Knut Bjørnstad

COMPUTERIZED ECHOCARDIOGRAPHY FOR EVALUATION OF CORONARY ARTERY DISEASE

Norwegian University of Science and Technology
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TAPIR

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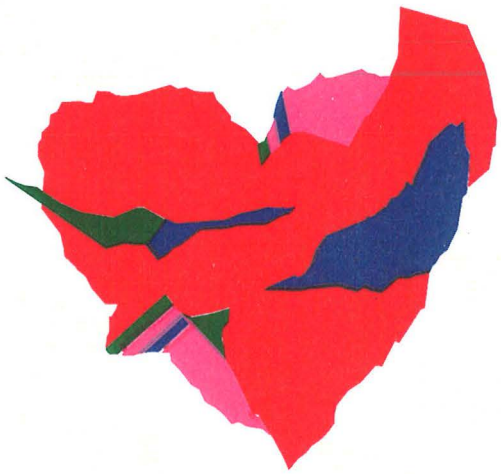

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LIST OF PAPERS

I: Bjørnstad K, Aakhus S, Hatle L. Digital high frame rate stress echocardiography for detection of coronary artery stenosis by high dose dipyridamole stress testing. Int J Cardiac Imaging 1995;11:163-170.

II: Bjørnstad K, Aakhus S, Lundbom J, Bolz KD, Rokseth R, Skjaerpe T, Hatle L. Digital dipyridamole stress echocardiography in silent ischemia after coronary artery bypass grafting and/or after healing of acute myocardial infarction. Am J Cardiol 1993;72:640-646.

III: Bjørnstad K, Aakhus S, Hatle L. Comparison of digital dipyridamole stress echocardiography and upright bicycle stress echocardiography for identification of coronary artery stenosis. Cardiology 1995;86:514-520.

IV: Bjørnstad K, Aakhus S, Torp HG. How does computer-assisted digital wall motion analysis influence observer agreement and diagnostic accuracy during stress echocardiography? Int J Cardiac Imaging 1997;13:105-114.

V: Bjørnstad K, Al Amri M, Lingamanaicker J, Oqaili I, Hatle L. Interobserver and intraobserver variation for analysis of left ventricular wall motion at baseline and during low- and high-dose dobutamine stress echocardiography in patients with high prevalence of wall motion abnormalities at rest. J Am Soc Echocardiogr 1996;9:320-328.

VI: Bjørnstad K, Maehle J, Aakhus S. Quantitative computerized analysis of left ventricular wall motion. In: Computerized echocardiography. Eds. Domenicucci S, Roelandt J, Pezzano A. Centro Scientifico, Torino, Italia 1993, pp 41-55.

VII: Bjørnstad K, Mæhle J, Aakhus S, Torp HG, Hatle LK, Angelsen BAJ. Evaluation of reference systems for quantitative wall motion analysis from three-dimensional endocardial surface reconstruction. Am J Cardiac Imaging 1996;10:244-253.

The papers will be referred to in the text by their Roman numerals.

INTRODUCTION

Cardiac ultrasound is widely used for diagnosis and characterization of coronary artery disease. During a study with two-dimensional echocardiography, left ventricular (LV) chamber size and volumes as well as the status of regional and global myocardial contraction can be assessed [1]. In patients with acute or previous myocardial infarction, the location and extent of dysfunctioning myocardium can be assessed by LV wall motion analysis [2-4], and within limits, assigned to specific coronary artery distributions [5]. Two-dimensional echocardiography is usually easy to perform and interprete by trained physicians, necessary equipment is available in all hospitals, and no post-processing is required to evaluate the results of the examination.

The present thesis extends the use of two-dimensional echocardiography in coronary artery disease in two directions: 1) Comparison of two-dimensional images obtained at rest and during stress, ie. stress echocardiography, may identify coronary artery stenosis indicated by reversible LV wall motion abnormality, and 2) Endocardial tracing of multiple two-dimensional imaging views of the LV facilitate quantitative wall motion analysis by three-dimensional reconstruction of endocardial surface.

The earliest reports on the use of stress echocardiography for diagnosis of coronary artery disease date back to 1979 [6,7]. The present work was carried out during an era with several proposed protocols for inducing cardiac stress. Our aim was to characterize advantages and limitations with alternative stress methods applied to relevant patient populations in a clinical setting. The work further introduced a new method for digital processing of images, and tested how this influenced diagnostic accuracy and inter- and intraobserver variation for stress echocardiographic interpretation.

The second part of the thesis presents a new algorithm for quantitative wall motion analysis from three-dimensional reconstruction of LV endocardial surface. This method is based on the same system for digital data transfer as used for the stress echocardiography studies. Although two-dimensional images may identify the presence and location of wall motion abnormalities [8-10], quantitative analysis of regional and global systolic function is limited to one imaging plane. In addition to determination of LV volumes and ejection fraction, an attractive feature with a three-dimensional approach is the possibility to assess regional contraction in different parts of the ventricle, and to quantify regions with abnormal systolic function. This, however, requires both a reliable reconstruction procedure as well as a method for comparison of end-diastolic and end-systolic surfaces.

AIMS OF THE STUDY

1. To evaluate dipyridamole stress echocardiography with computer-assisted wall motion analysis as a method to identify significant coronary stenosis in a clinically relevant population, and more specifically to assess its value in patients with asymptomatic ST-segment depression during bicycle exercise test after coronary bypass surgery or after myocardial infarction.

2. To assess and compare the diagnostic value of dipyridamole stress echocardiography and upright bicycle stress echocardiography for detection of coronary artery stenosis.

3. To assess the influence of a computer-assisted analysis system on inter- and intraobserver agreement and diagnostic accuracy during stress echocardiography.

4. To assess the observer variation for interpretation of wall motion abnormalities at rest and for evaluation of myocardial viability and ischemia during dobutamine stress echocardiography.

5. To discuss the value of various echocardiographic methods for quantitative assessment of regional LV wall motion, and to present and discuss potential clinical applications for a new algorithm for three-dimensional reconstruction of endocardial surfaces.

6. To perform quantitative wall motion analysis by three-dimensional reconstruction of endocardial surfaces in patients with and without myocardial infarction, and to evaluate alternative reference systems for localization and quantitation of wall motion abnormalities.

METHODS

Patient selection. The majority of the study patients undergoing stress echocardiography were recruited from referrals for coronary angiography to our institution. For the diagnostic part of the thesis (Papers I, II, and III), we studied patients with inconclusive results from standard exercise ECG tests to assess the value of stress echocardiography in such patients. For practical reasons, bicycle stress echocardiography was usually performed the day before and dipyridamole echocardiography the day after coronary angiography. Paper I included a total of 120 consecutive patients studied with dipyridamole stress echocardiography, and summarizes our experiences with this test for diagnosis of coronary artery stenosis. This material comprises the patients included in Paper II, in addition to patients with renal failure awaiting renal transplantation, patients unable to perform exercise testing due to physical limitations, and patients with baseline ECG changes and inconclusive interpretations of exercise ECG. In addition, this paper included 18 patients evaluated for chest pain syndromes with normal results at coronary angiography. These patients had dipyridamole stress echocardiography performed within 12 months of coronary angiography. Paper II comprised patients observed to have asymptomatic ST-segment depression during standard bicycle exercise-ECG testing after coronary bypass surgery or after myocardial infarction. Paper III was performed in a subgroup of 37 patients from Paper I who underwent both dipyridamole and bicycle stress echocardiography, and comprised some of the patients from Paper II. Paper IV was conducted on a subgroup of tests from Paper I with focus on observer variation and wall motion analysis. Paper V was conducted at King Faisal Specialist Hospital and Research Centre in Riyadh, Saudi Arabia. The 33 patients in this study were recruited from consecutive patients referred to dobutamine stress echocardiography as part of evaluation of myocardial ischemia and/or myocardial viability. The last paper (Paper VII) was performed with patients admitted with recent myocardial infarction, supplemented with a control group recriuted from hospital employees without evidence of coronary artery disease.

All study subjects gave informed consent to participate.

Methods used to induce cardiac stress. Upright bicycle stress test with simultaneous ECG monitoring is the most common method for identification of coronary artery stenosis in our country. The test provides physiological stress with increased heart rate, systolic blood pressure and myocardial oxygen demand, and independent information on the exercise capacity of the patient is gained. However, the test has well-known limitations both with regard to diagnostic accuracy and to feasibility [11]. With upright bicycle stress echocardiography, cardiac imaging was performed continuously

during exercise, using apical imaging views, and a standard exercise protocol was applied (Fig. 1, upper panel).

Pharmacological stress with dipyridamole infusion was used in all patients included in Paper I to IV. Dipyridamole induces coronary vasodilation by inhibition of cellular uptake and inactivation of endogenous adenosine [12]. The result is a substantial flow increase in normal epicardial coronary arteries, but regional flow may become reduced in patients with significant coronary stenosis due to a steal effect. The drug has been extensively used during nuclear myocardial imaging to induce perfusion heterogeneity in patients unable to perform regular exercise [13-15]. During stress echocardiography, a 50% higher dose is used to induce wall motion abnormalities [16] (Fig. 1, middle panel). The drug causes only minor changes in systemic hemodynamics [17].

Paper V was performed using dobutamine infusion [Fig. 1, lower panel]. Dobutamine is a synthetic catecholamine that causes dose-dependent stimulation of beta-1-receptors of the heart, and beta-2 and alpha-receptors of systemic arteries [18]. The hemodynamic effects are increased myocardial contractility and stroke volume at low dose, and significantly increased myocardial oxygen demand during high dose infusion (20-40 μg/kg/min), due to a combined inotropic and chronotropic stimulation [19,20].

Echocardiographic imaging. All studies were performed with commercially available echocardiographic equipment. A Vingmed ultrasound scanner CFM 750 with a 3.5 MHz annular array transducer was used for Paper I, II, III, IV, and VII, whereas a Vingmed CFM 800 with an integrated Macintosh computer was used for Paper V.

During pharmacological stress echocardiography, patients were imaged in the left lateral recumbent position. Representative sequences were videotaped at different stages of the test. In addition, images from standardized apical and parasternal imaging views were transferred to a computer at rest and at the level of maximal stress. During bicycle stress echocardiography, apical imaging was performed continuously during exercise, and the three standard apical views (apical 4-chamber, 2-chamber, and long-axis views) were obtained as cineloops at rest and at peak exercise. The same three standard apical imaging views were used also for Paper VII. During this study, all images were obtained at held end-expiration to minimize the effect of respiratory movement of the heart, and were transferred to the computer in the same manner as described above.

Computer display of echocardiographic images. The ultrasound scanner was interfaced with a computer (Macintosh II, Apple Computers Inc., Cupertino, CA, USA) for transfer of image data. The computer system used for image display and analysis in our stress echocardiography studies (EchoLoops and EchoDisp, Vingmed Sound A/S, Horten, Norway) differed from other analysis systems commonly used in

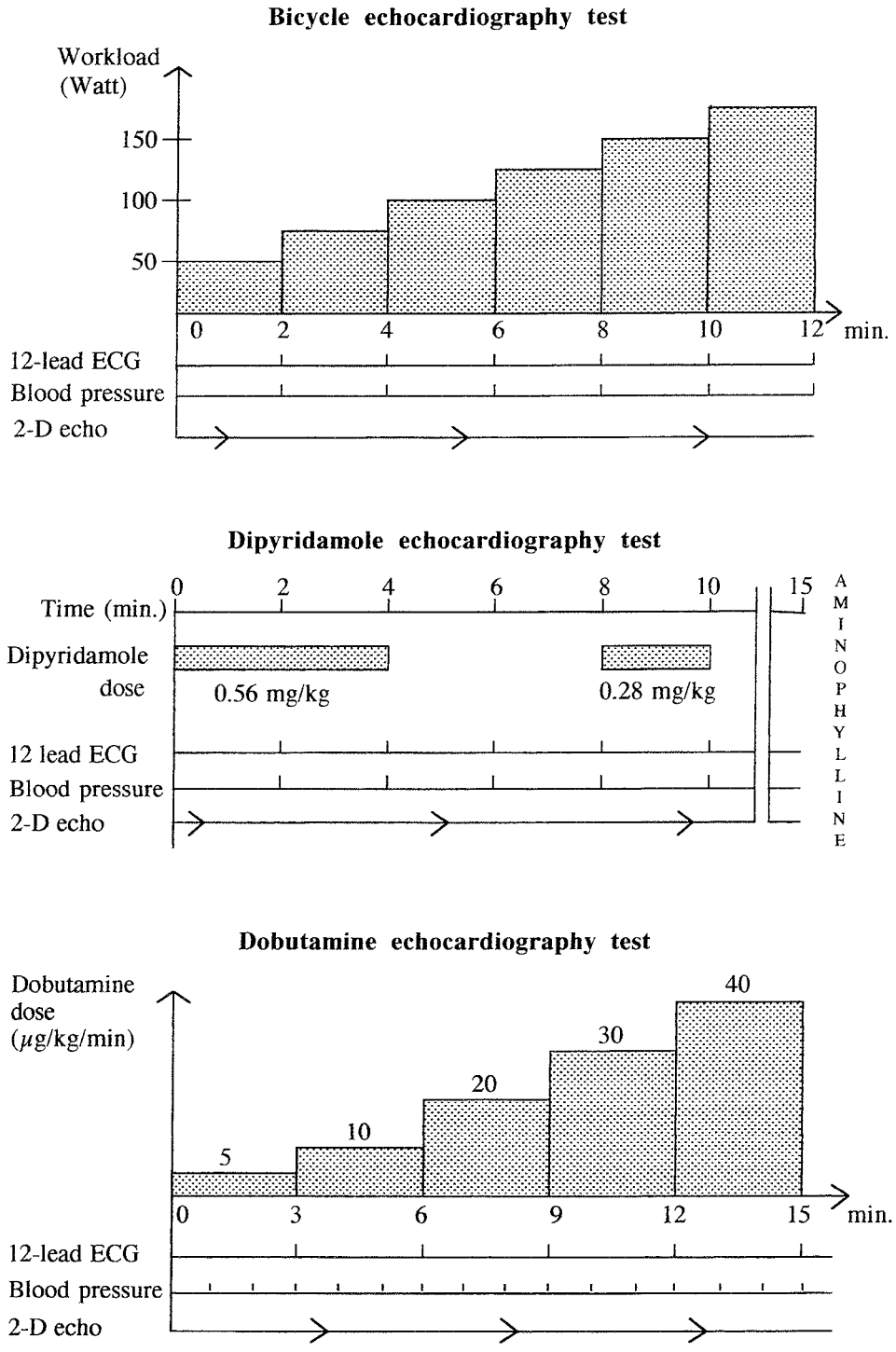

Figure 1. The three stress methods used in Papers I to V: *Upper panel:* bicycle echocardiography test; *middle panel:* dipyridamole echocardiography test; and *lower panel:* dobutamine echocardiography test.

stress echocardiography publications. Digital cineloops were displayed on the computer with a frame rate of 47 frames/s with standard sector depth and angle settings. The software allowed analysis of individual cineloops in slow motion as well as side-by-side display of multiple cineloops from different stress levels, synchronized for heart rate. The frame rate of 47 frames/s is higher than that provided by analysis systems based on digitized video signals [Fig. 4]. With these, frame rates of approximately 25 frames/s are obtained, or 8 frames per systole. In order to investigate the influence of frame rate on stress echocardiography analysis [Paper IV], we developed a specially designed software to omit every second frame in the original cineloop. In Paper V, the stress echocardiography software implemented in the CFM 800 ultrasound machine was used (EchoPac, Vingmed Sound A/S), and the standard digitized video signals with frame rate of 25 frames/s were used for analysis.

Wall motion score index (WMSI). Groups of cineloops from the same stress levels were displayed for calculation of WMSI. This index was obtained by assigning a score from 1 (normal) to 5 (aneurysmal) to each of 16 ventricular segments byvisual analysis of the three apical imaging views (Fig. 2), and the sum of segmental scores was divided by the number of segments scored. Thus, a normal ventricle without wall motion abnormality will have a score of 1.00; wheras indexes of 1.07 to 1.49, 1.50 to 1.99, and 2.00 or above indicate mild, moderate, and severe left ventricular dysfunction, respectively [21].

Stress echocardiography analysis. A positive stress echocardiography test was defined as a test with new or worsened regional wall motion induced by stress. Wall motion was assessed as regional endocardial excursion and myocardial thickening, and interpretation was performed by careful comparison of images from the different stress levels displayed side-by-side on the computer monitor. Wall motion abnormalities at baseline and during stress were assigned to specific coronary artery distributions (Fig. 2) and compared to results of coronary angiography.

To avoid biased interpretation, stress echocardiography studies were analyzed without knowledge of patient identity nor of the results of exercise ECG test and coronary angiography. Patient identity was hidden by a person not involved in analysis.

Three dimensional endocardial reconstruction. In Paper VII, a newly developed software was used to perform three-dimensional reconstruction of endocardial surfaces at end-diastole and end-systole. Endocardial borders of the three apical cineloops were traced by an automatic edge detection program (EdgeFinder, Vingmed Sound), supplemented with manual correction, and the endocardial surface was reconstructed by cubic spline interpolation. The algorithm and methodology are discussed in further detail in Paper VI and VII.

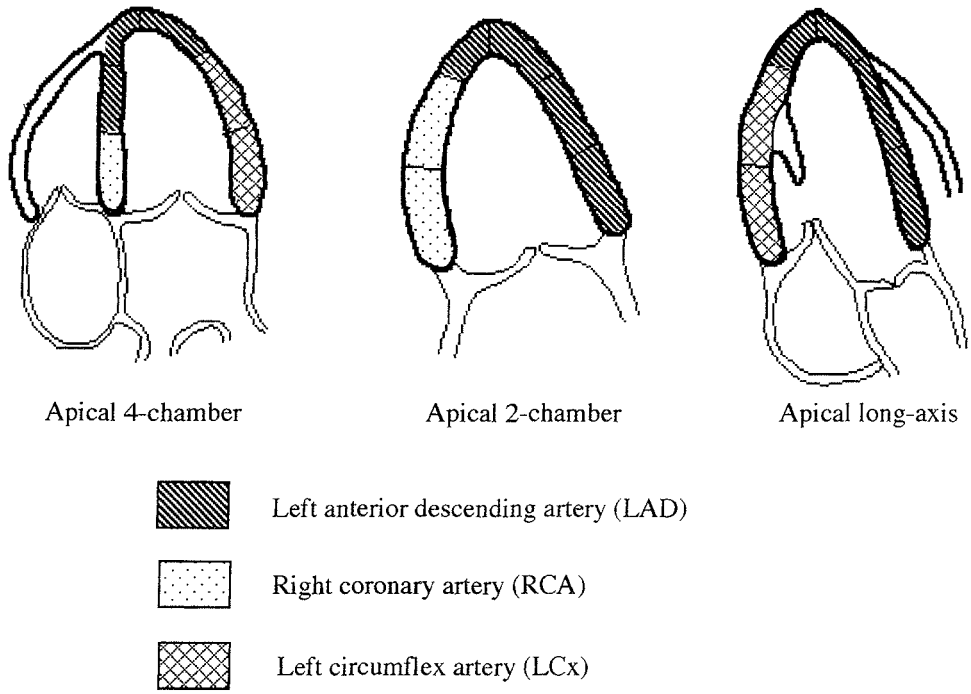

Figure 2. The common distribution of coronary blood flow related to the three echocardiographic apical imaging views.

SUMMARY OF PAPERS

Paper I

In this study, diagnostic accuracy of dipyridamole stress echocardiography was assessed by comparison to the results of coronary angiography in 94 patients, and adverse effects were assessed in the total population comprising 120 tests. High dose dipyridamole test was used (0.84 mg/kg i.v. during 10 minutes), and analysis was performed with digital systolic cineloops displayed with high frame rate for detection of wall motion changes during the test. An overall sensitivity of 73% was found for detection of coronary artery stenosis or retrograde collateral filling of occluded coronary arteries. Sensitivities for 1-, 2-, and 3-vessel disease were 43, 79, and 88%, respectively. Dipyridamole stress echocardiography was positive in 12 of 20 (60%) coronary distributions with retrograde collateral flow to an occluded artery. Multivessel disease was associated with more pronounced increase in WMSI, and with ischemic result occurring at an early stage of infusion. By assigning the location of myocardial ischemia to specific coronary artery distributions, 85% of stenotic lesions were correctly defined. The infusion caused symptomatic bradycardia and hypotension in six patients (5%). It is concluded that dipyridamole stress echocardiography has high specificity for detection of coronary stenosis, and sensitivity is good in patients with multivessel disease.

Paper II

In this study, digital dipyridamole stress echocardiography was performed in patients with previous coronary artery bypass grafting (14 patients) or myocardial infarction (16 patients). All patients included had ST-segment depression $\geq$ 1mm without chest pain during bicycle ECG test. The hypothesis was that dipyridamole stress echocardiography may be a suitable method to differentiate between patients with true and false positive ST-depression. The results of stress echocardiography showed good concordance with angiographic results. Dipyridamole echocardiography test identified patients with significant coronary lesions in both groups, in total 14 of 18 patients were identified. Sensitivity, specificity, and diagnostic accuracy of dipyridamole stress echocardiography for identification of patients with coronary stenosis or retrograde collateral flow to an occluded artery was 78, 100, and 83%, respectively. It is concluded that dipyridamole stress echocardiography is a valuable tool for assessment of true myocardial ischemia in patients with asymptomatic ST-depression after bypass surgery or myocardial infarction.

Paper III

In this study, the results of high dose dipyridamole stress echocardiography was compared to upright bicycle stress echocardiography in 37 patients. The patients included

had inconclusive results of standard bicycle ECG tests. With dipyridamole stress echocardiography, we found sensitivities for identification of 1-, 2-, and 3-vessel disease of 56, 69, and 83%, respectively, and for bicycle stress echocardiography 78, 88, and 83%, respectively. The differences between the two modalities were not statistically significant. Specificity was 100% (6 of 6 patients) for dipyridamole tests, and 67% (4 of 6 patients) for bicycle echocardiography. Interobserver agreement for positive or negative test result was higher for dipyridamole tests, 92 vs. 81%. We conclude that dipyridamole stress facilitates imaging during stable hemodynamic conditions and provides a test with low risk of false positive results. Bicycle stress echocardiography is less prone to be false negative in patients with mild coronary artery disease, and provides more physiological stress with significantly higher increase in systolic blood pressue and heart rate. This method is useful in patients who can avhieve a sufficient workload, and if facilities for computer-assisted analysis of image data are available.

