Professor of Pharmacology: Professional Nursing School of Ferrara, 1989-1992.
- Assistant Cardiologist in the Coronary Care Unit of Bovolone (Vr), 1991-1992.
- Permanent "Aiuto" Cardiologist in the Hospital of Badia Polesine (Ro), 1992-1995.
- Visitor Cardiologist in the Division of Cardiology of the University Hospital of Lausanne, Switzerland, (Prof. L. Kappenberger), 1993.
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- Cardiologist in the Hospitals of Sondalo (So) and Bentivoglio (Bo), 1998-2000.

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- Member of the Subgroup on Ventricular Function and Doppler Myocardial Imaging of the European Society of Cardiology (ESC).
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- Fellow of the Hospital Cardiologist Italian Association (ANMCO).
- Member of the Cardiovascular Research Foundation, Castelfranco V. Italy.

## LIST OF PUBBLICATIONS

### ARTICLES

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