Paper IV

This study focuses on the role of the image display system for observer agreement and diagnostic accuracy of stress echocardiography. Inter- and intraobserver agreement was assessed for 25 dipyridamole stress echocardiography tests analyzed from 1) videotape recordings, 2) computer displayed cineloops with high frame rate (47 frames/s), and 3) computer displayed cineloops with lower frame rate (24 frames/s). Coronary angiography was used as reference method for assessment of coronary artery patency. The results show that observer agreement is higher when analysis is performed with computer displayed cineloops than from videotape recordings, however, diagnostic accuracy is not significantly affected. Sensitivity for identification of coronary artery stenosis was similar using digital cineloops with high frame rate or videotape recordings (67% to 80% for both systems), and tended to be lower using cineloops with lower frame rate for analysis (53%).

Paper V

This paper investigated the inter- and intraobserver variation for analysis of wall motion at baseline and during low dose and high dose dobutamine infusion. Low dose (10 μg/kg/min) is used for assessment of myocardial viability in patients with baseline wall motion abnormalities, high dose is used for evaluation of myocardial ischemia. Thirty-three patients were studied, 25 had baseline wall motion abnormalities from previous myocardial infarction. Analysis was performed with digitized video signals using a continuous loop system with simultaneous display of cineloops from different stages of the test. We found complete interobserver agreement (100%) with regard to presence and

localization of baseline wall motion abnormalities. Interobserver agreement for viability and ischemia interpretation was 84 and 82%, respectively, and intraobserver agreement was 92 and 85%, respectively. Mean differences for assessment of WMSI were small and insignificant, but individual scores showed clinically important differences between the observers. We conclude that the subjective interpretation of wall motion analysis during stress echocardiography represents a methodological challenge. Semi-quantitative wall motion scoring is a useful parameter to describe regional systolic function, but for individual patient follow-up it is preferable that the same observer performs the scoring.

Paper VI

This paper presents an overview of different methods to perform computer-assisted quantitative LV wall motion analysis from two-dimensional images. The value of single plane methods and WMSI is discussed. A new algorithm for quantitative assessment of regional LV wall motion based on three-dimensional reconstruction of endocardial surfaces is presented. The input data are endocardial borders from three standard two-dimensional apical views (4-chamber, 2-chamber and long-axis views), traced in end-diastolic and end-systolic frames. The endocardial surface is reconstructed by cubic spline interpolation. End-diastolic and end-systolic surfaces are aligned in a common axis system, and regional wall motion is quantified. Total endocardial surface area can be calculated, and regions with systolic dysfunction can be calculated as a percentage of total end-diastolic area. Results are presented in "bull´s eye" maps, displaying the location and extent of wall motion abnormalities. The potential clincial use of the algorithm in quantitative assessement of regional dysfunction after acute myocardial infarction and during stress echocardiography is discussed. The major limitations for practical use of the algorithm are the necessity of clearly defined endocardial borders for correct data input, and finding a proper reference system for three-dimensional wall motion assessment.

Paper VII

This study applies the algorithm described in Paper VI for three-dimensional quantitative assessment and localization of LV wall motion abnormalities. The results obtained by application of six relevant computer implemented reference systems were compared with visual segmental wall motion analysis of standard apical two-dimensional images. For three-dimensional reconstruction, endocardial borders were traced in three apical echocardiographic views at end-diastole and end-systole in ten patients with myocardial infarction and five healthy subjects. End-diastolic and end-systolic surfaces were aligned according to the reference system applied, and systolic wall motion was assessed at 1024 points on the endocardial surface. The localization of abnormal wall motion was

displayed in bull´s-eye maps, and the area was determined as a percentage of total end-diastolic surface area. The segmental concordance between three-dimensional computerized and visual assessment was determined for each reference system. The best agreement with visual analysis was obtained with a reference system based on wall motion towards the major ventricular axis, whereas the poorest result was obtained using the center of LV cavity as reference. Correlation between the estimated area of wall motion abnormality and visually determined wall motion score index was best using the aligned center of mitral valve plane as reference ($r = 0.92$).

DISCUSSION AND CLINICAL APPLICATIONS

Clinical use of stress echocardiography.

Stress echocardiography is based on the use of two-dimensional imaging to detect abnormal LV wall motion induced by cardiac stress. Reduced endocardial excursion and/or wall thickening during stress are defined as evidence of ischemia, and is highly indicative of significant coronary artery stenosis. Regional myocardial contractile dysfunction due to acute coronary occlusion was described as early as 1935 [22], and has been proved to be a specific marker of ischemia, occurring at a lower level of stress than ischemic ECG-changes and angina pectoris [23-24]. During the last few years, stress echocardiography has become an accepted and widespread method for noninvasive identification of coronary artery stenosis, with diagnostic accuracy similar to more established methods such as myocardial scintigraphic techniques [25-29]. Most studies have found sensitivities for detection of coronary artery stenosis, defined as $\geq$ 50% vessel diameter stenosis at coronary angiography, in the range of 60 to 90%, depending on the severity of disease, and specificities in the range of 80 to 95%. The results of comparative studies indicate that stress echocardiography has slightly lower sensitivity for detection of single vessel coronary stenosis than myocardial scintigraphy, but the specificity of stress echocardiography is higher.

The indications for stress echocardiography are rapidly expanding. Extensive documentation has been provided on the prognostic value of positive or negative stress echocardiography [30-33], and its value in preoperative risk assessment [34-36]. Low-dose dobutamin infusion for detection of viable myocardium after myocardial infarction or in hibernating myocardium has received increasing attention recently [37-42]. Pharmacological stress agents have allowed continuous echocardiographic examination throughout stress, and are applicable to patients unable to undergo dynamic exercise testing. The introduction of computerized digital image processing has facilitated test interpretation by allowing off-line analysis of images obtained during different stress levels and displayed side-by-side on the computer monitor [43,44].

Paper I of this thesis was performed to evaluate dipyridamole stress echocardiography in a population in which the majority of patients had inconclusive exercise-ECG tests, or were unable to perform exercise. The results show that this test is highly specific for diagnosis of coronary artery stenosis, however, the sensitivity for single vessel coronary artery stenosis was only 43%. In other words, the test is suitable to rule out coronary stenosis in patients with false positive exercise-ECG tests, but is less suitable to identify patients with false negative results. Although it may be argued that single vessel disease with negative stress echocardiography test has good prognosis, this needs further documentation. In Paper II, dipyridamole stress echocardiography was

used to identify patients with false positive exercise ECG tests after myocardial infarction or after coronary bypass surgery. Other specific clinical situations with limited value of standard exercise-ECG testing where the benefit of stress echocardiography has been documented include stress testing in female patients [45,46], in the elderly [47], in patients with bundle branch block [48], and in hypertensive patients [49].

It may seem relevant to raise the question if stress echocardiography can substitute exercise ECG test as a "screening" method for detection of coronary artery stenosis. However, besides being more time-consuming, most stress echocardiographic studies to date have been performed in populations with high prevalence of coronary artery disease. The diagnostic accuracy in patients with lower pretest probability of coronary artery disease has not yet been properly defined [50,51]. In addition, although pharmacological stress testing has proved to be safe in the majority of patients, the risk of serious adverse effects should not be underestimated. Nevertheless, with increasing availability, stress echocardiography will undoubtedly play an increasing role in the evaluation of coronary artery disease in the future due to the considerable information obtained by this test.

Choosing the optimal modality for cardiac stress.

As shown in Table 1, several stress protocols have been proposed in association with stress echocardiography. In the present work, three different protocols were used: two pharmacological (dipyridamole and dobutamine infusion) and one dynamic exercise method (upright bicycle exercise). From these and other studies, advantages and disadvantages with each method have been identified. Although dynamic exercise is the established method to achieve physiological stress, pharmacological stress has distinct advantages. Drug infusion can be performed with the patient in the ideal position for echocardiographic imaging, thus assuring optimal image quality. Contraindications to drug infusion are few, and full dose can usually be given to all patients. Many patients with coronary artery disease can not achieve an adequate workload during dynamic exercise, but patients who are able to exercise can usually achieve a higher level of cardiac stress during dynamic exercise than during pharmacological stress. Several studies have compared diagnostic accuracy of different stress regimens [52-56]. Combining different pharmacological agents have been used, the most common combination being small boluses of atropine injected at peak dose of dobutamine infusion [57], or after dipyridamole infusion [58]. This procedure does not seem to increase the risk of adverse effects [59,60], and may improve the sensitivity for detection of coronary obstructions. However, combining drugs makes the stress protocol more complex, and the tachycardia induced may make the test more difficult to interprete. In Paper III, dipyridamole and upright bicycle stress echocardiography were compared. The product of heart rate and

Table 1. Commonly used stress methods during stress echocardiography:

I. Dynamic exercise.
- Treadmill exercise
- Bicycle exercise, upright or supine

II. Pharmacological.
- Dobutamine ± atropine
- Dipyridamole ± atropine
- Adenosine

III. Pacing.
- Transvenous
- Transoesophageal

systolic blood pressure, a determinator of myocardial oxygen demand, was significantly higher with dynamic exercise than during dipyridamole infusion. The study showed that the sensitivity for identification of coronary artery stenosis tends to be higher with the dynamic exercise approach, especially in patients with mild coronary artery disease. Similar results have been found by other investigators comparing dynamic and pharmacological stress methods [53,54], and these results may be related to the level of cardiac stress imposed by the different regimens. However, echocardiographic imaging and test interpretation is usually more convenient with pharmacological stress, and the results of Paper III indicate higher observer agreement and specificity with this type of stress.

Paper V was performed as an observer agreement study for wall motion analysis, and did not intend to establish the diagnostic accuracy for identification of coronary stenosis by dobutamine stress echocardiography. The sensitivity of only 50% was probably influenced by the high prevalence of baseline wall motion abnormalities among the patients included in the study, complicating the diagnosis of inducible ischemia [61]. Other investigators have found that dobutamine infusion is slightly more sensitive than dipyridamole for detection of coronary artery stenosis [53,62].

Safety and side effects are important aspects when choosing the optimal test. Dynamic exercise can safely be performed in patients with and without coronary disease, and the side effects are usually well tolerated. Pharmacological stress are accompanied by side effects that are not as well recognized from daily life, and the dosages used for cardiac stress are higher than what is recommended for other purposes. Extensive multicenter data has shown that both pharmacological agents are safe for stress testing in general [59,63]. However, serious adverse effects related to the drugs have occasionally

been reported [64-67]. During the 120 dipyridamole tests described in Paper I, one serious side effect occurred, and 5 additional episodes of symptomatic bradycardia and hypotension were observed. Whereas complications during exercise testing usually occur in patients with severe coronary artery disease, this may not necessarily be the case with pharmacological agents. This is illustrated by one of our patients who developed severe hypotension despite normal coronary vessels at angiography. Aminophylline can be used to reverse side effects of dipyridamole [13], however, the antagonistic action is neither immediate nor complete [65]. Drug-related adverse effects are not negligible with neither of the commonly used stress agents, and careful monitoring during all kinds of infusion protocols is mandatory.

The experiences with different stress methods in our studies suggest that the choice of stress method should be individualized, based on the characteristics of the particular patient. Dobutamine infusion is suitable for viability assessment and in the majority of patients referred for diagnosis of myocardial ischemia. However, bicycle stress echocardiography should be considered in patients with good exercise tolerance, particularly if a false negative dobutamine test is suspected, and if equipment for computer-assisted wall motion analysis is available.

Angiographic correlates for stress echocardiographic.

Although coronary angiography provides a strictly anatomical description of coronary artery anatomy, a high correlation with stress echocardiography results are reported in most studies [68]. Based on studies with quantitative coronary angiography, a stenosis of 50% of the luminal diameter, or 75% area stenosis, is considered significant, and is used to differentiate between true and false positive stress echocardiography results [69]. However, collateral coronary circulation is also important for myocardial oxygen delivery and the occurrence of ischemia during stress testing. It has been shown that myocardium supplied by retrograde collateral flow to an occluded coronary artery may become ischemic during stress [70,71]. This is frequently seen in patients with ischemic manifestations after myocardial infarction. Patients with this finding were defined as having true positive stress echocardiography tests in our studies when a new wall motion abnormality was induced in this coronary distribution.

A distinction must be made between patients with wall motion abnormalities at rest and patients with reversible ischemia. The aim of stress echocardiography is to identify coronary artery *stenosis*, manifested by inducible wall motion abnormalities. Echocardiography may identify wall motion abnormalities at rest, indicating previous myocardial infarction or myocardial hibernation, but this is not defined as a positive stress echocardiography test. In Paper I, sensitivity for diagnosing coronary artery stenosis in

patients with triple vessel disease with dipyridamole stress echocardiography was 88%, however, all patients with triple vessel disease had regional wall motion abnormalities at rest, and the sensitivity for diagnosis of coronary artery *disease* was thus 100%.

Factors influencing observer agreement.

Stress echocardiography interpretation is observer dependent and thus subjective. Two of the studies in the present thesis (Paper IV and V) focuse on inter- and intraobserver agreement for test analysis. The results of such studies depend on several variables: 1) the level of the individual observer experience and their coworking experience; 2) the image quality; 3) the prevalence and severity of coronary artery disease in the population studied; and 4) the presence of wall motion abnormalities at rest [61]. Based on our results, two additional factors can be added: 5) the display system used for test analysis (videotape or computer-assisted analysis); and 6) the method used for inducing cardiac stress. The influence of observer training was investigated by Picano et al, who stated that experience from more than 100 tests was needed for optimal accuracy [72]. With adequate training, more subtle markers of myocardial ischemia can be recognized, such as lack of hyperkinesia during dobutamine or exercise, worsening or further extension of pre-existing wall motion abnormalities, or abnormal pattern of diastolic relaxation. The use of a high quality digital computer system with rest and stress images side-by-side facilitates detection of such subtle changes [43,73]. Dipyridamole infusion induces less tachycardia, and stress echocardiography performed with this agent is easier to interprete than tests performed with dynamic exercise or dobutamine infusion. Interobserver variation for interpretation of myocardial viability was specificallly addressed in Paper V. The results showed inter- and intra-observer agreement of 84% and 92%, respectively, for viability assessment, quite similar to the results obtained for assessment of ischemia.

Quantitative wall motion analysis.

Computer processing of echocardiographic image data is a rapidly expanding field in cardiology. Off-line data analysis facilitates utilization of user-defined software. The aim in terms of quantitative echocardiography has often been to obtain reliable estimates of LV volume and ejection fraction from three-dimensional reconstruction of the ventricular cavity [74-78]. Different methodologies have been applied, however, their use in clinical practice have been limited by complex systems for acquisition of images or time-consuming postprocessing of data.

Paper VI and VII deal with a different aspect of three-dimensional reconstruction: quantitative wall motion analysis by endocardial surface reconstruction. Quantitation of

regional and global LV systolic contraction has important clinical applications. The extent of myocardial injury is a major determinant of post-infarction prognosis [79,80], and serial studies can be used to assess ventricular remodelling after myocardial infarction, or to evaluate the effects of coronary interventions [81,82]. The algorithm described in Paper VI and VII has previously been shown to reproduce accurately volumes of symmetric and deformed in vitro objects with different sizes and shapes, and has good repeatability in the clinical setting [78]. LV surface reconstruction is performed from the three standard apical imaging views described in the previous work on stress echocardiography.

In contrast to previously proposed methods for three-dimensional reconstruction of LV surface for quantititative wall motion analysis [83-85], the method presented does not rely on visual assessment of the extent of wall motion abnormality, and is completely computerized except for the manual tracing of endocardial borders. No additional equipment is required for spatial orientation of images. However, as discussed, the accuracy for quantitative wall motion analysis can be improved by using more than three apical imaging views for reconstruction. This will require an automated stepper device to obtain apical images at predefined angles of rotation. A critical issue for quantitative wall motion analysis is to apply an appropriate reference system for comparison of end-diastolic and end-systolic surfaces and determination of endocardial excursion. Clinical potential, limitations, and suggestions for future improvements are further discussed in Paper VI and VII.

Conclusions and future perspectives.

Computer transfer of digital two-dimensional images allows detailed analysis of LV wall motion for diagnostic and quantitative purposes. Images can be displayed side-by-side on the computer monitor for accurate comparison of regional wall motion, facilitating the diagnosis of myocardial viability or ischemia during stress echocardiography. In addition, specific software can be applied to combine information from multiple images to perform three-dimensional reconstruction of endocardial surfaces. A key to further progress in the work for more objective information from echocardiographic images, is to improve myocardial and endocardial visualization. Promising results have been described by new technology for automatic edge detection to quantitate LV function at rest and during stress echocardiography [86,87]. Furthermore, echocardiographic contrast agents may play an important role in evaluation of LV wall motion and perfusion [88,89]. Last, but not least, futher integration and development of computer technology will certainly be an important factor in the handling of image data for characterization of coronary artery disease in the future.

Abbreviations:

ECG = electrocardiography

LV = left ventricle

WMSI = wall motion score index.

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ERRATA:

Paper I:

- p. 166: Second column, first sentence: Accordingly, positive low-dose dipyridamole test identified 7 and 17% of patients with 1- or 2-vessel disease, respectively.
- p. 167: Table 3; adverse effects: Bradycardia/hypotension: n = 6 (5%).
- p. 167: Second column, Discussion section, 10th line: disease was detected with sensitivities of 7 an 17% with this dose.

Paper II:

- p. 643: Table III, patient no. 9: Right coronary artery normal, left circumflex artery occluded with retrograde flow.

Paper IV:

- p 108: Statistics section, 5th line: a p-value < 0.05 was considered statistically significant.

Paper I

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Digital high frame rate stress echocardiography for detection of coronary artery stenosis by high dose dipyridamole stress testing *

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Key words: coronary artery disease, dipyridamole, echocardiography

Abstract

Diagnostic accuracy of high dose dipyridamole stress echocardiography (0.84 mg i.v./kg) for detecting coronary artery stenosis was assessed in 94 patients undergoing coronary angiography, and adverse effects were registered in the total study population of 120 patients. Echocardiographic analysis was performed with digital systolic cineloops with high frame-rate (47 frames/sec) for optimal left ventricular wall motion display. Results showed sensitivity of 73% for detection of arterial luminal stenosis $\geq$ 75% or retrograde collateral flow to an occluded coronary artery. Sensitivity for detection of 1-vessel stenosis was 43% (6 of 14 patients), and for 2- and 3-vessel disease 79% (19 of 24) and 88% (16 of 18), respectively. Specificity was 92% (35 of 38), diagnostic accuracy 81%. The stenosed coronary artery was correctly localized in 85% of positive tests. Dipyridamole-induced increase in wall motion score index differed significantly between patients with 1-, 2-, and 3-vessel disease (0.02 ± 0.17, 0.15 ± 0.17, and 0.27 ± 0.24, respectively), and early positive tests (dipyridamole dose of 0.56 mg/kg) were almost exclusively seen in patients with multivessel disease. Six patients (5%) developed symptomatic bradycardia and hypotension during the test. In conclusion, dipyridamole stress echocardiography is useful for detection and localization of coronary artery stenosis, particularly in patients with multivessel disease.

Introduction

Dipyridamole infusion has been used for many years as cardiac stress during myocardial scintigraphic imaging in patients unable to perform regular exercise [1–3]. Dipyridamole induces coronary vasodilation by inhibition of cellular uptake and inactivation of endogenous adenosine [4]. The result is a substantial flow increase in normal epicardial coronary arteries, however, regional flow may become reduced in patients with significant coronary stenosis, presumably due to a steal effect. A higher dipyridamole dose than the 0.56 mg/kg used for scintigraphic imaging has been used to induce myocardial ischemia and detectable wall motion abnormalities during stress echocardiography [5], and the value of this method has been documented in various clinical situations where exercise electrocardiography test has limited value [6–10]. However, the potential of dipyridamole infusion for inducing myocardial ischemia in patients with less severe coronary artery disease has been questioned [11, 12]. As previous studies with dipyridamole stress echocardiography largely have been performed without the availability of digital analysis systems, the present study was performed using computerized display of digital cineloops with high frame rate for optimal display of left ventricular wall motion. Our aim was to study the diagnostic value as well as limitations of this method in a clinical setting.

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Material and methods

Patient selection

The study population comprised 120 consecutive patients undergoing dipyridamole stress echocardiography. The results were compared to coronary angiog-

Table 1. Baseline patient characteristics (n = 120).

Age, years, mean ± SD (range):	58.5 ± 10.2	(31–77)
Female/male, n	41/79	
	n	%
Previous AMI:	35	29%
Anterior wall:	14	12%
Inferior wall	19	16%
Lateral wall	2	2%
Baseline ECG changes:		
LBBB/RBBB:	2/6	7%
Q-wave	24	20%
Unspecific ST-T changes	17	14%
Previous CABG:	23	19%
Previous PTCA:	4	3%
Concurrent diseases:		
Hypertension	19	16%
Hypercholesterolemi	12	10%
Renal failure	9	8%
Claudication	7	6%
Diabetes mellitus	3	3%
Medications:		
Beta-blocker	61	51%
Longacting nitrates	49	41%
Calcium channel blocker	42	35%
Digitalis	7	6%
ACE-inhibitor	5	4%

ACE = angiotensin converting enzyme; AMI = acute myocardial infarction; CABG = coronary artery bypass grafting; ECG = electrocardiographic; LBBB/RBBB = left/right bundle branch block; PTCA = percutaneous transluminal coronary angioplasty.

raphy in 94 patients, while adverse effects were assessed in the entire study group. The indications for performing stress echocardiography were chest pain syndromes with or without previous myocardial infarction or coronary interventional procedures, inconclusive results at bicycle exercise electrocardiography test, physical inability to undergo exercise testing, or as preoperative screening before major vascular surgery or renal transplantation.

Baseline patient characteristics are presented in Table 1. Patients with unstable angina, obstructive pulmonary disease, congestive heart failure, or baseline systolic blood pressure < 90 mmHg were excluded. All patients gave informed consent to participation, and the protocol was approved by the regional ethical committee.

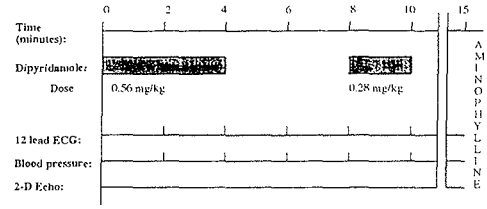

Fig. 1. High dose dipyridamole echocardiography test. ECG = electrocardiogram; 2-D = 2-dimensional echocardiography.

Dipyridamole stress echocardiography

Stress echocardiography was performed within 2 days of coronary angiography except in a group of 18 patients with chest pain syndromes and normal coronary angiography, who had stress echocardiography performed within 12 months. Coffee or tea were not allowed for 12 hours prior to the test, and patients were fasting for 3 hours. Cardiac medications were not taken at the day of the test. The high-dose dipyridamole test [5] was used as shown in Fig. 1. A maximal dose of 0.84 mg/kg was infused intravenously over 10 minutes in an antecubital vein. Initially, 0.56 mg/kg was infused over 4 minutes. If no obvious wall motion abnormality was observed during the next 4 minutes, a second dipyridamole dose of 0.28 mg/kg was infused over the next 2 minutes. At least 5 minutes later, aminophylline 90–150 mg was infused intravenously over 2–5 minutes to antagonize the dipyridamole effect. Twelve lead electrocardiography and brachial arterial blood pressure measured by oscillometry (UA-751 Takeda Medical, Tokyo, Japan), were monitored at 2 minutes intervals throughout the test.

An ultrasound scanner (CFM 750, Vingmed Sound, Horten, Norway) was used with a 3.25 MHz transducer. The scanner was interfaced to a personal computer (Macintosh II series, Apple Computers, Cupertino, California, USA) for transfer of digital image data. During the test, left ventricular wall motion was examined continuously with 2-dimensional echocardiography from both apical and parasternal positions. Systolic cineloops with a frame rate of 47 per second were obtained from apical 4-chamber, 2-chamber and long-axis view, and parasternal short-axis view at mid-papillary level. Images were transferred at: 1) rest, 2) maximal dipyridamole effect or when a new or increased wall motion abnormality was observed,

and 3) $\geq$ 5 minutes after aminophylline infusion. The cineloops comprised total systole, defined as the interval from the peak of the R-wave to the S2 signal on phonocardiography. Cineloops were transferred as scanline data without loss of ultrasound information. All cineloops were previewed on the scanner screen before transfer to the computer.

A specially designed computer software (Echo-Loops, Vingmed Sound) was used for analysis of regional wall motion. This software allows analysis of individual cineloops in slow motion as well as side-by-side comparison of synchronized cineloops from different stress levels. Positive stress echocardiography test was defined as a new or worsened wall motion abnormality induced by dipyridamole, affecting $\geq$ 1 myocardial segments with normal or hypokinetic wall motion at baseline. When compared to coronary angiography, results of dipyridamole stress echocardiography was considered as 'true positive' only if at least 1 coronary artery was stenosed, or showed retrograde filling to occluded artery. The tests were interpreted by one investigator, blinded for patient data and results of coronary angiography. All tests were also analysed by a second, independent investigator for assessment of interanalyzer variability.

Wall motion score index was calculated at baseline and during stress, by visual assessment of wall motion and thickening. A 16-segment model of the left ventricle was used [13], and segmental wall motion was graded as 1 (normal or hyperkinetic), 2 (hypokinetic), 3 (akinetic), 4 (dyskinetic) or 5 (aneurysmal). The score index was calculated as the sum of the segmental scores divided by the number of segments visualized. Wall motion abnormalities at baseline and during stress were assigned to the distributions of the left anterior descending artery, left circumflex artery, and right coronary artery, as described elsewhere [10].

Coronary angiography

Selective cineangiography (50 frames/sec) was performed by standard Judkins technique. Left and right anterior oblique views with additional cranial and caudal angle projections were used. If the origin of a venous graft could not be visualized, additional biplane aortic root angiography was performed. Angiograms were interpreted visually by a consensus of experienced angiographers without knowledge of the result of the dipyridamole test. Positive coronary angiography was defined as vessel diameter reduction of $\geq$ 50%, corresponding to cross-sectional area reduction of $\geq$ 75%, or retrograde collateral filling of a coronary artery with proximal occlusion. Lesions in the 3 major coronary arteries and the major branches (diagonal, right posterior descending or obtus marginal), were described. The number of diseased vessels was determined as the sum of occluded and stenotic coronary arteries. A lesion of the left main coronary artery was counted as a lesion of both left anterior descending and left circumflex arteries. Venous bypass grafts were described as patent or occluded. An occluded coronary artery was defined as a native vessel occlusion without patent bypass graft.

Statistical analysis

Data are presented as means $\pm$ SD, range in parenthesis. Sensitivity, specificity and diagnostic accuracy for dipyridamole echocardiography test were calculated according to the standard definitions [14], with results of coronary angiography as reference. Comparisons of wall motion score index between patient groups were performed with unpaired Student's t-test, 1- or 2-sided test as appropriate. Student t-test for matched pairs was used for determination of interanalyzer variation for wall motion score index. Significance was set at the 5% level.

Results

Coronary angiography

Of the 94 patients who underwent coronary angiography, 56 (60%) had coronary artery stenosis. Of these, 14 (15%) had 1-vessel disease, 24 (26%) had 2-vessel disease, and 18 (19%) had 3-vessel disease. Left anterior descending artery or the diagonal branch were stenosed in 38 patients (40%), the diagonal branch alone in 8 patients. Left circumflex artery or the obtus marginal branch were stenosed in 25 patients (27%), obtus marginal branch alone in 7. The right coronary artery was stenosed in 27 patients (29%), none had isolated stenosis of the right posterior descending branch. Left main coronary artery was stenosed in 5 patients. Thirty-eight patients did not have significant coronary stenosis, of these, 2 had total coronary artery occlusions. Occluded vessels were found in 36 patients (38%), 20 of these had retrograde collateral filling of the occluded artery.

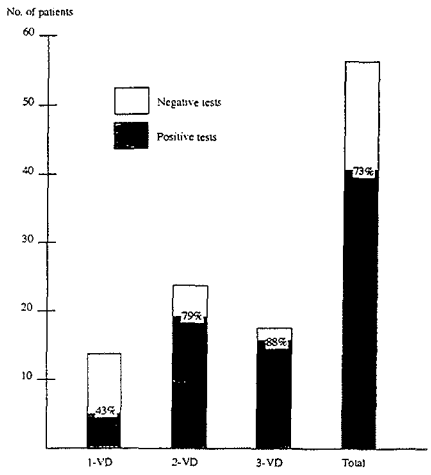

Fig. 2. Bar plot of sensitivity for dipyridamole stress echocardiography test in patients with angiographic coronary artery stenosis. 1-VD = single vessel disease; 2-VD = 2-vessel disease; 3-VD = 3-vessel disease.

Table 2. Tabular display of agreement between the results of dipyridamole stress echocardiography and coronary angiography. n = no. of patients; VD = no. of vessels diseased.

Dipyridamole echocardiography	Coronary angiography No stenosis	1-VD	2-VD	3-VD
Positive	3	6	19	16
Negative	35	8	5	2
Total	38	14	24	18

Dipyridamole echocardiography

All patients had interpretable stress echocardiographic images. Wall motion abnormalities at baseline were identified in 61 patients (65%) undergoing coronary angiography. Comparison of the results of high-dose dipyridamole stress echocardiography and coronary angiography is shown in Fig. 2 and Table 2.

Fifteen tests (16%) were interupted after low-dose dipyridamole (0.56 mg/kg) due to positive tests. Of these, 9 had 3-vessel disease, 4 had 2-vessel disease, 1 had 1-vessel disease, and 1 had normal coronary arteries but left bundle branch block by electrocardiogram.

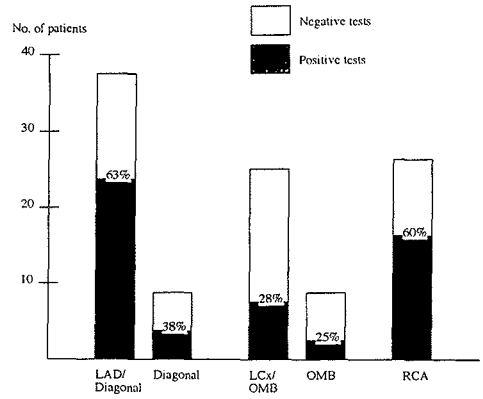

Fig. 3. Bar plot of sensitivity for detection of specific coronary artery stenosis. LAD = left anterior descending artery; LCx = left circumflex artery; OMB = obtus marginal branch; RCA = right coronary artery.

Accordingly, positive low-dose dipyridamole test identified 7 and 8% of patients with 1- or 2-vessel disease, respectively, but 50% of patients with 3-vessel disease.

During high-dose dipyridamole test, 41 of the 56 patients with coronary artery stenosis had positive dipyridamole tests, while 3 of the 38 patients without significant stenosis had dipyridamole-induced wall motion abnormality. Thus, overall sensitivity, specificity and diagnostic accuracy for detection of coronary artery stenosis were 73, 92 and 81%, respectively. Sensitivity for detection of 1-, 2-, and 3-vessel disease was 43, 79, and 88%, respectively. Seventeen of the 20 patients with retrograde flow to an occluded coronary artery had positive tests (85%), and in 12 of these patients the wall motion abnormality corresponded to the coronary distribution of the occluded artery.

Diagnosis of specific coronary artery stenosis

The sensitivities for diagnosis of specific coronary artery stenoses are displayed in Fig. 3. Sensitivity was lowest for lesions of the left circumflex artery distribution (28%). Left anterior descending and right coronary artery lesions were detected with sensitivities of 63 and 60%, respectively. Of 41 patients with positive results at both dipyridamole echocardiography test and coronary angiography, the wall motion abnormality was described in a myocardial region corresponding

to angiographic stenosis in 35 patients (85%). Twenty-four patients had angiographic multivessel stenoses, of these 13 (54%) developed wall motion abnormalities in multiple coronary distributions during the test.

Wall motion score index

Mean wall motion score index at rest was 1.20 ± 0.25 (range 1.00–2.00) and increased during stress to 1.29 ± 0.30, (range 1.00–2.25), $p < 0.0001$. Mean increase in wall motion score index during dipyridamole was significantly different between groups of patients with single-, 2-, and 3-vessel disease, 0.02 ± 0.17, 0.15 ± 0.16, and 0.27 ± 0.24, respectively.

Interobserver agreement

The two independent observers agreed on positive or negative test in 89 of the 94 tests (95%). The observers agreed on the vessel involved in 34 (89%) of the 38 tests interpreted as positive by both. There were no significant differences between the observers in calculated wall motion score index at rest (1.20 ± 0.25 vs. 1.18 ± 0.29) or during stress (1.28 ± 0.30 vs. 1.25 ± 0.32).

Electrocardiographic changes and chest pain

At peak dipyridamole, ST-segment depression ≥ 1 mm occurred in 17 patients (18%). All but 1 of these had positive dipyridamole echocardiography test, all had positive coronary angiography. Thus, ST-segment depression had a specificity of 100% for detection of coronary artery stenosis, sensitivity was 30%. Chest pain occurred in 25 patients (27%). Of these, 15 had positive dipyridamole test, 20 had positive coronary angiography, and 11 had ST-depression ≥ 1 mm. Thus, occurrence of chest pain during dipyridamole infusion had sensitivity of 36% and specificity of 80% for detection of coronary artery stenosis.

Adverse effects

Adverse effects occurred in 46 of the 120 patients (38%) during dipyridamole infusion, and are listed in Table 3. The test was prematurely interrupted in 7 patients (6%) due to hypotension/bradycardia (6 patients) or borborygmia (1 patient). One patient with permanent atrial fibrillation at baseline had sudden onset cardiac arrest after finishing the dipyridamole infusion, but recovered without sequelae after a thump on the chest. The other side effects were generally mild in severity.

Table 3. Adverse effects occurring during 120 dipyridamole echocardiography tests.

	n	(%)
-Headache	23	(19)
-Flushing	7	(6)
-Dyspnea	7	(6)
-Bradycardia/hypotension	5	(4)
-Anxiety	3	(3)
-Borborygmia	2	(2)
-Cough	1	(1)

Discussion

Diagnostic accuracy of dipyridamole stress echocardiography

The present study emphasizes the necessity of using high-dose dipyridamole infusion in order to provoke myocardial ischemia detectable with echocardiography. In the population studied, low-dose dipyridamole induced or aggravated wall motion abnormalities in only 25% of patients with coronary artery stenosis, with high-dose dipyridamole the sensitivity was 73%. Interestingly, 50% of the patients with 3-vessel disease were identified after the low-dose, but 1- or 2-vessel disease was detected with sensitivities of 7 and 8% with this dose. Our findings are in agreement with the results of Margonato et al. [12] who showed that dipyridamole infusion with 0.6 mg/kg was unlikely to induce ischemia in patients without multi-vessel disease, and the abnormal wall motion was confined to the distribution of the coronary artery with most limited flow reserve. In our study, high-dose dipyridamole induced detectable left ventricular wall motion abnormalities in 83% of patients with multivessel coronary artery disease, and in 43% of patients with 1-vessel stenosis. These results reflect that dipyridamole echocardiography test, like other noninvasive cardiac stress tests, has low sensitivity for detection of mild coronary artery disease, even when using the high-dose dipyridamole protocol. Previtali et al. found dobutamine stress echocardiography to be slightly more sensitive for detection of 1-vessel disease than dipyridamole, 50

vs. 31%, however, the difference was not statistically significant [15]. Thus, both the pharmacological agents most commonly used for stress echocardiography often fail to induce sufficient ischemia to elicit wall motion abnormalities in patients with mild coronary artery disease. Recently, the addition of atropine injections to dipyridamole infusion has been suggested to increase the overall sensitivity of the test [16], as has previously been shown for dobutamine stress echocardiography [17]. Doppler echocardiography during dipyridamole infusion has not proved to be helpful for detection of coronary artery disease unless severe multivessel disease is present [18–20]. In our study, electrocardiographic ST-depression during dipyridamole infusion was a specific, but not a sensitive marker for coronary artery stenosis, and the occurrence of chest pain was neither sensitive nor specific.

Three of our study patients had positive dipyridamole tests despite negative coronary angiography, 1 patient even during low-dose dipyridamole. This patient had left bundle branch block, not known to the interpretors. Conduction disturbances may cause abnormal contraction pattern that may mimick ischemic wall motion. Another 'false positive test' occurred in a patient with dipyridamole-induced hypotension. In this case, the abnormal wall motion may have been provoked by a decrease in coronary perfusion pressure. Generally, studies with dipyridamole stress echocardiography report high specificity for detection of coronary artery stenoses [5, 6]. This may be related to the modest change in heart rate and inotropic state induced by dipyridamole. During exercise or dobutamine stress echocardiography, vigorous movement of the hypercontractile heart may complicate the interpretation of left ventricular wall motion. Absence of augmented wall motion during these tests is often considered as evidence of myocardial ischemia, and this may increase the risk of false positive interpretation [21].

Diagnostic accuracy for stress echocardiography is calculated using angiographic diameter stenosis of the major epicardial coronary vessels as reference. However, regional coronary supply is also influenced by the collateral circulation, not easily assessed by coronary angiography. In the present study, patients with retrograde coronary flow to arteries with proximal occlusion were considered as having positive coronary angiography, and 12 of the 20 patients with this finding had positive dipyridamole tests in this specific coronary distribution. In a coronary perfusion study with positron emission tomography, Demer et al. [22] showed that dipyridamole induced coronary steal from the collateral circulation in patients with angiographic collaterals. Nishimura et al. [23] recently reported that ST-depression during adenosine infusion was strongly associated with the presence of angiographic collaterals in patients without previous myocardial infarction. Similarly, we have previously reported that the majority of patients with occluded coronary arteries and retrograde collateral filling showed evidence of ischemia during dipyridamole infusion, manifested by both echocardiographic wall motion abnormalities and ST-depression during exercise testing [10]. Thus, stress echocardiography using adenosine or dipyridamole as stress agent may be particularly useful for evaluation of collateral flow, and may provide functional information complementary to the anatomic evaluation obtained by coronary angiography.

Detection of specific coronary artery stenosis

Dipyridamole induced new or worsened wall motion abnormalities in multiple coronary distributions in 54% of patients with angiographic multivessel stenosis. Stenoses of left anterior descending and right coronary artery were detected with sensitivities of 63 and 60%, respectively, while the sensitivity for left circumflex artery stenosis was lower, 28%. These findings are comparable to the results obtained by Armstrong et al. with exercise echocardiography [24]. The low sensitivity for detection of left circumflex stenoses may thus be related to echocardiographic visualization of this myocardial distribution, rather than to the use of dipyridamole as a stress agent. In our study population, 16 of the patients had stenosis of the diagonal branch of left anterior descending artery or of the obtus marginal branch of the circumflex artery, 5 of these patients (31%) developed wall motion abnormality in the corresponding coronary distribution. This result shows that dipyridamole stress echocardiography has limited value in identifying stenosis in smaller sized arteries.

Adverse effects

Six patients in our study experienced symptomatic hypotension and bradycardia. The safety of both low dose (0.56 mg/kg) and high dose (0.84 mg/kg) dipyridamole infusion has been assessed in multicenter studies [25, 26]. In the latter study, comprising more than 10000 high dose dipyridamole tests, side effects necessitated premature termination in 1.2% of patients, and major complications were attributed to

unrecognized myocardial ischemia. In our study, limiting hypotension occurred in 1 patient with normal coronary angiography, and 2 of the other 5 patients with this complication had negative tests at the time of interruption. All patients developing hypotension and bradycardia had history of atrioventricular conduction disorders, or were treated with betablocking agents. Dipyridamole exerts influence on sinoatrial and atrioventricular conduction by increasing coronary levels of adenosine [27, 28], although this effect is less pronounced than with exogenous adenosine used therapeutically for supraventricular tachyarrhythmias. It is noteworthy that aminophylline, although claimed to reverse the dipyridamole effect promptly [1], did not provide immediate reversal of these side effects. This phenomenon has been described in a previous case report with severe, prolonged ischemic reaction during dipyridamole infusion [29]. Patients undergoing stress testing with dipyridamole, as with other stress modalities, should be carefully monitored for occurrence of unexpected emergencies, and an automatic blood pressure device should be used for immediate recognition of hypotension. Our experiences indicate that the safety of high dose dipyridamole stress test in patients with conduction abnormalities should be further investigated.

Methodological considerations

Generally, the patients studied showed mild degree of myocardial ischemia, indicated by a small increase in wal motion score index and a low incidence of electrocardiographic ST-depression during the test. Among patients with positive tests, the change in wall motion score index ranged from a mean of 0.02 for patients with 1-vessel disease to 0.30 for the 3-vessel disease group, this increase corresponds to < 4 myocardial segments with normal wall motion at rest becoming hypokinetic during dipyridamole infusion, or < 2 segments becoming akinetic. Although minor changes may be recognized with on-line analysis or review of video tape, a high level of experience in stress echocardiography interpretation is required [30], particularly in patients with baseline wall motion abnormalities from previous myocardial infarction. A computerized system with high temporal resolution was used for wall motion analysis, and provided systolic cineloops with high frame-rate (47 frames/sec, or 18 frames/systole), facilitating detection of subtle changes. The advantages of computerized display for stress echocardiography interpretation are well accepted, however, the benefit of high frame rate display on diagnostic accuracy has not yet been documented.

Interobserver agreement on test results in our study was 95%, despite the minor changes in wall motion score. We believe the modest increase in heart rate induced by dipyridamole facilitated interpretation of the test and contributed to the high interobserver agreement observed.

Study limitations

The sensitivity of dipyridamole echocardiography test in our study may have been underestimated as the patients were taking antianginal medications until the day of the test [31, 32]. However, it is impractical to withdraw medications for a longer period before stress testing in outpatient practice.

Clinical implications

The results of the present study show that dipyridamole stress echocardiography has high specificity for detection of significant coronary artery disease, and the sensitivity is good in patients with multivessel disease using the high-dose dipyridamole protool. Dipyridamole is an interesting alternative to regular exercise or dobutamine stress testing, providing optimal imaging conditions and a different hemodynamic profile. The combination of dipyridamole and other stress agents should be further encouraged in order to improve diagnostic accuracy in patients with less severe coronary disease, and to reduce the risk of adverse effects associated with infusion of the higher dose of dipyridamole used during stress echocardiography.

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Paper II

Digital Dipyridamole Stress Echocardiography in Silent Ischemia After Coronary Artery Bypass Grafting and/or After Healing of Acute Myocardial Infarction

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This study evaluates dipyridamole stress echocardiography in silent ischemia. Fourteen patients with previous coronary artery bypass grafting (group A) and 16 patients with healed myocardial infarction (group B) were studied. All had ≥1 mm ST depression without chest pain during bicycle exercise testing. Left ventricular wall motion was analyzed using a computerized display of digital systolic cineloops with a high frame rate. Test results were compared with coronary angiography. Dipyridamole echocardiography accurately identified patients with significant coronary artery stenosis in both groups (3 of 4 in group A, 11 of 14 in group B). Retrograde flow to the occluded native artery was associated with positive results on dipyridamole testing in 6 of 7 patients in group A and all 3 in group B. Sensitivity, specificity and diagnostic accuracy for detecting significant coronary stenosis or occlusions with retrograde flow was 78, 100 and 83%, respectively. Patients with angiographic multivessel disease had a significantly larger increase in wall motion score index during dipyridamole stress than patients with 0- or 1-vessel disease, 0.18 ± 0.11 versus 0.05 ± 0.18 ($p < 0.05$). Two patients developed symptomatic bradycardia and hypotension during dipyridamole infusion. It is concluded that dipyridamole echocardiography accurately identifies myocardial regions with restricted coronary flow. Stress echocardiography is a valuable tool for assessing coronary flow in silent ischemia.

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Asymptomatic ST depression is frequently found during exercise testing or ambulatory electrocardiographic monitoring in patients with known coronary artery disease.[1,2] Exercise-induced ST depression ≥1 mm after myocardial infarction (MI) is associated with a 10-fold increase in cardiac mortality,[3] and patients with silent ischemia have the same mortality rate and risk of sudden death as symptomatic patients.[4–6] The severity of ischemia, the extent of coronary artery disease and left ventricular dysfunction are the most important prognostic determinants after MI, regardless of symptoms.[7] The significance of exercise-induced ST depression after coronary artery bypass grafting (CABG) is more controversial.[8] ST depression during exercise has been found to be a poor predictor of subsequent cardiac events in these patients.[9,10]

Dipyridamole stress echocardiography is a noninvasive method with high specificity for detection of coronary artery obstruction in various subsets of patients.[11–13] In the present study, 30 patients with silent ST depression during bicycle exercise testing after CABG or MI underwent dipyridamole echocardiography and coronary angiography. The aim was to evaluate dipyridamole echocardiography as a method for identifying myocardial ischemia in patients with silent ST depression during exercise.

METHODS

Patients: Patients referred to coronary angiography for suspected silent ischemia after CABG or MI were included consecutively. The inclusion criterion was ≥1 mm horizontal or downsloping ST-segment depression without chest pain during upright bicycle exercise testing. ST depression was measured 0.08 second after J point in ≥3 consecutive beats. Cardiac medications were not taken at the day of the test. Exercise work load started at 50W and increased with 25W every 2 minutes. Twelve-lead electrocardiography and manometer blood pressure were recorded at baseline and at every stage. Predefined end points were chest pain, general fatigue, ST-segment depression ≥4 mm, arrhythmias or heart rate >85% of age-predicted maximum. Exclusion criteria were digitalis therapy, bundle branch block or ST depression at rest, unstable angina pectoris, manifest heart failure, obstructive pulmonary disease or systolic blood pressure <90 mm Hg at rest.

Group A was selected from 206 patients with previous CABG who had a bicycle exercise test as part of a follow-up study. Silent ST depression was found in 14

TABLE I Group A: Individual Baseline Characteristics

Patient Number	Age (yr) & Sex	Coronary Artery Bypassed					Previous Infarction	Bicycle Exercise Test		Medication
		Right	LAD	FD	LOM	MB		Max. Load (W)	ST Depr. (mm)	
1	70F	+	0	+	+	0	0	100	1.5	0
2	66M	0	+	0	+	0	0	125	1.5	1
3	66M	0	+	0	+	0	0	125	1.5	2
4	64M	0	+	+	+	0	Inferior	125	1.0	1
5	68M	0	+	+	+	+	0	100	2.0	0
6	48M	0	+	0	0	0	Inferior	175	1.5	1
7	60M	+	+	0	0	+	Anterior	125	1.0	1, 2
8	63M	0	+	0	+	0	0	150	1.0	0
9	47M	0	+	0	0	0	Inferior	125	2.0	1
10	61F	+	+	0	+	0	0	75	1.0	3
11	66M	0	+	0	0	0	0	150	2.0	0
12	53F	+	+	0	+	+	0	100	2.0	1, 2
13	64M	0	+	0	0	+	0	150	1.0	0
14	67M	+	+	0	+	0	0	125	1.5	1, 2

Depr. = depression; FD = first diagonal branch of left anterior descending artery; LAD = left anterior descending coronary artery; LOM = left obtuse marginal branch of the left circumflex artery; Max. = maximal; MB = marginal branch of left circumflex other than obtuse marginal. Medication: 0 = none; 1 = β-blocking agent; 2 = calcium antagonist; 3 = long-acting nitroglycerin.

TABLE II Group B: Individual Baseline Characteristics

Patient Number	Age (yr) & Sex	MI Characteristics (ECG)	Streptokinase	Bicycle Exercise Test		Medication
				Max. Load (W)	ST Depr. (mm)	
1	48M	Anterior	0	125	2.0	1, 3
2	67M	Inferior	+	100	2.0	1, 3
3	61M	Inferior	+	125	1.0	1, 3
4	55M	Inferior	0	125	1.0	1, 3
5	58F	Lateral	+	75	1.0	1, 3
6	66M	Inferior	0	50	2.0	1
7	69M	Lateral	0	125	2.5	1
8	63M	Inferior	0	75	2.0	1, 3
9	66M	Inferior	+	100	1.0	1, 3
10	59F	Anterior	0	125	2.0	2, 3
11	62M	Inferior	0	175	2.5	1, 3
12	51M	Inferior	+	125	1.5	1, 3
13	40F	Anterior	0	75	1.5	1
14	39M	Inferior	+	200	1.5	1
15	51F	Anterior	0	100	3.0	1
16	76M	Inferior	0	100	3.0	1, 3

ECG = electrocardiogram; other abbreviations as in Table I.

patients (6.8%), 3 of whom were women. Age at inclusion was 62 ± 7 years (mean ± SD), (range 47 to 70). Four patients had MI before the operation. Time between surgery and inclusion was 70 months (range 26 to 91). Twelve patients (86%) were asymptomatic during daily activities, and 2 reported episodes of angina on effort. Exercise-induced ST depression was 1.5 ± 0.4 mm (range 1.0 to 2.0), and maximal work load was 125 ± 26 W (range 75 to 175). Individual baseline characteristics are listed in Table I.

Group B comprised 16 patients (5 women and 11 men aged 58 ± 10 years [range 39 to 76]) with previous MI. Electrocardiographically, MI was located in the left ventricular inferior wall in 10 patients (63%), lateral wall in 2 (13%) and anterior wall in 4 (25%). Q wave was found in 7 patients (44%). Thrombolytic treatment was administered to 6 patients (38%) on admission for acute MI. Mean time between MI and inclusion was 13 months (range 3 to 63). Fourteen patients (88%) had no angina during daily activities, 2 had angina on effort. Exercise-induced ST depression was 1.8 ± 0.7 mm (range 1 to 3), and maximal work load 113 ± 38 W (range 50 to 200). Individual baseline characteristics are listed in Table II.

All patients were in sinus rhythm. One had diabetes mellitus; 3 were treated for hypertension and 1 had electrocardiographic signs of left ventricular hypertrophy. The protocol was approved by the regional ethical committee; all patients gave informed consent to participate.

Dipyridamole stress echocardiography: Stress echocardiography was performed within 2 days of coronary angiography. Coffee or tea were not taken for 12 hours before the test, and patients were fasting for ≥3 hours. Cardiac medications were not taken in the morning before the test. The high-dose dipyridamole test was used.[14] An initial intravenous dose of 0.56 mg/kg was infused over 4 minutes with a cannula in an antecubital vein. If no obvious wall motion abnormality was observed during the next 4 minutes, a second dipyridamole infusion of 0.28 mg/kg was given over the next 2 min-

utes. At least 5 minutes later, aminophylline 90 to 150 mg was administered intravenously over 2 to 5 minutes to reverse the dipyridamole effect. Twelve-lead electrocardiography and brachial arterial blood pressure measured by oscillometry (UA-751 Takeda Medical, Tokyo, Japan), were monitored every 2 minutes throughout the test.

An ultrasound scanner (CFM 750, Vingmed Sound, Horten, Norway) was used with a 3.25 MHz annular array transducer. The scanner was interfaced to a personal computer (Macintosh II, Apple Computers) for transfer of digital image data. Systolic cineloops obtained from apical (4- and 2-chamber, and long-axis) and parasternal short-axis views, were transferred at 3 stages: (1) rest, (2) maximal dipyridamole effect or when a new or increased wall motion abnormality was observed, and (3) ≥5 minutes after aminophylline infusion. The cineloops consisted of total systole, defined as the interval from the peak of the R wave to the aortic valve closure on phonocardiography. The cineloops obtained had a frame rate of 47 frames/s with the standard sector angle. All cineloops were previewed on the scanner screen before transfer to the computer.

A specially designed computer software (Echo-Loops, Vingmed Sound, Horten, Norway) was used for analysis. This software allows regional wall motion analysis of individual cineloops in slow motion and comparison with synchronized cineloops from other stress levels. A positive stress echocardiography test was defined as a new or increased wall motion abnormality induced by dipyridamole. The tests were interpreted by the principal investigator unaware of patient data and the results of coronary angiography. All tests were also analyzed by a second, independent investigator, for assessment of interanalyzer variability.

Wall motion score index was calculated at rest and during stress, based on visual analysis of the cineloops. A 16-segment model of the left ventricle was used[15]

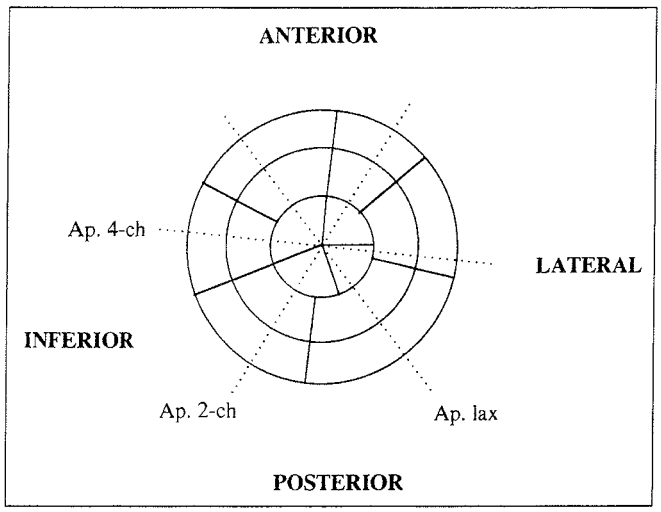

FIGURE 1. Bull's eye plot of left ventricular wall motion represented by 16 myocardial segments generated from the 3 apical views. Ap. 2-ch = apical 2-chamber; Ap. 4-ch = apical 4-chamber; Ap. lax = apical long axis.

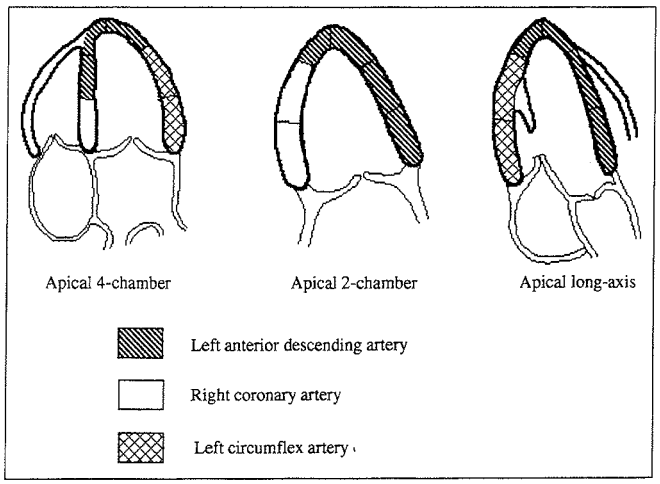

FIGURE 2. The common distribution of coronary flow as related to the 3 standard apical echocardiographic image planes.

TABLE III Group A: Individual Results of Dipyridamole Stress Echocardiography and Coronary Angiography

Patient Number	Baseline Echocardiography				Dipyridamole Echocardiography					Coronary Angiography								
		Region of WMA					Region of WMA			Occlusions			Retrograde Flow			Stenosis		
	WMSI	Right	LAD	LC	Result	WMSI	Right	LAD	LC	Right	LAD	LC	Right	LAD	LC	Right	LAD	LC
1	1.31	0	+	0	0	1.12	0	0	0	0	0	0	0	0	0	0	0	0
2	1.31	+	0	0	+	1.44	+	0	0	+	0	0	+	0	0	0	0	0
3	1.56	+	0	+	0	1.25	0	0	0	0	0	0	0	0	0	0	0	+
4	1.06	+	0	0	+	1.38	+	+	0	0	0	0	0	0	0	+	0	0
5	1.19	+	0	0	+	1.50	+	+	0	+	0	0	+	0	0	0	+	0
6	1.12	0	0	+	+	1.24	0	0	+	+	0	0	+	0	0	0	0	+
7	1.88	+	+	0	0	1.50	0	0	0	0	0	0	0	0	0	0	0	0
8	1.06	0	+	0	0	1.00	0	0	0	+	0	0	0	0	0	0	0	0
9	1.62	+	+	0	0	1.56	0	0	0	+	0	0	0	0	0	0	0	0
10	1.00	0	0	0	+	1.12	0	+	0	+	+	+	+	+	0	0	0	0
11	1.19	+	0	0	0	1.00	0	0	0	0	0	0	0	0	0	0	0	0
12	1.06	0	+	0	+	1.19	+	0	+	+	+	+	+	+	0	0	0	0
13	1.50	+	+	0	+	1.69	0	+	0	0	+	0	0	+	0	0	0	0
14	1.00	0	0	0	0	1.00	0	0	0	0	0	0	0	0	0	0	0	0

LAD = left anterior descending artery; LC = left circumflex artery; WMA = wall motion abnormality; WMSI = wall motion score index.

(Figure 1). Segmental wall motion was graded as 1 (normal or hyperkinetic), 2 (hypokinetic), 3 (akinetic), 4 (dyskinetic) or 5 (aneurysmal). The score index was calculated as the sum of the segmental scores divided by the number of segments visualized. Wall motion abnormalities at rest and during stress were assigned to the distributions of the left anterior descending artery, left circumflex artery, and right coronary artery (Figure 2). Considerable overlap exists between the left circumflex and right coronary artery distributions.[16] Thus, abnormal wall motion in the inferior, inferoposterior or posterolateral wall was considered to be in agreement with angiography if a lesion of 1 of these vessels was found.

Coronary angiography: Selective cineangiography (50 frames/s) was performed by the standard Judkins technique. Five cranial and caudal angle projections were used. If the origin of a venous graft could not be visualized, additional biplane aortic root angiography was performed. The angiograms were interpreted visually by 2 independent angiographers without knowledge of the result of the dipyridamole test, and a consensus statement was then made. Venous bypass grafts were described as patent or occluded. An occluded coronary artery was defined as a native vessel occlusion without patent bypass graft. Retrograde coronary flow was defined as collateral filling of a native vessel with proximal occlusion. Significant stenosis was defined as a diameter reduction of ≥50% of a native artery, corresponding to cross-sectional area reduction of ≥75%. Lesions in the 3 major coronary arteries or their major branches (diagonal, right posterior descending or obtuse marginal) were described. The number of diseased vessels was determined as the sum of occluded and stenotic coronary arteries. A lesion of the left main coronary artery was considered as a combined lesion of the left anterior descending and left circumflex arteries.

Statistical analysis: Data are presented as mean ± SD. Sensitivity, specificity and diagnostic accuracy for dipyridamole echocardiography testing were calculated according to the standard definitions, with angiographic results as reference. Wall motion score index between groups were compared using nonparametric Mann-Whitney U test. Wilcoxon's matched pairs statistics were used for calculation of interanalyzer variation on wall motion score index. Significance was set at the 5% level.

RESULTS

Coronary angiography: Individual angiographic results are presented in Tables III (group A) and IV (group B).

GROUP A: Occluded coronary vessels were found in 8 patients (57%), and 7 had retrograde flow to the occluded artery. Significant stenosis of native coronary arteries were identified in 4 patients (29%). Two patients had both a stenotic coronary artery and an occluded vessel with retrograde flow. Four patients had no significant coronary lesions, 6 had 1-vessel, 2 had 2-vessel, and 2 had 3-vessel disease.

GROUP B: Occluded coronary vessels were found in 11 patients (69%), and 3 had retrograde flow to the occluded artery. Coronary artery stenoses were identified in 14 patients (88%), and 8 patients had >1 stenotic artery. Left main coronary artery stenosis was found in 2 patients, stenosis of the left anterior descending artery in 9, left circumflex in 6, and right coronary artery in 4. One-vessel disease was found in 4 patients, 8 had 2-vessel, and 4 had 3-vessel disease.

Dipyridamole echocardiography test: Individual results are presented in Tables III (group A) and IV (group B), overall results in Table V.

GROUP A: Baseline wall motion abnormalities were identified in 12 patients (86%). Dipyridamole echocardiography test was positive in 7 patients (50%). Of 4 patients with coronary artery stenosis, 3 had positive test results, whereas 1 patient with isolated stenosis of the obtuse marginal had a negative test result (patient 3, Table III). The location of wall motion abnormality corresponded to coronary artery stenosis in all patients with positive tests. Dipyridamole echocardiography yielded positive results in 6 of the 7 patients with retrograde flow to an occluded coronary artery and specifically identified the vessel with retrograde flow in 5 patients. All 4 pa-

TABLE IV Group B: Individual Results of Dipyridamole Stress Echocardiography and Coronary Angiography

Patient Number	Baseline Echocardiography				Dipyridamole Echocardiography					Coronary Angiography								
		Region of WMA					Region of WMA			Occlusions			Retrograde Flow			Stenosis		
	WMSI	Right	LAD	LC	Result	WMSI	Right	LAD	LC	Right	LAD	LC	Right	LAD	LC	Right	LAD	LC
1	1.62	0	+	0	+	1.75	0	+	+	0	+	0	0	+	0	0	+	+
2	1.19	0	0	+	0	1.19	0	0	0	0	0	+	0	0	0	+	0	0
3	1.25	+	0	0	+	1.38	0	+	0	+	0	0	0	0	0	0	+	0
4	1.25	+	0	0	0	1.25	0	0	0	+	0	0	0	0	0	0	0	0
5	1.06	0	0	+	0	1.06	0	0	0	0	0	0	0	0	0	0	+	0
6	1.06	+	0	0	+	1.50	+	+	0	0	0	+	0	0	0	+	+	0
7	1.00	0	0	0	0	1.00	0	0	0	0	0	0	0	0	0	0	0	+
8	1.00	0	0	0	+	1.25	+	+	0	0	0	0	0	0	0	+	+	0
9	1.00	0	0	0	+	1.12	0	+	0	0	0	+	0	0	0	0	+	+
10	1.44	0	+	0	+	1.56	0	0	+	0	0	0	0	0	0	+	+	+
11	1.12	+	0	0	+	1.19	0	0	+	0	0	+	0	0	0	0	+	0
12	1.50	+	0	0	+	1.69	0	+	+	+	0	0	+	0	0	0	+	+
13	1.62	0	+	0	+	1.88	0	+	+	0	+	+	0	+	0	0	0	+
14	1.19	0	0	+	0	1.19	0	0	0	0	0	+	0	0	0	0	0	0
15	1.06	0	+	0	+	1.25	0	+	0	0	0	0	0	0	0	0	+	+
16	1.19	0	0	+	+	1.44	0	+	+	+	0	0	0	0	0	0	+	+

Abbreviations as in Table III.

TABLE V Sensitivity, Specificity and Diagnostic Accuracy for Identification of Obstructive Coronary Disease with Dipyridamole Stress Echocardiography

	Sensitivity			
	Coronary Stenosis	Retrograde Flow	Specificity	Diagnostic Accuracy
	No.(%)	No.(%)	No.(%)	No.(%)
Group A	3/4 (75)	6/7 (86)	5/5 (100)	12/14 (86)
Group B	11/14 (79)	3/3 (100)	2/2 (100)	13/16 (81)
Total	14/18 (78)	9/10 (90)	7/7 (100)	25/30 (83)

tients with angiographic 2- or 3-vessel disease had positive test results, and all 4 patients without significant coronary lesions had negative test results.

GROUP B: Baseline wall motion abnormalities were identified in 13 patients (81%). In all of them, the region with abnormal wall motion corresponded to the location of MI as determined by electrocardiography. Dipyridamole echocardiography was positive in 11 patients (69%). The new wall motion abnormality corresponded to a coronary vessel with stenosis or retrograde flow in 10 patients, whereas in 1 (no. 11, Table IV), wall motion abnormality occurred in a distribution with occluded coronary vessel. Nine patients with positive stress echocardiography had baseline wall motion abnormality. The wall motion abnormality induced by dipyridamole occurred in a remote myocardial region in 4 patients, in the same region in 1, and in both a remote and the same region in 4. Of the 14 patients with coronary stenosis, 3 (21%) had negative test results. These patients had stenosis of the left anterior descending, left circumflex and right coronary arteries, respectively. The test was negative in both patients without coronary artery stenosis or retrograde flow. Echocardiography identified wall motion abnormalities in >1 coronary distribution in 9 of the 12 patients with angiographic 2- or 3-vessel disease.

Wall motion score index: Mean wall motion score index in group A was 1.28 ± 0.27 (range 1.00 to 1.88) at baseline, and did not change significantly during stress. Six patients had improved wall motion score index during dipyridamole infusion. In group B, wall motion score index at rest was 1.22 ± 0.21 (range 1.00 to 1.62), and increased significantly to 1.36 ± 0.26 (range 1.00 to 1.88) ($p < 0.001$) during stress. When both groups were combined, patients with 2- or 3-vessel disease had a significantly larger increase in wall motion score index during dipyridamole infusion than patients with 0- or 1-vessel disease, 0.18 ± 0.11 versus −0.05 ± 0.18 ($p < 0.05$).

Dipyridamole-induced electrocardiographic changes and chest pain: ST depression ≥1 mm during dipyridamole infusion was found in 5 patients in group B, but none in group A. Two patients in group A and 4 in group B had chest pain during the test, 1 without electrocardiographic changes.

Dipyridamole time: None of the patients in group A, but 4 in group B had positive test results before the end of the second dipyridamole infusion (all of these had multivessel disease).

Adverse effects: Adverse effects during dipyridamole infusion occurred in 12 patients (40%). Two patients (7%) had symptomatic hypotension and bradycardia during or shortly after dipyridamole infusion. One of them (no. 5, Table IV) had the test interrupted after 9 minutes. Mild to moderate headache was reported by 6 patients (20%) and flushing by 4 patients (13%).

Interobserver variability: The 2 independent observers agreed on positive or negative test results in 28 of the 30 tests (94%). In 3 cases of positive tests, the observers disagreed on location of the wall motion abnormality. There was no significant difference between the observers in calculated wall motion score index at rest or during stress.

DISCUSSION

Stress echocardiography has previously been shown to be useful for evaluation of patients after CABG or

MI.[17–19] The present study shows that dipyridamole stress echocardiography is a valuable method also for evaluation of silent ischemia in such patients. Fourteen of 18 patients with significant coronary artery stenosis were identified as having positive tests (sensitivity 78%). Interestingly, retrograde flow to the occluded native artery was associated with a positive dipyridamole test result in 9 of 10 patients (9 of 12 coronary distributions). The hypoperfusion occurring in such regions can be explained by decreased collateral flow induced by dipyridamole.[20] Objective evidence of myocardial ischemia in coronary distributions with collateral coronary flow may have therapeutic consequences; however, the prognostic impact has not yet been established.

Coronary obstructions were more common in group B patients, both by echocardiographic and angiographic criteria. This finding is in agreement with the results of a previous study, showing that silent ST depression during exercise after CABG cannot reliably predict graft occlusion or native coronary artery stenosis.[21] The specificity for identification of coronary flow limitations with dipyridamole echocardiography was excellent; thus, this method can be used to identify patients with ST depression during exercise electrocardiography testing who have true myocardial ischemia.

During stress echocardiography, the presence of multivessel coronary disease can be identified by assigning baseline and stress-induced wall motion abnormalities to specific coronary distributions. In this study, patients with angiographic multivessel disease had a significantly larger increase in mean wall motion score index during dipyridamole infusion than patients without it. All patients with an early positive test result had 2- or 3-vessel disease, in accordance with a previous study showing that this finding indicates extensive coronary artery disease.[22] Five group A patients had baseline wall motion abnormalities, suggesting restricted coronary flow in the absence of coronary occlusions. Interestingly, wall motion score index improved in all these patients during dipyridamole infusion. Dipyridamole exerts a moderate positive inotropic effect on nonischemic myocardium, and has been shown to be valuable in identifying myocardial viability after acute MI.[23] Furthermore, lack of augmented regional wall motion during dipyridamole administration has been found to be a sensitive indicator of a ≥70% coronary stenosis.[24] Thus, the response to dipyridamole in myocardial regions with baseline abnormalities may increase the diagnostic value of stress echocardiography in such patients.

Benefit of computer-assisted cineloop display: Investigator experience is recognized as an important factor in analysis of stress echocardiography.[25] Interpretation may be difficult in patients with baseline wall motion abnormalities and moderate ischemia. Computerized display of cineloops may increase the accuracy of the test in such patients, as simultaneous display of synchronized cineloops from different stress levels facilitates identification of even subtle wall motion changes. The system used for data acquisition and data processing in this study differed from other commercially available systems. Digital scanline data rather than digital video signals are transferred directly from the scanner to the computer, providing cineloops without loss of information. The high frame rate provides 16 to 20 frames during systole, substantially higher than the frame rate obtained by digital video signals. When the cineloop is reviewed in slow motion, smoother and more detailed display of myocardial wall motion is provided.

Study limitations: Although cardiac medications were not taken at the day of the test, the washout period was too short to eliminate the anti-ischemic effect of all medication. This is a common clinical situation with outpatient stress testing, but might have lowered the sensitivity of the test.[26,27] The results of dipyridamole echocardiography were compared with coronary angiography. Systolic wall motion depends not only on the major coronary arteries or the patency of bypass grafts, but also on coronary microcirculation and collateral function.[28] Thus, coronary angiography has important shortcomings as a reference method, particularly in evaluating patients with bypass grafts.

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Paper III

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Comparison of Digital Dipyridamole Stress Echocardiography and Upright Bicycle Stress Echocardiography for Identification of Coronary Artery Stenosis

Key Words
Coronary artery disease
Stress echocardiography
Dipyridamole
Bicycle exercise test

Abstract
This study compared the diagnostic accuracy of dipyridamole (0.84 mg i.v./10 min) and bicycle stress echocardiography in 37 patients with inconclusive standard bicycle electrocardiography (ECG) tests; all underwent coronary angiography. Sensitivity for detection of coronary stenosis with dipyridamole echocardiography was 68% (21 of 31 patients), and for 1-, 2- and 3-vessel disease 56, 69 and 83%, respectively. Overall bicycle echocardiography sensitivity was 84%, and 78, 88 and 83% for patients with 1-, 2- and 3-vessel disease, respectively. Dipyridamole echocardiography was negative in all 6 patients with negative coronary angiography (specificity 100%), bicycle echocardiography was positive in 2 (specificity 67%). We conclude that dipyridamole echocardiography tends to be less sensitive in patients with mild disease, but is more specific than bicycle echocardiography.

Introduction

Stress echocardiography has become a widespread method for noninvasive identification and localization of coronary artery stenosis. Several stress protocols are currently used and comprise dynamic stress with bicycle or treadmill exercise [1–3] and pharmacological stress with dipyridamole, adenosine or dobutamine infusion [4–6]. Only a few studies have compared the diagnostic value of different tests in the same population. In the present study, we compared intravenous dipyridamole stress and bicycle stress echocardiography, two tests with widely different cardiovascular effects. Dipyridamole induces coronary vasodilation by increasing the level of adenosine [7], and may cause myocardial ischemia in the presence of coronary artery stenosis by a steal mechanism. The value of dipyridamole echocardiography has been documented in different subsets of patients with coronary artery disease [8–10]. Bicycle exercise may cause myocardial ischemia by an increase in oxygen demand if the coronary blood flow is limited by stenosis. This method has not become widely applied, mainly due to difficulties in obtaining satisfactory images during peak stress. However, the use of computerized display of selected images from left ventricular systole has improved the feasibility of this method.

In the present study, the diagnostic accuracy of these two tests was compared in a selected population with

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inconclusive results of standard bicycle electrocardiography (ECG) test. For optimal analysis of left ventricular wall motion, we used a computer system with high frame rate display of digitally transferred cineloops at baseline and during stress.

Methods

Patient Selection. The included patients were referred for coronary angiography due to chest pain syndromes with or without previous coronary artery bypass operation or healed myocardial infarction. All patients had performed initially maximal symptom-limited standard bicycle exercise ECG test with inconclusive result. The protocol excluded patients with inability or contraindications to the two tests, such as physical disorders, unstable angina pectoris, obstructive pulmonary disease, congestive heart failure, blood pressure ≥200/100 mm Hg or systolic blood pressure ≤90 mm Hg.

Of 40 patients initially evaluated, 3 were withdrawn from analysis, 1 due to adverse effects during dipyridamole infusion necessitating premature discontinuation, 1 due to technical problems during cineloop transfer and 1 due to incomplete imaging during bicycle stress echocardiography. The study group thus comprised 37 patients, with a mean age of 58 ± 10 years (39–76), 7 were women. All patients were in sinus rhythm, 22 (59%) had previous myocardial infarction documented by clinical history, ECG and cardiac enzymes, and 14 (38%) had undergone coronary artery bypass surgery. Twenty patients (54%) had baseline ECG abnormalities such as Q-waves, T-wave inversions, or unspecific ST-T changes, and 1 had left bundle branch block. Cardiac medications were not taken in the morning before the tests, and the tests were performed after 3 h of fasting. Both stress tests were performed within 2 days of coronary angiography, 13 patients had both stress tests on the same day, but at least 2 h apart. The protocol was approved by the regional ethical committee, and all patients gave informed consent to participation.

Dipyridamole Stress Echocardiography. Patients were told to avoid coffee and tea for 12 h prior to the test. The high-dose dipyridamole test was used [11] (fig. 1), with an initial dose of 0.56 mg/kg infused intravenously over 4 min through a cannula in an antecubital vein. If no wall motion abnormality was observed during the next 4 min, a second dipyridamole infusion of 0.28 mg/kg was given over the following 2 min. At least 5 min later, aminophylline 90–150 mg was infused over 2–5 min to reverse the dipyridamole effect. Twelve-lead ECG and brachial arterial blood pressure measured by the oscillometric technique (UA-751 Takeda Medical, Tokyo, Japan), were monitored every 2 min during the test.

Upright Bicycle Stress Test. Symptom-limited exercise test was performed with the patient in the upright position. The workload started at 25 or 50 W and was increased with 25 W every 2 min. Twelve-lead ECG and blood pressure were recorded at each stage. ST-segment depression was analyzed 0.08 s after the J-point, and was considered significant if ≥1 mm. Predefined end points for the test were chest pain, systolic blood pressure >220 or diastolic pressure >110 mm Hg, symptomatic hypotension, heart rate ≥90% of age-predicted maximum, dyspnea or general fatigue.

Echocardiographic Imaging. An ultrasound scanner (CFM 750, Vingmed Sound, Horten, Norway) was used with a 3.25-MHz annular array transducer. The scanner was interfaced via a data port (NB-DIO-24, National Instruments, Austin, Tex., USA) to a personal

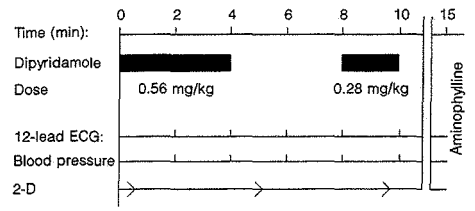

Fig. 1. High dose dipyridamole echocardiography test. 2-D = Two-dimensional echocardiography.

computer (Macintosh II series, Apple Computers, Cupertino, Calif., USA) for transfer of digital image data. On the computer, ultrasound data are displayed as left ventricular cineloops, each comprising sequentially recorded images during 1 cardiac systole. During dipyridamole tests, cineloops were obtained from apical 4-chamber, 2-chamber and long-axis views, and parasternal short-axis views. Cineloops were transferred at three stages: (1) rest, (2) maximal dipyridamole effect or when a new or increased wall motion abnormality was observed and (3) at least 5 min after aminophylline infusion. During bicycle tests, only the three apical imaging views were transferred at: (1) baseline, (2) peak exercise and (3) 5 min after exercise. All cineloops comprised at least the total systole, as defined by an interval of 450 ms starting at the R-wave of the ECG. The cineloops were transferred as scanline data, that is, without loss of ultrasound information, providing a frame rate of 47 frames/s with the standard sector angle and depth. All cineloops were previewed on the scanner screen before transfer to the computer.

Stress Echocardiography Analysis. The criteria for positive test were detection of a new left ventricular regional wall motion abnormality induced by stress, or worsening of a wall motion abnormality identified at rest. Unchanged regional wall motion was not used as a criterium for positive test, even during bicycle stress test. The interobserver agreement of dipyridamole stress echocardiography interpretation in our laboratory has previously been shown to be 94% [12]. In the present study, all tests were analyzed off-line by the same observer, without knowledge of patient data or to the results of other tests performed. In addition, an independent observer analyzed the tests for determination of interobserver agreement for the two different tests. A specially designed computer software (Echo Loops, Vingmed Sound) was used for interpretation. This software allows analysis of regional wall motion of the individual cineloops in slow motion, and synchronized cineloops from corresponding views from different stress levels can be compared side by side.

Wall motion score index was calculated at rest and during stress, based on visual interpretation of the cineloops. A 16-segment model of the left ventricle was used [13]. Segmental wall motion was graded as 1 (normal or hyperkinetic), 2 (hypokinetic), 3 (akinetic), 4 (dyskinetic) or 5 (aneurysmal). The score index was calculated as the sum of the segmental scores divided by the number of segments visualized, and was used as an index of global left ventricular wall motion. With this scale, a left ventricle with normal segmental wall motion will have a score index of 1.00, and a ventricle with 4 of the 16 segments being akinetic will have an index of 1.50. Wall motion abnormalities

Table 1. Individual findings at coronary angiography, dipyridamole echocardiography, bicycle ECG and bicycle echocardiography

Patient No.	Age/sex	Coronary angiography			Dipyridamole stress echocardiography			Bicycle ECG			Bicycle stress echocardiography		
		coronary stenosis	occluded vessel(s)	collateral flow	result	coronary distribution	dWMSI	W	ST-depression	angina	result	coronary distribution	dWMSI
1	70/F	0	0	0	0	0	−0.19	100	1.5	0	0	0	−0.12
2	66/M	0	RCA	RCA	+	RCA	0.13	100	1.5	0	+	RCA	0.31
3	66/M	LCx	0	0	0	0	−0.31	125	1.0	0	+	RCA	0.23
4	64/M	RCA	0	0	+	LAD, RCA	0.32	125	0	0	0	0	0.00
5	70/M	RCA	LAD, LCx	LAD	+	RCA	0.06	100	1.0	+	0	0	0.06
6	66/M	0	0	0	0	0	−0.06	100	0 (LBBB)	0	+	LAD	0.25
7	48/M	LCx	RCA	RCA	+	LCx	0.00	175	1.5	0	+	RCA	0.19
8	60/M	0	0	0	0	0	0.38	150	1.0	0	+	LAD	0.44
9	63/M	0	RCA	0	0	0	0.06	150	1.0	0	0	0	0.00
10	47/M	0	LCx	LCx	0	0	0.06	125	2.0	0	+	LCx	0.13
11	61/F	0	LAD, LCx, RCA	LAD, RCA	+	LDA	0.12	75	1.0	0	+	LAD	0.06
12	53/F	0	LAD, LCx, RCA	LAD, RCA	+	LCx, RCA	0.13	100	2.0	0	+	RCA	0.31
13	64/M	LCx	LAD	0	+	LAD	0.06	150	0	0	+	LAD	0.50
14	67/M	0	0	0	0	0	0.00	125	1.5	0	0	0	0.00
15	51/F	LAD, LCx	0	0	+	LAD, LCx	0.19	100	3.0	0	+	LAD	0.31
16	70/M	LAD, LCx	RCA	0	0	0	0.00	125	3.0	0	+	LAD, LCx	0.25
17	62/M	LAD	LCx	0	+	LCx	0.07	175	2.5	0	+	LCx	0.31
18	55/M	LAD	RCA	0	0	0	0.00	125	0	0	+	RCA	0.50
19	76/M	LAD, LCx	RCA	0	+	LAD, LCx	0.25	100	3.0	0	+	LAD, LCx	0.50
20	69/M	LCx	0	0	0	0	0.00	125	2.5	0	+	LCx	0.69
21	61/M	LAD	RCA	0	+	RCA	0.13	125	1.0	0	+	RCA	0.44
22	58/F	LAD, LCx	0	0	0	0	0.00	75	0	0	+	LAD	0.31
23	51/M	LAD	RCA	0	+	RCA	0.19	125	0	0	+	RCA	0.06
24	63/F	LAD, RCA	0	0	+	LAD, RCA	0.38	75	1.5	0	+	LAD, RCA	0.19
25	40/F	LCx	LAD	LAD	+	LAD, LCx	0.26	75	1.0	+	+	LAD, LCx	0.19
26	66/M	LAD, LCx	0	0	+	LAD	0.12	50	0	+	+	LCx	0.25
27	39/M	0	LCx	0	0	0	0.00	200	1.0	0	0	0	−0.12
28	67/M	RCA	LCx	0	0	0	0.00	100	2.0	0	0	0	−0.19
29	66/M	LAD, RCA	LCx	0	+	LAD, RCA	0.44	50	2.0	0	+	RCA	0.25
30	48/M	LAD, LCx	LAD	LAD	+	LAD	0.13	125	2.0	0	+	LAD	0.50
31	50/M	LAD	LCx	LCx	0	0	0.00	125	2.0	+	+	LAD, LCx	0.63
32	41/M	LAD, LCx	0	0	+	LAD	0.12	125	0	+	+	LAD	0.06
33	59/M	RCA	0	0	+	RCA	0.19	150	1.0	0	+	RCA	0.19
34	42/M	LAD, LCx	0	0	0	0	0.00	150	0	0	0	0	−0.19
35	50/M	0	RCA	RCA	+	RCA	0.19	125	0	+	+	RCA	0.38
36	54/M	RCA	0	0	0	0	0.00	100	0	+	0	0	0.00
37	50/M	LAD	0	0	+	LAD	0.12	175	0	+	+	LAD	0.06

dWMSI = Difference in wall motion score index at baseline and during stress: positive value denotes increased wall motion abnormality during stress; LAD = left anterior descending coronary artery; LBBB = left bundle branch block; LCx = left circumflex coronary artery; RCA = right coronary artery; W = bicycle workload in watts.

at rest and during stress were assigned to the distributions of the left anterior descending artery, left circumflex artery and right coronary artery, as defined elsewhere [12].

Coronary Angiography. Selective cineangiography (50 frames/s) was performed by standard Judkins technique. Multiple cranial and caudal angle projections were used. If the origin of a venous graft could not be visualized, additional biplane aortic root angiography was performed. The angiograms were interpreted by two or more angiographers who did not know the result of the dipyridamole test, and a consensus statement was made. Venous bypass grafts were described as patent or occluded. An occluded coronary artery was defined as a native vessel occlusion without patent bypass graft. Retrograde coronary flow was defined as collateral filling of a native vessel with proximal occlusion. Significant stenosis was defined as a diameter reduction of $\geq 50\%$ of a native artery, corresponding to cross-sectional area reduction of $\geq 75\%$. Lesions in the three major coronary arteries or their major branches (diagonal, right-posterior descending or marginal obtus), were described. The number of diseased vessels was determined as the sum of occluded and stenotic coronary arteries. A lesion of the left major coronary artery was considered as a combined lesion of left anterior descending and left circumflex arteries.

Statistical Analysis. Data are presented as means ± SD, range in parentheses. Sensitivity, specificity and diagnostic accuracy for each method were calculated according to standard definitions, with angiographic results as reference method. Comparison of accuracies was performed using nonparametric Fisher's exact test, and wall motion score indices were compared using Student's t test. Hemodynamic data from dipyridamole and bicycle stress tests were compared with paired t test. Significance was set at the 5% level.

Results

Individual patient results of coronary angiography, dipyridamole and bicycle stress ECG and echocardiography are presented in table 1, and the sensitivities for identification of patients with 1-, 2- or 3-vessel disease by the two echocardiographic methods are displayed in figure 2.

Coronary Angiography. Thirty-one patients (84%) had coronary artery stenosis and/or retrograde collateral filling of an artery with proximal occlusion. Coronary artery stenosis was found in 26 patients (70%), 21 had coronary occlusions, and retrograde collateral filling was noted in 10. Eleven patients had single vessel disease, 9 of these had coronary artery stenosis, or occlusion with retrograde collateral flow. The number of patients with 2- or 3-vessel disease was 16 and 6, respectively.

Dipyridamole Stress Echocardiography. Dipyridamole stress echocardiography identified 21 of the 31 patients with coronary artery stenosis or retrograde collateral flow (sensitivity 68%). Sensitivity for detection of single vessel stenosis or retrograde flow was 56%, 2- or 3-vessel disease was identified with sensitivities of 69 and 83%, respectively. All the 6 patients without coronary artery stenosis or retrograde flow had negative tests (specificity 100%). Presence or absence of coronary artery stenosis was correctly diagnosed in 27 of the 37 patients (diagnostic accuracy 73%). Chest pain during dipyridamole infusion occurred in 9 patients, and 9 patients developed ST-segment depression ≥ 1 mm. Side effects were noted in 12 patients, and comprised headache (5 patients), flushing (4 patients), bradycardia with symptomatic hypotension (2 patients) or nausea (1 patient).

Bicycle Stress ECG and Echocardiography. Mean workload during bicycle exercise was 119 ± 34 W (50–200). The exercise test was stopped due to general fatigue in 29 patients (78%), and chest pain in 8 patients (22%). ST-depression occurred in 25 patients (68%), mean ST-depression was 1.1 ± 1.0 mm (0–3). Twenty-six of the 31 patients with coronary artery stenosis or retrograde collateral flow had positive tests (sensitivity 84%). Sensitivity for detection of single vessel stenosis or retrograde flow

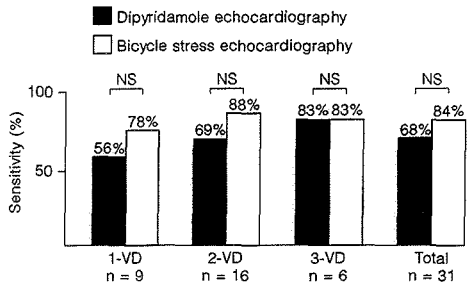

Fig. 2. Bar plot of sensitivities for dipyridamole stress echocardiography and bicycle stress echocardiography in patients with coronary artery stenosis. VD = Vessel disease.

was 78%, 2- or 3-vessel disease was identified with sensitivities of 88 and 83%, respectively. Two of the 6 patients without vessel stenosis were diagnosed as having positive tests (specificity 67%). Presence of coronary artery stenosis was correctly predicted in 30 of the 37 patients (diagnostic accuracy 81%).

Agreement between the Two Tests. The two stress echocardiography tests yielded concordant results (positive or negative) in 26 of the 37 patients (70%), 19 had positive tests with both methods. For these, mean change in wall motion score index was higher with bicycle stress than with dipyridamole (0.27 ± 0.15 vs. 0.16 ± 0.09, $p < 0.05$). The two methods showed equal accuracy for identification of the specific coronary artery affected by stenosis, 17 of 21 (81%) for dipyridamole versus 21 of 26 (81%) for bicycle stress. Wall motion abnormalities occurred in at least 1 equivalent coronary distribution in 17 of the 19 patients (89%) with positive results by both methods.

Interobserver Data. The two observers agreed on the presence or absence of positive tests for 34 of the dipyridamole tests, and for 30 of the bicycle tests, thus, interobserver agreement was 92 and 81%, respectively. Both observers had the same concordance for the interpretations of dipyridamole and bicycle echocardiography tests, 26 of the 37 tests (70%). The vessel considered stenotic was concordant in 16 of the 18 dipyridamole tests (89%) interpreted as positive by both observers, and in 20 of 23 bicycle echocardiography tests (87%).

Hemodynamic Data. The different hemodynamic profiles of the two tests are shown in table 2, displaying mean changes in heart rate, systolic blood pressure, and double

Table 2. Hemodynamic alterations during dipyridamole and bicycle stress tests, n = 30 (81% of study population)

		HR	SBP	DP
Dipyridamole	Baseline	62±14	119±15	7,397±2,352
	Stress	82±22	118±19	9,905±3,984
	Percent change	31±18	−1±12	31±28
Bicycle stress	Baseline	71±16	136±18	9,706±2,636
	Stress	130±20	159±28	21,067±4,506
	Percent change	89±33*	17±18**	125±47*

* p = 0.0001, ** p = 0.0002 bicycle vs. dipyridamole data. HR = Heart rate (beats/minute); SBP = systolic blood pressure (mm Hg); DP = double product (HR × SBP).

products (defined as the product of heart rate and systolic blood pressure) caused by stress. Bicycle stress resulted in significantly higher increases in heart rate, systolic blood pressure, and double product than dipyridamole stress.

Discussion

Standard exercise ECG is the established method for noninvasive identification of coronary artery disease. However, the value of this test is limited by low sensitivity and specificity, especially in patients with baseline ECG abnormalities. The diagnostic accuracy of exercise testing has been shown to be higher when echocardiographic imaging is used to detect stress-induced wall motion abnormalities as a specific marker of ischemia [3, 14]. Two-dimensional echocardiography also facilitates localization of myocardial ischemia to specific coronary artery distributions, and the diagnosis of multivessel disease can thus be made [15].

The present study compared the value of bicycle stress echocardiography and pharmacological stress echocardiography with dipyridamole infusion in a population able to perform bicycle exercise, but with inconclusive results during exercise ECG test. The results imply that both methods can be a valuable supplement in these patients. Although the overall accuracy was comparable for the two stress echocardiography methods, clinically important differences were found. Bicycle stress echocardiography was positive in a higher number of patients with single- or 2-vessel disease than dipyridamole echocardiography.

This difference presumably reflects the relatively weak ischemic effect exerted by dipyridamole in patients with mild degree of coronary artery disease, as has been documented in previous studies [16–18]. The change in wall motion score index reflects the extent of ischemia, and was significantly smaller during dipyridamole test than during bicycle test. Dipyridamole has only a modest effect on the rate-pressure product [19], and hemodynamic data obtained in this study showed a significantly higher increase in heart rate, systolic blood pressure, and double product during bicycle stress. Dipyridamole induces ischemia predominantly by a coronary steal mechanism. This effect on coronary flow pattern is advantageous when dipyridamole is used with perfusion scintigraphic techniques, but may be insufficient to elicit ischemic wall motion abnormalities that can be detected with echocardiography. Recently, it has been shown that increasing heart rate with atropine injections at the end of the dipyridamole protocol enhanced the sensitivity of dipyridamole stress echocardiography without reducing the specificity of the test [20].

In this study, both modalities had a similar and high sensitivity for detection of coronary artery stenosis in patients with 3-vessel disease. Nevertheless, 1 of the 6 patients (17%) with this angiographic feature was missed by each method. In both patients, baseline wall motion abnormalities were identified as evidence of previous myocardial infarction, but stress did not induce worsening or detectable ischemia in other myocardial distributions.

The specificity obtained with dipyridamole stress in this study was excellent, and is in agreement with previous reports showing specificities in the range of 90–100% [11, 12]. The moderate increase in contractility and heart rate as compared to dynamic stress may be favorable in order to avoid false-positive interpretations. In the present study, bicycle echocardiography was positive in 2 patients with negative coronary angiography, corresponding to a specificity of 67%. Previous studies comparing peak and post-exercise imaging indicate that imaging at peak exercise increases sensitivity, but may reduce the

specificity of the test [21–23], presumably due to the rapid heart rate at maximal stress. One of the 2 patients with false-positive bicycle stress echocardiography had left bundle branch block, not known by the interpreter. The abnormal septal motion associated with this condition may be difficult to differentiate from ischemia, particularly with the altered heart rate and loading conditions that occur during exercise. A study with perfusion scintigraphy indicated that pharmacological stress may be more accurate than exercise stress for diagnosis of coronary artery disease in patients with left bundle branch block [24], but this difference is not yet documented for stress echocardiography.

Methodological Considerations

The lower interobserver agreement of 81% for bicycle stress echocardiography in our study is probably influenced by the difficulties with interpretation of regional wall motion during pronounced exercise-induced tachycardia. In our experience, images obtained during dipyridamole stress are easier to interpret due to the modest effect on heart rate, and this is also reflected by the higher observer agreement for analysis we obtained with this modality (92%). Unlike dipyridamole stress echocardiography, upright bicycle exercise echocardiography has not yet become a widespread method for identification of coronary artery stenosis. Echocardiographic imaging during exercise is considered more difficult, and continuous high-quality imaging may often not be possible throughout the exercise test. In our study only 1 patient had to be excluded, from analysis due to uninterpretable images during bicycle stress. This high success rate for peak stress imaging is probably attributable to the use of computer-assisted analysis of digitally transferred images of left ventricular systolic cineloops [25]. With this system, cardiac cycles with optimal image quality can be captured for transfer and subsequent analysis, and studies performed before this technique became available showed a limited success rate [26]. The system used for digital transfer of images in our study provided computerized display of cineloops with 47 frames/s, that is a considerably higher frame rate than provided by systems based on digitized video signals (25 frames/s). Theoretically, a higher frame rate may enhance detection of subtle changes in contractility during stress, however, the benefit of high frame rate in a clinical setting is yet to be proved.

Apical views only were obtained during bicycle stress echocardiography, while an additional parasternal short-axis view was used during dipyridamole tests. In our experience, it is impractical to use more than one transducer position during bicycle stress echocardiography. The apical views provided visualization of all 16 myocardial segments as defined by the American Society of Echocardiography [13], and parasternal short-axis views may cause false interpretations if the imaging plane is skewed [27].

Limitations of the Study

Due to the design of the study, the feasibility of the two stress methods was not compared, as all patients studied were able to perform both tests. In an unselected group of patients referred for coronary angiography, dipyridamole stress may be expected to be more applicable than bicycle stress due to few contraindications, and to the prevalence of physical limitations that may preclude dynamic stress. In a population less familiar to bicycle exercise, the stress level achieved may be limited, ultimately affecting the diagnostic value of this test.

Clinical Implications

The different characteristics of dipyridamole and bicycle stress echocardiography indicated by this study have clinical importance. Dipyridamole stress facilitates imaging during more stable hemodynamic conditions and provides a highly feasible test with low risk of false-positive results. Bicycle stress echocardiography is less prone to be false negative in patients with mild coronary artery disease and provides more physiological stress with marked increase in double product. However, the interobserver agreement is lower, probably due to the pronounced effect on heart rate. This method is useful in patients who can achieve a sufficient workload, and if facilities for computer-assisted analysis of image data are available. Both methods provide additional information on coronary status in patients with inconclusive results of standard exercise ECG.

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Paper IV

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How does computer-assisted digital wall motion analysis influence observer agreement and diagnostic accuracy during stress echocardiography?

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Abstract

This study assessed interobserver and intraobserver variation and diagnostic accuracy during 25 dipyridamole stress echocardiography tests interpreted with different analysis systems: a) computer display of high frame rate digital cineloops (47 frames/s); b) computer display of lower frame rate digital cineloops (24 frames/s); and c) videotape recordings. The majority of the patients (84%) had documented coronary artery disease with baseline wall motion anormalities due to previous myocardial infarctions and/or coronary bypass surgery, thus comprising a population with difficult interpretation of stress echocardiography. Diagnostic accuracy was assessed using coronary angiography as reference method. Interobserver and intraobserver agreement was highest when analysis was performed from computer-displayed cineloops, 96 and 92%, respectively, compared to 84 and 80% respectively, using videotape recordings. Sensitivity for identification of coronary artery stenosis was similar using digital cineloops with high frame rate or videotape recordings (67% to 80% for both systems), and tended to be lower using cineloops with lower frame rate for analysis (53%). Inter- and intraobserver differences for wall motion score index were not significantly influenced by the analysis system. We conclude that computer assisted analysis with high frame rate of the displayed cineloops provides optimal observer agreement and diagnostic accuracy in the same range as videotape analysis in patients undergoing stress echocardiography.

Abbreviation: WMSI – wall motion score index

Introduction

Stress echocardiography has become a widespread method for noninvasive identification of coronary artery disease [1, 2], with documented diagnostic and prognostic value in several subsets of patients [3–6]. Diagnostic accuracy has been shown to be comparable to more established modalities such as myocardial scintigraphy [7]. A positive stress echocardiography test is defined as a new or worsened left ventricular wall motion abnormality induced by cardiac stress, and predicts significant coronary flow obstruction. Interpretation of the test is based on visual, subjective assessment by the observer. Computers are commonly used for digital display of left ventricular contraction, allowing side-by-side comparison of cineloops from different stages of the stress test [8], and this technique has contributed to the increased popularity of stress echocardiography. Higher frame rate of the computer-displayed cineloops allows slow motion display and more detailed analysis of left ventricular contraction. However, the value of digital image processing in terms of improved diagnostic accuracy has been questioned [9], and the value of higher frame rate has not been documented. The aim of this study was to assess how different analysis systems influence observer agreement and diagnostic accuracy for stress echocardiography. Three different systems for analysis and display of images were used: 1) digital cineloops with high frame rate (47 frames/s); 2) digital cineloops with lower frame rate (24 frames/s), to equal the frame rate obtained with digitized video-signals; and 3) review

Table 1. Patient baseline characteristics

Pat. no.	Age/sex	MI	Bypass grafts	Coronary angiography		
				Stenosis	Occlusion	Retrograde flow
1	68/m	-	LAD, LCX	LAD, RCA	-	
2	62/m	Inferior	-	LAD	LCX	-
3	63/f	Inferior	-	LAD, RCA	-	
4	59/f	-	-	-	-	
5	69/m	Lateral	-	LCX	-	
6	65/m	-	LAD, RCA	-	-	
7	41/m	-	-	-	-	
8	48/m	Anterior	-	LAD, LCX	-	
9	66/m	Inferior	-	LAD, RCA	LCX	-
10	66/m	-	LAD, LCX	-	-	
11	51/f	Anterior	-	LAD, LCX	-	
12	62/f	-	-	-	-	
13	39/m	Inferior	-	-	LCX	-
14	59/f	Anterior	-	LAD, LCX, RCA	-	
15	66/m	Inferior	-	LAD, LCX	OM	-
16	70/f	-	LCX, RCA	-	-	
17	60/m	Anterior	LAD, LCX, RCA	-	-	
18	53/f	-	LAD, LCX, RCA	LAD, RCA	LCX	-
19	67/m	-	LAD, LCX, RCA	-	-	
20	55/m	Inferior	-	LAD	RCA	-
21	47/m	Inferior	LAD	LAD	LCX	+
22	63/m	-	LAD, LCX	LAD	RCA	-
23	51/m	Inferior	-	LAD	RCA	-
24	46/f	-	-	-	-	
25	40/f	Anterior	-	LCX	Diag.	+

Diag. = diagonal branch of left anterior descending artery; LAD = left anterior descending artery; LCX = left circumflex artery; OM = obtus marginal branch of LCX; RCA = right coronary artery; MI = myocardial infarction.

of videotape recordings. The majority of the patients had baseline wall motion abnormalities, thus comprising a population with difficult interpretation of stress echocardiography.

Material and methods

Patient selection

The 25 tests included in the study were randomly selected from 40 consecutive dipyridamole stress echocardiography tests performed in patients evaluated for ischemic heart disease. This selection was performed by a person not involved in the analysis. Twenty-one patients were referred for coronary angiography due to asymptomatic ST-depression during standard exercise electrocardiography testing after healed myocardial infarction (12 patients), or at long-term follow-up after coronary artery bypass grafting (9 patients). The remaining four patients were evaluated for atypical chest pain, all of these had negative exercise electrocardiography tests and normal coronary angiography. Mean age was 57 ± 10 years (39–70 years), 16 were male and 9 were female, all were in sinus rhythm. Individual baseline characteristics and results of coronary angiography are shown in Table 1.

Dipyridamole stress echocardiography

Echocardiographic imaging was performed with the patient in the left lateral recumbent position. Coffee and tea were avoided at least 12 hours prior to the test. The high-dose dipyridamole test was used [10] with an initial dose of 0.56 mg/kg infused intravenously over four minutes through a cannula in an antecubital vein. If no wall motion abnormality was observed during the next four minutes, a second dipyridamole

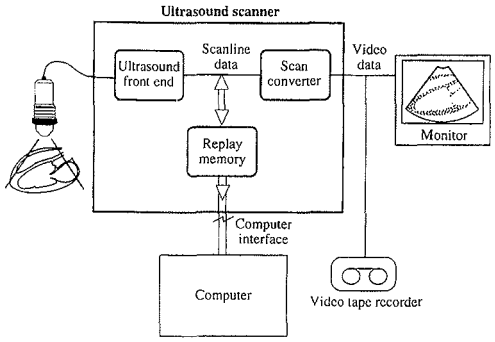

Figure 1. A schematic drawing of the architecture of the scanner system, its interface to the computer, and to the video monitor and video recorder. The ultrasound signals from each scanline are received by the ultrasound probe, processed in the front end, and stored in the replay memory. The data acquisition time for each image was 21 msec, giving a frame rate of 47 frames/s. The scanconverter converts the scanline data into images with correct geometry. At the same time, the frame rate is synchronized to the standard video frame rate for display and VCR recording. In our study, the European video standard PAL was used, with a frame rate of 25 frames/s.

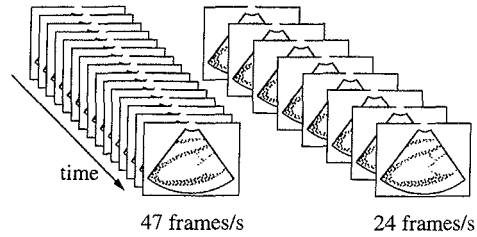

Figure 2. Illustration of the difference in digital cineloop frame rate used for analysis in the study. With a high frame rate of 47 frames/s, a cardiac systole will be represented by 16-18 frames. Using a frame rate of 24 frames/s, systole will be represented by 8-9 frames.

infusion of 0.28 mg/kg was given over the following two minutes. At least five minutes later, aminophylline 90-150 mg was infused over 2-5 minutes to reverse the dipyridamole effect. A 12 lead electrocardiogram and brachial arterial blood pressure measured by oscillometric technique (UA-751 Takeda Medical, Tokyo, Japan), were monitored every two minutes during the test.

Ultrasound data acquisition and stress echocardiography analysis

An ultrasound scanner (CFM 750, Vingmed Sound, Horten, Norway) was used with an annular array 3.25 MHz transducer. The scanner was interfaced to a computer (Macintosh II series, Apple Computers, Cupertino, California, USA) for transfer of digital image data from the internal replay memory of the scanner. The architecture of the scanner system, its interface to the computer, and to the video monitor and video recorder is illustrated in Figure 1.

During dipyridamole infusion, left ventricular wall motion was examined continuously with two-dimensional echocardiography from the apical and parasternal positions. Regional wall motion was assessed by analysis of both endocardial excursion and wall thickening at baseline and during stress. A positive stress echocardiography test was defined as a new or worsened wall motion abnormality induced by dipyridamole, affecting at least one myocardial segment with normal or hypokinetic wall motion at baseline. The result of stress echocardiography was considered as "true positive" only if at least one coronary artery was stenosed, or showed retrograde filling to an occluded artery at coronary angiography. Images from all views were recorded on videotape at baseline and during the different stages of the test. For computer-assisted analysis, systolic cineloops were obtained from apical four-chamber, two-chamber and long-axis view, and parasternal short-axis view at mid-papillary level. Cineloops were transferred at three stages:

- at rest,
- at maximal dipyridamole effect or when a new or increased wall motion abnormality was observed, and
- $\geq$ 5 minutes after aminophylline infusion.

The cineloops comprised total systole, defined as the interval from the peak of the R-wave to the S2 signal on phonocardiography. Cineloops were transferred as scanline data with a frame rate of 47 frames/s with standard sector depth and angle settings. A specially designed computer software (Echo-Loops, Vingmed Sound) was used for wall motion analysis. This software allows display of individual cineloops in slow motion as well as side-by-side comparison of multiple synchronized cineloops from different stress levels. In addition, each test was analyzed with a 50% reduction of frame rate. This was achieved by using a specially dedicated program omitting every second frame of the cineloop (Figure 2), developed to imitate display of digital videosignals with a frame rate of 25 per second.

Wall motion score index (WMSI) was calculated for each patient at baseline and during peak stress,

using visual assessment of segmental wall motion and thickening. A 16-segment model of the left ventricle was used according to the recommendations of American Society of Echocardiography [11]. Segmental wall motion was graded as 1 (normal or hyperkinetic), 2 (hypokinetic), 3 (akinetic), 4 (dyskinetic) or 5 (aneurysmal). WMSI was calculated as the sum of the segmental scores divided by the number of segments visualized. Wall motion abnormalities during stress were assigned to the distributions of the left anterior descending artery, left circumflex artery, and right coronary artery, as described elsewhere [12].

Test interpretations of test result and of segmental wall motion scoring were performed by two independent observers (analysis A and B1), blinded for patient data, symptoms, or electrocardiographic changes during the test, as well as for angiographic findings. For the purpose of intraobserver analysis, observer B performed an additional analysis (analysis B2) of digital cineloop tests and videotape recordings three months after the first analysis. Hence, each of the 25 dipyridamole tests were analyzed as follows:

- analysis of computer-displayed cineloops with high frame rate (47 frames/s), by observer A once and observer B twice (analysis B1 and B2);
- analysis of computer-displayed cineloops with lower frame rate (approximately 24 frames/s) analyzed by observer B once;
- analysis of videotape recordings of the tests, analyzed by observer A once, and by observer B twice (analysis B1 and B2).

Coronary angiography

Sensitivity and specificity for each analysis system was calculated using the results at coronary angiography as reference method. Selective cineangiography (50 frames/s) was performed by standard Judkins technique. Multiple views with additional cranial and caudal angle projections were used. In patients with coronary artery bypass grafts, additional biplane aortic root angiography was performed if the origin of a venous graft could not be visualized. Angiograms were interpreted visually by a consensus of experienced angiographers without knowledge of the result of the dipyridamole test. Lesions in the three epicardial coronary arteries and their major branches (diagonal, right posterior descending or obtus marginal), were described. Positive coronary angiography was defined as vessel diameter reduction of $\geq$50%, corresponding to cross-sectional area reduction of $\geq$75%, or retrograde collateral filling of a coronary artery with proximal occlusion. The number of diseased vessels was determined as the sum of occluded and stenotic coronary arteries. A lesion of the left main coronary artery was counted as a lesion of both left anterior descending and left circumflex arteries. Venous bypass grafts were described as patent or occluded. An occluded coronary artery was defined as a native vessel occlusion without patent bypass graft.

Individual results of coronary angiography are shown in Table 1. Coronary stenoses were found in 15 patients and coronary occlusions in 10 patients, two of these had retrograde collateral flow to the occluded artery. Ten patients had no coronary stenosis or retrograde flow to occluded arteries, and were thus expected to have negative results of the stress echocardiography test.

Statistics

The agreement between the two observers with regard to test result (positive or negative test for myocardial ischemia) was expressed as percentages. WMSI calculations were compared using 2-sided paired Student t-test, a p-value geq0.05 was considered statistically significant. The results were displayed as regression plots and as Bland-Altman plots [13], with the average of the two observers' WMSI values plotted along the x-axis, and the difference of the values plotted along the y-axis. Sensitivities and specificities for identification of coronary artery stenosis were calculated according to standard definitions [14], with coronary arteriography as reference method.

Results

Interobserver and intraobserver agreement on test result

The results of test interpretations for individual patients are shown in Table 2 (digital cineloop analysis) and Table 3 (analysis of videotape recordings).

Interobserver agreement for the results of computer assisted analysis based on high frame rate digital cineloops was 96%, whereas intraobserver agreement was 92%. Interobserver agreement for analysis of videotape recordings was 84%, and intraobserver agreement was 80%.

Table 2. Observer interpretations of computer displayed digital cineloops

	Observer A:				Observer B, 1st analysis:				Observer B, 2nd analysis:				Observer B, low frame rate:			
Pat. no.	Result	Cor. art.	WMSI 1	WMSI 2	Result	Cor. art.	WMSI 1	WMSI 2	Result	Cor. art.	WMSI 1	WMSI 2	Result	Cor. art.	WMSI 1	WMSI 2
1	+	RCA	1.38	1.44	+	LAD, RCA	1.19	1.44	+	LAD, RCA	1.19	1.50	-	-	1.38	1.38
2	+	LCX	1.06	1.13	+	LCX	1.13	1.19	+	LCX	1.13	1.19	-	-	1.00	1.00
3	+	RCA	1.25	1.38	+	RCA	1.19	1.31	+	LAD, RCA	1.25	1.38	+	RCA	1.00	1.13
4	-	-	1.00	1.00	-	-	1.00	1.00	-	-	1.00	1.00	-	-	1.00	1.00
5	-	-	1.13	1.00	-	-	1.00	1.00	-	-	1.00	1.00	-	-	1.00	1.00
6	+	RCA	1.44	1.50	+	RCA	1.13	1.25	+	RCA	1.19	1.31	+	RCA	1.13	1.13
7	-	-	1.00	1.00	-	-	1.00	1.00	-	-	1.00	1.00	-	-	1.00	1.00
8	+	LAD, LCX	1.63	1.81	+	LAD	1.56	1.81	+	LAD	1.62	1.75	+	LAD	1.56	1.63
9	+	LCX, RCA	1.00	1.63	+	LAD, RCA	1.06	1.44	+	LAD, RCA	1.06	1.56	+	LAD, RCA	1.19	1.56
10	-	-	1.31	1.31	-	-	1.31	1.13	-	-	1.44	1.38	-	-	1.25	1.13
11	+	LAD	1.25	1.60	+	LAD	1.06	1.44	+	LAD	1.06	1.25	+	LAD, LCX	1.00	1.25
12	-	-	1.00	1.00	-	-	1.00	1.00	-	-	1.00	1.00	-	-	1.00	1.00
13	-	-	1.25	1.25	-	-	1.62	1.56	-	-	1.19	1.19	-	-	1.50	1.44
14	+	LAD	1.25	1.38	+	LAD	1.44	1.62	+	LAD	1.44	1.56	+	LAD	1.63	1.56
15	-	-	1.00	1.00	-	-	1.06	1.06	+	LAD	1.00	1.13	+	LAD	1.00	1.13
16	-	-	1.00	1.00	-	-	1.19	1.06	-	-	1.31	1.13	-	-	1.00	1.00
17	+	LAD	2.00	2.06	-	-	1.88	1.81	-	-	1.88	1.50	-	-	2.19	1.44
18	+	LAD	1.25	1.31	+	LCX	1.00	1.31	+	LCX	1.19	1.31	-	-	1.13	1.13
19	-	-	1.00	1.00	-	-	1.00	1.00	-	-	1.00	1.00	-	-	1.00	1.00
20	-	-	1.06	1.06	-	-	1.25	1.25	+	RCA	1.13	1.25	-	-	1.25	1.25
21	-	-	1.31	1.31	-	-	1.31	1.25	-	-	1.63	1.56	-	-	1.50	1.38
22	-	-	1.31	1.31	-	-	1.06	1.00	-	-	1.06	1.00	-	-	1.00	1.00
23	+	LAD	1.31	1.31	+	RCA	1.31	1.56	+	RCA	1.50	1.69	+	RCA	1.00	1.25
24	-	-	1.00	1.00	-	-	1.00	1.00	-	-	1.00	1.00	-	-	1.00	1.00
25	+	LAD, LCX	1.69	2.13	+	LAD, LCX	1.38	1.75	+	LAD, LCX	1.63	1.88	+	LAD, LCX	1.63	1.69

Cor. art. = coronary artery distribution; WMSI = wall motion score index at baseline (WMSI1), and at peak stress (WMSI2). Other abbreviations as in Table 1.

Table 3. Observer interpretations from analysis of video-recordings

	Observer A:				Observer B, 1st analysis:				Observer B, 2nd analysis:			
Pat. no.	Result	Cor. art.	WMSI 1	WMSI 2	Result	Cor. art.	WMSI 1	WMSI 2	Result	Cor. art.	WMSI 1	WMSI 2
1	+	RCA	1.38	1.31	+	RCA	1.31	1.38	+	LAD, RCA	1.50	1.75
2	-	-	1.00	1.00	-	-	1.13	1.13	-	-	1.06	1.00
3	+	LAD	1.19	1.38	+	LAD	1.31	1.44	+	LAD	1.19	1.56
4	-	-	1.00	1.00	-	-	1.00	1.00	-	-	1.00	1.00
5	+	LAD	1.00	1.13	+	LCX	1.00	1.13	+	LCX	1.00	1.13
6	-	-	1.25	1.25	+	RCA	1.13	1.44	-	-	1.13	1.13
7	-	-	1.00	1.00	-	-	1.00	1.00	+	RCA	1.00	1.13
8	+	LAD, LCX	1.56	1.75	+	LAD	1.44	1.62	+	LAD, LCX	1.62	1.88
9	+	LAD, RCA	1.06	1.44	+	LAD, RCA	1.19	1.62	+	LAD, RCA	1.13	1.56
10	+	LCX	1.13	1.19	-	-	1.13	1.13	-	-	1.56	1.13
11	+	LAD	1.06	1.38	+	LAD, LCX	1.44	1.88	+	LAD	1.38	1.50
12	-	-	1.00	1.00	-	-	1.00	1.00	-	-	1.00	1.00
13	-	-	1.25	1.25	-	-	1.56	1.56	+	RCA	1.31	1.44
14	-	-	1.56	1.56	-	-	1.75	1.63	-	-	1.50	1.50
15	+	LCX	1.00	1.31	+	LCX	1.13	1.25	+	LCX, RCA	1.00	1.38
16	-	-	1.00	1.00	-	-	1.00	1.00	-	-	1.00	1.00
17	-	-	1.94	1.69	-	-	1.56	1.56	+	RCA	1.81	1.94
18	+	LAD, LCX	1.38	1.50	+	LAD, RCA	1.00	1.44	+	LAD, RCA	1.00	1.44
19	+	RCA	1.06	1.13	-	-	1.19	1.19	-	-	1.19	1.13
20	+	RCA	1.06	1.19	-	-	1.31	1.31	-	-	1.25	1.25
21	+	LAD	1.50	1.63	+	LAD	1.31	1.38	-	-	1.19	1.19
22	-	-	1.25	1.25	-	-	1.38	1.38	-	-	1.31	1.31
23	+	RCA	1.19	1.25	+	LCX, RCA	1.31	1.69	+	RCA	1.44	1.69
24	-	-	1.00	1.00	-	-	1.06	1.06	-	-	1.00	1.00
25	+	LAD, LCX	1.50	2.19	+	LAD, LCX	1.50	1.69	+	LCX	1.44	1.75

Abbreviations as in Table 1 and 2.

Table 4. Sensitivity, specificity and diagnostic accuracy for each analysis method and observer, 25 patients

Analysis modality:	Observer	Sensitivity		Specificity		Diagn. accuracy	
		n	%	n	%	n	%
Digital cineloops, high frame rate	A	10/15	67	8/10	80	18/25	72
	B1	10/15	67	9/10	90	19/25	76
	B2	12/15	80	9/10	90	21/25	84
Digital cineloops, lower frame rate	B	8/15	53	9/10	90	17/25	68
Video-recordings	A	12/15	80	8/10	80	20/25	80
	B1	11/15	73	9/10	90	20/25	80
	B2	10/15	67	7/10	70	17/25	68

Abbreviations as in Table 2.

Diagnostic accuracy

Diagnostic accuracy calculations are summarized in Table 4. The sensitivity for detection of significant coronary artery stenosis was similar using digital cineloops with high frame rate or videotape recordings as analysis method (67 to 80%), and tended to be lower using lower frame rate cineloop display (53%). Specificity and diagnostic accuracy were in the same range regardless of the analysis system used.

Wall motion score index

Individual patient WMSI as assessed by the different observers are shown in Table 2 and 3. There were no interobserver or intraobserver differences reaching statistical significance for mean WMSI comparisons at baseline or at peak stress with digital cineloop analysis or videotape recording analysis. Mean interobserver and intraobserver WMSI differences with digital cineloop analysis ranged from 0.03 ± 0.14 at baseline to 0.05 ± 0.19 at peak stress. Videotape recording analysis showed mean differences ranging from 0.01 ± 0.18 at baseline to 0.05 ± 0.20 at peak stress. All mean differences were smaller for intraobserver than for interobserver comparisons. Maximal individual patient difference during digital cineloop analysis was 0.37 for interobserver and 0.43 for intraobserver analysis. With videotape analysis, maximal WMSI interobserver difference was 0.50, and maximal intraobserver difference was 0.43. Regression plots and Bland-Altman plots for inter- and intraobserver WMSI comparisons at peak stress are shown in Figure 3 to 6.

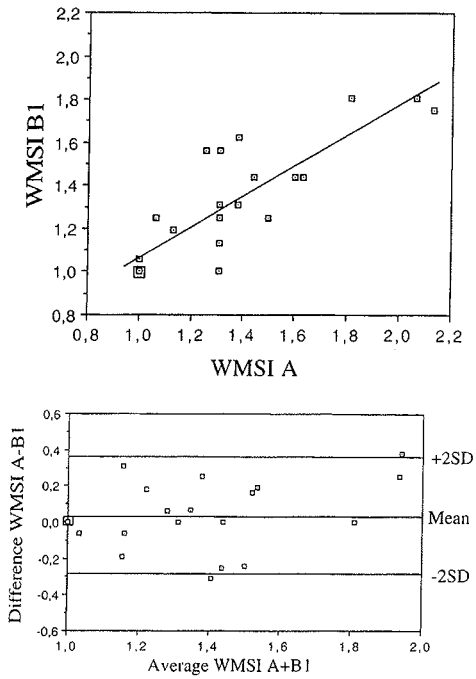

Figure 3. Digital cineloop display: Interobserver comparisons for WMSI at maximal dipyridamole dose. Double boxes denotes the patients with WMSI = 1.00 by both observers. *Top panel:* Regression plot, with regression slope: y = 0.72x + 0.35; r-value 0.85. *Bottom panel:* Bland Altman plot, with the average of the 2 observers' WMSI calculations along the x-axis, and the differences along the y-axis. A = WMSI calculations by observer A; B1 = WMSI calculations by observer B, first analysis.

Discussion

The present study showed that observer agreement for stress echocardiography interpretations varies with different analysis and display systems. Inter- and intraobserver agreement was optimal using a digital cineloop system, reaching 96 and 92%, respectively, whereas analysis of videotape recordings yielded agreement of 84 and 80%, respectively. Computerized cineloop systems allow detailed analysis of regional wall motion by continuous wall motion display. Cardiac cycles with optimal image quality can be selected, and the influence of respiration and cardiac motion can be minimized. A major limitation with computer-assisted display is the fact that the interpretation is based on a single cardiac cycle from each imaging view [15], whereas analysis in real time or from review of videotape recordings is based on longer sequences and facilitates detection of transient ischemia during the test. In a recent study, Castini et al. [9] found improved diagnostic accuracy using analysis of videotapes compared to digitized cineloops for dobutamine stress echocardiography, 72 ± 9% versus 63 ±10%. The same authors reported similar interobserver agreement for videotape and digitized cineloop analysis, 84 and 80%, respectively. Importantly, the frame rate used in their study corresponds to the lower frame rate of our study, with each cineloop consisting of 8 systolic frames. In the present study, images were digitally recorded with 47 frames/s, facilitating review of the images at 1/3 speed without loss of quality. Digital stress echocardiography systems based on video frame-grabber recording do not offer this slow motion possibility. The human eye will perceive a sequence of images as a continuous film when the frame rate exceeds 15 frames/s. For real time display, the standard video frame rate is therefore high enough to give a smooth display. However, faster data acquisition offers the possibility of high quality slow motion replay, a technique well known from the sport arena, where special cameras with high frame rate are used for this purpose. In the present study, we developed a computer program to make a 50% reduction in frame rate, and analysis performed with these

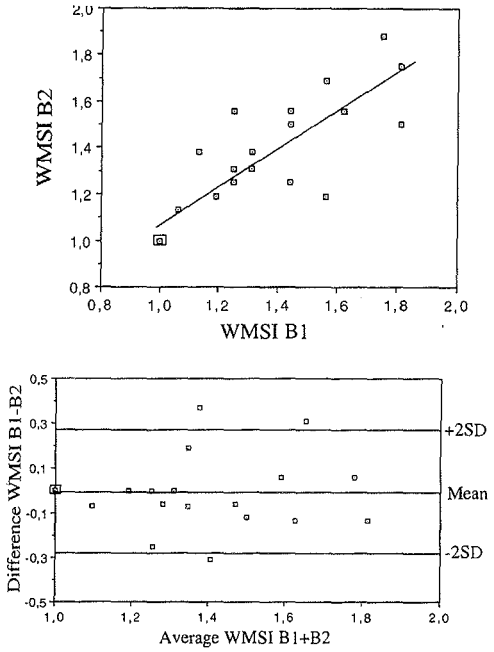

Figure 4. Digital cineloop display: Intraobserver comparisons for WMSI at maximal dipyridamole dose. Double boxes denotes the patients with WMSI = 1.00 by both analysis. *Top panel:* Regression plot, with regression slope: y = 0.83x + 0.23; r-value 0.86. *Bottom panel:* Bland Altman plot, as explained in Figure 3. B1 = WMSI calculations by observer B, first analysis; B2 = WMSI calculations by observer B, second analysis.

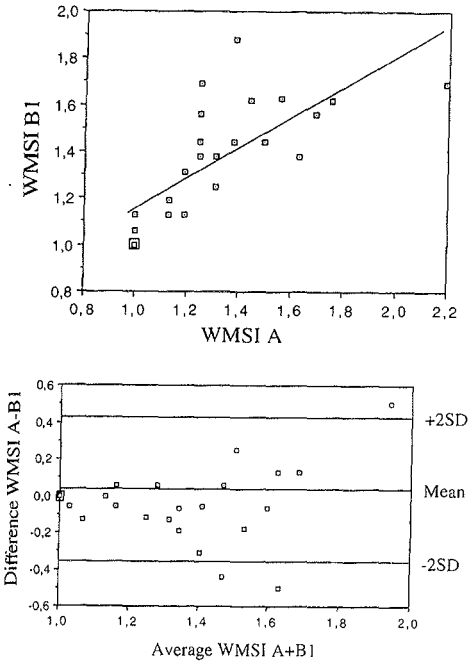

Figure 5. Videotape recordings: Interobserver comparisons for WMSI at maximal dipyridamole dose. Double boxes denotes the patients with WMSI = 1.00 by both observers. *Top panel:* Regression plot, with regression slope: y = 0.65x + 0.50; r-value 0.73. *Bottom panel:* Bland Altman plot, as explained in Figure 3. A = WMSI calculations by observer A; B1 = WMSI calculations by observer B, first analysis.

lower frame rate cineloops tended to reduce sensitivity for identification of coronary artery stenosis compared to the high frame rate system. A higher frame rate may identify more subtle wall motion abnormalities and increase the diagnostic accuracy of the test. Polyphasic contraction pattern or tardokinesia may be seen as initial manifestations of ischemia [16], and are easier to identify when the higher frame rate is applied. High frame rate display of left ventricular diastolic wall motion may reveal segments with abnormal relaxation, recently shown to be a sensitive marker of myocardial ischemia [17]. Digital ultrasound scanner systems with very high frame rates ($\geq$ 200 frames/s) have recently been developed [18], and may prove to be valuable for more accurate diagnosis of myocardial ischemia.

Only a few other studies have specifically addressed observer agreement and reproducibility of stress echocardiography. Oberman et al. [19] performed exercise echocardiography on different days in the same group of patients and found highly reproducible results of wall motion scoring and ejection fraction. Picano et al. [20] assessed the influence of observer experience, and concluded that experience from more than 100 stress echocardiography tests was required in order to obtain reliable results. In their study, the results were based on wall motion analysis from videotape recordings without cineloop display.

The method used for inducing cardiac stress may influence the observer agreement. Dipyridamole infusion induces myocardial ischemia by a coronary steal mechanism [21]. The effects on heart rate and systolic blood pressure are less pronounced than with other modalities of stress echocardiography such as dynamic exercise or dobutamine infusion [22]. In a previous study performed with the digital high frame rate cineloop system, we found higher interobserver

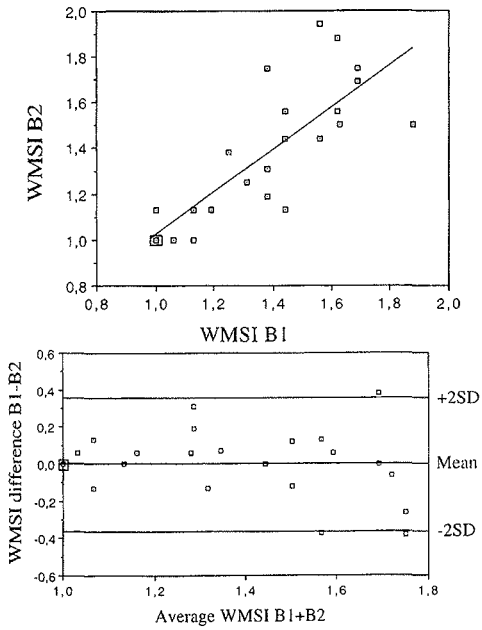

Figure 6. Videotape recordings: Intraobserver comparisons for WMSI at maximal dipyridamole dose. Double boxes denotes the patients with WMSI = 1.00 by both observers. *Top panel:* Regression plot, with regression slope: y = 0.92x + 0.1; r-value 0.81. *Bottom panel:* Bland Altman plot, as explained in Figure 3. B1 = WMSI calculations by observer B, first analysis; B2 = WMSI calculations by observer B, second analysis.

agreement with dipyridamole tests than with bicycle stress echocardiography (92% versus 81%), presumably due to the more difficult interpretation of tests with significant tachycardia [23]. In our laboratory, the interobserver agreement for analysis of dobutamine stress echocardiography was in the same range as for bicycle echocardiography (82%) [24] when computer displayed cineloops were used for analysis.

The results of this type of study depend on observer characteristics as well as on the image quality and severity of coronary artery disease of the population studied. The observers in this study had more than two years of cooperative experience with stress echocardiography and wall motion analysis. The patients were selected from consecutive dipyridamole tests, and were not excluded due to unsatisfactory image quality. Of the 25 patients included, 21 (84%) had documented coronary artery disease with coronary bypass surgery and/or myocardial infarctions. The majority of the patients thus had baseline wall motion abnormalities, a factor that makes the diagnosis of myocardial ischemia during stress echocardiography more difficult [25]. The analysis was performed solely on the basis of echocardiographic data, without knowledge of occurrence of electrocardiographic changes or angina pectoris provoked by the test. In a clinical setting, such information complements wall motion analysis, and may improve observer agreement and diagnostic accuracy.

Segmental wall motion scoring

WMSI is a common method for semi-quantitative description of left ventricular systolic function after myocardial infarction [26, 27]. During stress echocardiography, WMSI describes the presence and severity of baseline wall motion abnormalities as well as the extension and severity of the change induced by stress. The mean inter- and intraobserver differences in WMSI were small throughout the stress tests, and no significant differences between the analysis systems were found. These results show that WMSI, although based on visual, subjective interpretation, is a reproducible parameter that can be used with any type of image display system.

Conclusions

Computerized display of digital cineloops contribute to optimal observer agreement for stress echocardiographic interpretations in patients with difficult interpretation due to baseline wall motion abnormalities. High frame rate of computer displayed cineloops tends to increase test sensitivity as compared to standard lower frame rate display.

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Paper V

Interobserver and Intraobserver Variation for Analysis of Left Ventricular Wall Motion at Baseline and During Low- and High-Dose Dobutamine Stress Echocardiography in Patients With High Prevalence of Wall Motion Abnormalities at Rest

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Interobserver and intraobserver variation for analysis of left ventricular regional wall motion during dobutamine stress echocardiography was assessed. Computer-displayed cineloops from 33 patients, 25 with baseline wall motion abnormalities, were analyzed by two observers blinded for patient data. Assessment included (1) baseline wall motion abnormalities, (2) evidence of myocardial viability at 10 μg/kg/min dobutamine, and (3) evidence of myocardial ischemia at 30 to 40 μg/kg/min. Wall motion score index was calculated at each stage. Interobserver and intraobserver agreement for baseline wall motion abnormalities was 100%. Interobserver agreement for viability and ischemia was 84% and 82%, respectively; intraobserver agreement was 92% and 85%, respectively. Mean interobserver differences in wall motion score index ranged from 0.06 ± 0.14 at baseline to 0.09 ± 0.20 at high doses ($p < 0.05$ at all levels); mean intraobserver differences ranged from 0.001 ± 0.14 to 0.01 ± 0.15 (difference not significant at all levels). (J Am Soc Echocardiogr 1996;9:320-8.)

Stress echocardiography is an emerging noninvasive technique for the evaluation of coronary artery disease.[1-3] The method is highly applicable and allows assessment of left ventricular global and regional function at baseline and during cardiac stress. Diagnostic accuracy is comparable to myocardial scintigraphic techniques when coronary angiography is used as a reference method for coronary artery stenosis,[4] and the prognostic value has been documented in different subsets of patients with coronary artery disease.[5-7] Pharmacologic agents can be used in patients unable to undergo dynamic exercise and provide optimal imaging conditions with minimal respiratory interference. The synthetic cathecholamine dobutamine increases myocardial contractility and heart rate, with only mild effects on peripheral hemodynamics.[8,9] The occurrence of new or increased regional wall motion abnormalities during high-dose dobutamine infusion suggests significant coronary stenosis,[10-12] whereas low-dose dobutamine infusion can identify viable myocardium after acute myocardial infarction[13] or hibernating myocardium associated with chronic hypoperfusion.[14] Improved regional contractility during low-dose dobutamine infusion predicts myocardial recovery at follow-up after coronary revascularization.[15-17]

Interpretation of stress echocardiographic studies is based on visual assessment of two-dimensional cardiac images and is, accordingly, strictly subjective and observer dependent.[18] The lack of objective criteria for positive or negative test results is a major methodologic challenge. In this study, results of 33 dobutamine stress echocardiographic tests were analyzed by two experienced observers for assessment of interobserver and intraobserver agreement with regard to baseline wall motion abnormalities and myocardial viability and ischemia. Wall motion score index (WMSI) was assessed at each stage to study the reproducibility of this semiquantitative index for describing left ventricular systolic function.

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METHODS

Patient Selection

The study population consisted of 33 consecutive patients undergoing stress echocardiography with low- and high-dose dobutamine infusion. The majority of patients were expected to have baseline wall motion abnormalities as a result of previous myocardial infarctions, thus representing a group of patients with difficult interpretations of stress-induced changes. Indications for stress echocardiography were chest pain syndromes with or without previous acute myocardial infarction or evaluation of myocardial viability or ischemia before planned coronary revascularization. Patients with unstable angina pectoris, recent myocardial infarction (<5 days before examination), recent ventricular arrhythmias, hypertrophic cardiomyopathy, severe hypertension (brachial artery systolic blood pressure ≥200 mm Hg or diastolic blood pressure ≥100 mm Hg), hypotension (systolic blood pressure <90 mm Hg), or congestive heart failure were excluded. A poor echocardiographic window was not used as an exclusion criterion. Individual patient characteristics are shown in Table 1. The mean age was 53 ± 12 years (35 to 79 years); six patients were women and 27 were men. Twenty-three patients (70%) had documented previous myocardial infarction by clinical, electrocardiographic, and enzymatic criteria. Of these, 14 had Q wave and nine had non-Q wave infarction. Electrocardiograms showed anterior wall infarction in 14 patients, inferior in seven, both anterior and inferior in one, and lateral in one. One patient had atrial fibrillation; all the others were in sinus rhythm.

Dobutamine Infusion Protocol

Dobutamine was administered with an infusion pump to an intravenous line in the left forearm of the patient. Patients were monitored with blood pressure recording every minute (Dinamap; Critikon Inc., Tampa, Fla.), a 12-lead electrocardiogram every 3 minutes throughout the test, and continuous cardiac rhythm monitoring on the ultrasound scanner. The dobutamine dose was started at 5 μg/kg/min and increased every 3 minutes to 10, 20, 30, and 40 μg/kg/min. Predetermined end points were completed dobutamine protocol (40 μg/kg/min for 3 minutes), tachycardia (>85% of age-predicted maximal heart rate), chest pain, electrocardiographic ST segment depression of 3 mm or greater, systolic hypertension (blood pressure >220 mm Hg) or hypotension (blood pressure ≤80 mm Hg), ventricular arrhythmias, or severe patient discomfort. Of the patients studied, 30 (91%) received 40 μg/kg/min dobutamine, whereas in three patients the test was stopped at 30 μg/kg/min because of sinus tachycardia. The test was not terminated because of chest pain or ST segment depression in any of the patients.

Echocardiographic Imaging

The patients were imaged in the left lateral recumbent position. An ultrasound scanner (CFM 800; Vingmed Sound A/S, Horten, Norway) with an annular-array 3.25 MHz transducer was used for two-dimensional imaging. Images were obtained from left ventricular apical and parasternal positions. Standardized views of apical four-chamber, two-chamber, long-axis, and parasternal short-axis positions at the midpapillary muscle level were transferred digitally to a computer for subsequent reviewing and storing on optical disks. The same sequence of images was transferred at baseline, during the last minute of infusion at 10 μg/kg/min, and at maximal dobutamine dose. All images were previewed on the scanner monitor before storing to ensure comparable views. The computer software allowed the best of three consecutive cardiac cycles to be selected from each view.

Stress Echocardiographic Analysis

Analysis was performed independently by two observers (observer A and observer B1), assessing regional wall motion abnormalities at baseline, evidence of myocardial viability (10 μg/kg/min), and evidence of ischemia at maximal dose (30 or 40 μg/kg/min). Observer B did additional analysis more than 6 months after the initial analysis for assessment of intraobserver variation (analysis B2). The images were organized on the computer monitor as a side-by-side display of cineloops from the same view at different stress levels. Evidence of myocardial viability was defined as increased wall motion or wall thickening in at least two contiguous myocardial segments with baseline wall motion abnormality. Myocardial ischemia was defined as the occurrence of a new or worsened wall motion abnormality affecting at least one myocardial segment with normal or hypokinetic baseline wall motion.

WMSI was calculated according to a 16-segment representation of the left ventricular myocardium as recommended by the American Society of Echocardiography.[19] The abnormal segments were assigned to the territory of the left anterior descending artery (LAD), the left circumflex artery (LCX), or the right coronary artery (RCA), assuming the coronary distribution as described previously.[20] Segmental wall motion was scored as 1 = normal; 2 = hypokinetic, 3 = akinetic, 4 = dyskinetic, or 5 = aneurysmal, and WMSI was calculated as the total score divided by the number of scored segments. A WMSI of 1.00 thus indicates normal wall motion. Indexes of 1.00 to 1.49, 1.50 to 1.99, and 2.00 or greater indicate mild, moderate, and severe left ventricular dysfunction, respectively.[16]

Image Quality

To assess the influence of image quality on interobserver agreement, each test was scored subjectively by observer B, on a scale from 1 (excellent) to 4 (very poor) based on echocardiographic visualization of left ventricular endocardium.

Coronary Angiography

Coronary cineangiograms were obtained in 22 patients (67% of study population) with clinical indications for this

Table 1 Baseline characteristics for individual patients

Patient no.	Age (yr)/sex	MI	Localization	Q wave	Coronary angiography	Occlusion	Stenosis
1	63/F	–	—	–	–		
2	63/M	+	Anterior	+	+	—	LAD
3	79/M	+	Anterior	+	+	LAD	—
4	55/M	+	Anterior	–	+	—	LCX
5	40/M	–	—	–	+	—	LCX, RCA
6	54/F	–	—	–	–		
7	60/M	+	Anterior	+	+	—	LAD, LCX, RCA
8	72/M	–	—	–	–		
9	68/M	+	Anterior	–	–		
10	35/M	+	Anterior	+	+	LAD	—
11	55/F	–	—	–	–		
12	39/M	+	Anterior + inferior	+	+	LCX	LAD
13	48/M	–	—	–	–		
14	55/F	–	—	–	–		
15	60/M	+	Inferior	+	+	—	RCA
16	48/M	+	Inferior	–	+	RCA	LAD
17	46/M	+	Inferior	+	+	RCA	LAD
18	45/M	+	Anterior	–	+	—	LAD
19	55/M	+	Anterior	+	+	LAD	—
20	37/M	+	Anterior	+	+	LAD, RCA	—
21	42/M	+	Anterior	–	+	—	LAD
22	59/M	+	Anterior	–	–		
23	55/M	+	Anterior	+	–		
24	67/M	+	Inferior	+	+	—	LAD, LCX, RCA
25	40/M	+	Lateral	–	+	LCX, RCA	—
26	73/F	–	—	–	+	LCX	—
27	44/M	+	Inferior	+	+	—	LAD
28	58/M	+	Anterior	+	+	LAD, LCX	—
29	40/M	–	—	–	+	LCX, RCA	—
30	63/M	+	Inferior	–	–		
31	36/M	+	Anterior	–	+	—	LAD
32	55/M	–	—	–	–		
33	60/F	+	Inferior	+	+	—	RCA

MI, Myocardial infarction; *LAD*, left anterior descending artery; *LCX*, left circumflex coronary artery; *RCA*, right coronary artery.

procedure, according to the femoral artery approach. Biplane selective coronary arteriography was performed with left and right Judkins coronary catheters (Scimed Life Systems Inc., Maple Grove, Minnesota, USA) with multiple projections. Angiograms were analyzed visually by an experienced observer not otherwise involved in the study. A 50% diameter stenosis (correponding to a 75% reduction in lumenal area) was considered a significant lesion. Lesions in the three major coronary vessels and their main branches were assessed.

Statistical Analysis

The agreement between the observers (observer A versus observer B1 and observer B1 versus observer B2) with regard to baseline wall motion abnormalities, myocardial viability, and ischemia was calculated as percentages. Interobserver and intraobserver WMSI comparisons were performed according to correlation factors (r values) and two-sided Student t tests and were displayed as regression plots and Bland-Altman plots.[21] A p value <0.05 was considered statistically significant. Sensitivities and specificities for identification of coronary artery stenosis were calculated according to standard definitions,[22] with coronary arteriography used as the reference method.

RESULTS

Observer A, B1, and B2 interpretations of regional left ventricular wall motion for individual patients at baseline and low-dose and high-dose dobutamine are displayed in Table 2. WMSI calculations are shown in Table 3.

Baseline Wall Motion Abnormality

The interobserver and intraobserver agreement on the presence or absence of baseline wall motion abnormality was 100% (33 of 33 patients). The coronary distribution affected was concordant in all 25

Table 2 Observer interpretations for baseline wall motion abnormalities, viability, and ischemia

Patient no.	Observer A			Observer B1			Observer B2		
	Baseline WMA	Viability	Ischemia	Baseline WMA	Viability	Ischemia	Baseline WMA	Viability	Ischemia
1	—	—	—	—	—	—	—	—	—
2	LAD	—	—	LAD	—	—	LAD	—	—
3	LAD	LAD	—	LAD	—	—	LAD	—	—
4	LAD	—	—	LAD	—	—	LAD	—	—
5	—	—	—	—	—	—	—	—	—
6	—	—	RCA	—	—	RCA	—	—	RCA
7	LAD	—	—	LAD	—	—	LAD	LAD	LAD
8	LAD	LAD	—	LAD	LAD	—	LAD	LAD	—
9	LAD	LAD	—	LAD	—	LAD	LAD	—	LAD
10	LAD	—	RCA	LAD	—	LAD, RCA	LAD, RCA	—	RCA
11	—	—	—	—	—	—	—	—	LAD
12	LAD	LAD	—	LAD	LAD	—	LAD	LAD	—
13	—	—	—	—	—	—	—	—	—
14	—	—	—	—	—	RCA	—	—	RCA
15	RCA	RCA	—	RCA	RCA	RCA	RCA	RCA	RCA
16	RCA, LCX	—	—	RCA	RCA	—	RCA	RCA	—
17	LAD	LAD	—	LAD, RCA	LAD, RCA	RCA	LAD, RCA, LCX	LAD, LCX	—
18	LAD	—	—	LAD	LAD	—	LAD	LAD	—
19	LAD	LAD	—	LAD, RCA	LAD, RCA	—	LAD, RCA	LAD	—
20	LAD	—	—	LAD	—	—	LAD	LAD	—
21	LAD	LAD	—	LAD	LAD	—	LAD	LAD	—
22	LAD	—	—	LAD	—	—	LAD	—	—
23	LAD	—	LCX	LAD	—	—	LAD	—	—
24	RCA	RCA	RCA	RCA	RCA	RCA	RCA	RCA	RCA
25	LCX, RCA	RCA	RCA	LCX	LCX	LCX	LAD, LCX	LCX	LCX
26	—	—	—	—	—	—	—	—	—
27	LAD	LAD	LAD	LAD	LAD	LAD	LAD	LAD	LAD
28	LAD	—	—	LAD	—	—	LAD	—	LAD
29	LAD, LCX, RCA	LAD	—	LAD, LCX, RCA	LAD	—	LAD, RCA	LAD, RCA	—
30	RCA	RCA	—	RCA	RCA	—	RCA	RCA	—
31	LAD	LAD	—	LAD	LAD	—	LAD	LAD	—
32	—	—	—	—	—	—	—	—	LAD
33	RCA	RCA	—	RCA	RCA	RCA	RCA	RCA	RCA

Observers B1 and B2 denote the first and second analysis, respectively, performed by observer B.
WMA, Coronary distribution of wall motion abnormality; other abbreviations are given in Table 1.

patients with abnormal wall motion. The number of coronary artery distributions affected differed in four patients, by both interobserver and intraobserver analysis. Compared with clinical data, the 23 patients with documented previous myocardial infarction were found to have a wall motion abnormality at baseline (sensitivity 100%). In addition, two patients without previous infarction had a wall motion abnormality (specificity 80%). Of these, one patient had a mild wall motion abnormality in the LAD distribution at rest, with baseline WMSI of 1.13 and 1.19, respectively, showing normalization during low-dose dobutamine testing. The other patient had global myocardial dysfunction involving all three coronary distributions. The coronary angiography in this patient showed occluded LCX and RCA, but the patient had no clinical history of myocardial infarction. For patients who underwent coronary angiography, abnormal baseline wall motion identified coronary occlusions with a sensitivity of 91% (10 of 11 patients). Baseline wall motion abnormalities showed a low specificity for coronary occlusions of 10%, because 10 of 11 patients without coronary occlusions had abnormal regional wall motion at baseline. However, of these 10 patients, nine had significant stenosis of the coronary artery supplying the myocardial distribution with abnormal wall motion, indicating that chronic hypoperfusion could be the underlying mechanism.

Viability Interpretation

Of the 25 patients with baseline wall motion abnormalities, observers A and B1 agreed on the presence

Table 3 WMSI calculations at baseline, low-dose, and maximal-dose dobutamine infusion

	Observer A			Observer B1			Observer B2		
Patient no.	Baseline	Low dose	Maximum dose	Baseline	Low dose	Maximum dose	Baseline	Low dose	Maximum dose
1	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
2	1.50	1.50	1.50	1.38	1.38	1.31	1.44	1.44	1.44
3	1.81	1.69	1.69	1.69	1.69	1.50	1.56	1.63	1.63
4	1.75	1.75	1.75	1.75	1.75	1.75	1.63	1.63	1.63
5	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
6	1.00	1.00	1.19	1.00	1.00	1.13	1.00	1.00	1.13
7	1.88	1.88	1.88	1.88	1.88	1.88	1.69	1.44	1.69
8	1.19	1.00	1.00	1.13	1.00	1.00	1.13	1.00	1.00
9	1.50	1.25	1.25	1.44	1.38	1.50	1.44	1.44	1.50
10	1.69	1.69	2.00	1.69	1.63	1.81	1.88	1.88	1.94
11	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.31
12	2.00	1.88	1.94	1.94	1.69	1.56	2.00	1.63	1.56
13	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
14	1.00	1.00	1.00	1.00	1.00	1.31	1.00	1.00	1.25
15	1.44	1.31	1.31	1.50	1.25	1.69	1.50	1.13	1.44
16	1.38	1.38	1.38	1.44	1.25	1.19	1.50	1.19	1.19
17	2.19	2.06	2.13	2.31	1.50	1.50	2.25	1.88	1.56
18	1.63	1.56	1.56	1.63	1.38	1.38	1.56	1.31	1.25
19	1.88	1.63	1.63	2.19	1.69	1.50	1.88	1.69	1.56
20	1.75	1.69	1.69	1.69	1.63	1.56	1.75	1.56	1.50
21	1.44	1.13	1.13	1.19	1.00	1.00	1.31	1.13	1.06
22	2.00	2.00	2.00	1.94	1.94	1.94	1.94	1.94	1.94
23	1.94	2.00	2.13	1.88	2.06	2.06	1.69	1.69	1.69
24	1.25	1.06	1.25	1.19	1.06	1.19	1.19	1.06	1.25
25	1.75	1.56	1.69	1.19	1.06	1.12	1.44	1.19	1.25
26	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
27	1.25	1.13	1.38	1.19	1.06	1.19	1.25	1.06	1.19
28	1.69	1.63	1.63	1.50	1.50	1.50	1.63	1.63	1.81
29	2.25	2.06	2.06	2.13	2.00	2.00	2.00	1.69	1.69
30	1.50	1.25	1.25	1.31	1.06	1.06	1.38	1.13	1.13
31	1.56	1.38	1.38	1.38	1.25	1.19	1.25	1.25	1.19
32	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
33	1.44	1.31	1.31	1.19	1.06	1.31	1.38	1.19	1.31

WMSI, Wall motion score index.

or absence of improved wall motion or wall thickening in 21 patients (84%). Each of the observers interpreted 15 of the test results as positive for myocardial viability or 60% of the 25 patients with baseline wall motion abnormalities. The coronary distribution showing viability was concordant for the observers in all patients except one; in this patient the observers disagreed on the RCA or the LCX as the coronary distribution showing viability. Two (22%) of the nine patients with non-Q wave myocardial infarction and 11 (79%) of the 14 patients with Q wave infarction were interpreted as having positive test results for viability by both observers. Intraobserver data showed concordant interpretation for viability in 23 (92%) of the 25 patients with baseline wall motion abnormalities.

Myocardial Ischemia

Interobserver analysis showed that 27 (82%) of the 33 test results were interpreted equally by the observers as positive or negative for myocardial ischemia at the maximal dobutamine dose. Ischemia was diagnosed in six test results by observer A, 10 test results by observer B1, and 13 test results by observer B2. Compared with coronary angiography, in seven (50%) of the 14 patients with coronary artery stenosis test results were interpreted as positive by observer A, observer B1, or both. When patients with baseline wall motion abnormalities were included, 13 (93%) of the 14 patients with coronary artery stenosis had abnormal wall motion at rest or during maximal dobutamine infusion. None of the patients with myocardial ischemia at maximal doses had normal coronary angiograms (specificity 100%). Intraobserver interpretation of myocardial ischemia was concordant in 28 (85%) of the 33 test results.

Wall Motion Scoring

Regression plots and Bland-Altman plots of interobserver and intraobserver results for WMSI at maxi-

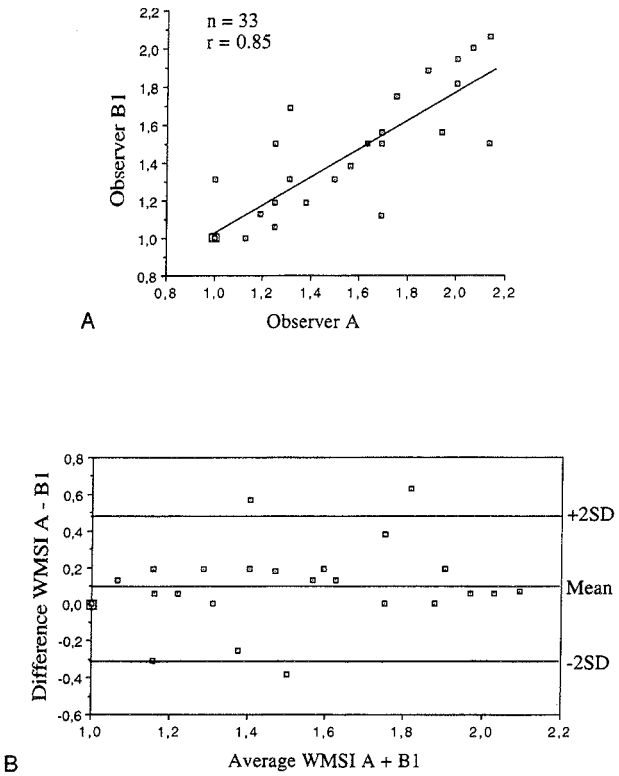


Figure 1 Interobserver comparisons for wall motion score index *(WMSI)* at maximal dobutamine dose. *Double boxes* denote seven patients with WMSI = 1.00 by both observers. **A,** Regression plot, with regression slope: $y = 0.74x + 0.26$. **B,** Bland-Altman plot, with average of two observers' WMSI calculations along x axis and differences along y axis. (*A,* WMSI calculations by observer A; *B1,* WMSI calculations by observer B, first analysis.)

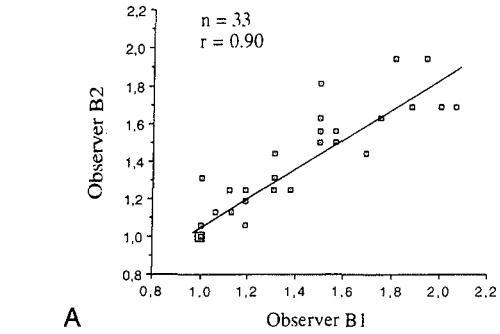
mal dobutamine doses are shown in Figures 1 and 2,respectively. Mean interobserver differences forWMSI were 0.06 ± 0.14 at baseline, 0.08 ± 0.14 at low dose, and 0.09 ± 0.20 at high-dose dobutamine and were statistically significant at all stress levels ($p < 0.05$). The maximal differences between the observers for individual patients were 0.56 (baseline and low dose) and 0.63 (high dose). Intraobserver differences for mean WMSI tended to be smaller than for interobserver analysis—0.002 ± 0.12 at baseline, 0.01 ± 0.15 at low-dose, and 0.001 ± 0.14 at high-dose dobutamine—and were not statistically significant at any stress level. Maximal WMSI intraobserver differences for individual patients were also smaller: 0.31 (baseline), 0.44 (low dose), and 0.37 (high dose).

Image Quality

With the subjective scoring for left ventricular endocardial visualization, 15 test results (45%) were scored as 1 (excellent), 14 test results (43%) as 2, and four test results as 3 (12%). None of the test results were graded as 4 (very poor). The five tests with discordant interobserver interpretation for viability were scored as image quality of 1 or 2, whereas only one of the six tests with disagreement for ischemic interpretation was scored as 3, the others as 1 (three tests) or 2 (two tests).

DISCUSSION

The results of our study show that the identification of baseline left ventricular wall motion abnormalities is highly reproducible, with interobserver and intraobserver agreement in all patients (33 of 33 patients). However, interobserver disagreement on the presence or absence of myocardial viability and myocardial ischemia was found in 16% and 18% of pa-



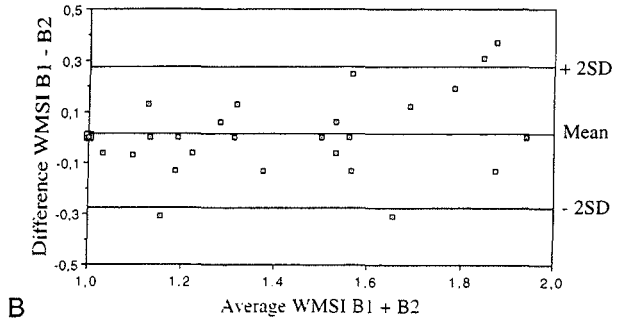


Figure 2 Intraobserver comparisons for wall motion score index *(WMSI)* at maximal dobutamine dose. *Double boxes* denote six ps with WMSI = 1.00 by both analyses. **A,** Regression plot, with regression slope: $y = 0.78x + 0.3$. **B,** Bland-Altman plot, as explained in Figure 1. (*B1,* WMSI calculations by observer B, first analysis; *B2,* WMSI calculations by observer B, second analysis.)

tients, respectively, and in 8% and 15% of patients, respectively, by intraobserver analysis. These discrepancies were not related to poor image quality. Dobutamine-induced changes in regional contractility associated with myocardial viability or myocardial ischemia may be subtle and, hence, remain unrecognized or interpreted differently by the observers. The impact of observer experience for correct stress echocardiographic interpretation has been documented previously.[18] In this study, both observers had several years of experience with wall motion analysis during stress echocardiography and had been cooperating in the same echocardiographic laboratory for approximately 1 year.

Viability Assessment

The low-dose dobutamine test is used to document myocardial functional reserve and to select patients who are likely to benefit from coronary revascularization procedures. Currently there is no standard definition of viability in terms of echocardiographic criteria.[15-17] In our study, visually improved wall motion or wall thickening in two or more contiguous myocardial segments was used to define viability. This criterion reduces the risk of interpreting a minimal wall motion improvement caused by tethering as evidence of viability. Interpretation of viability may be particularly difficult in patients with extensive myocardial akinesia at baseline, such as the majority of our study patients, when the improved contractility is limited to the periphery of the akinetic region. Such changes may be due to true viability or a tethering phenomenon with hypercontraction of surrounding, normal myocardium[23] and may be an explanation for the different interpretation. In our study, intraobserver agreement was higher than in-

terobserver agreement (92% versus 84% of patients). Wall thickening may be a more specific marker of myocardial viability than wall motion. Although thickening can be assessed visually by two-dimensional echocardiography, as in our study, M-mode echocardiography has higher temporal resolution and may give more accurate measurement of wall thickening. However, visual assessment of two-dimensional images, as used in our study, is so far the most common method for echocardiographic evaluation of myocardial viability.

Ischemia Assessment

Interobserver and intraobserver agreement for identification of coronary ischemia during high-dose dobutamine stress echocardiography was 82% and 85%, respectively, in our study. The interpretations were based solely on computer display of left ventricular images transferred at standardized dobutamine doses, and transient ischemia occurring before the termination of infusion was thus not subjected to assessment. The observers were strictly blinded for all clinical and angiographic information. Knowledge of data such as patient history and chest pain or electrocardiographic changes during the stress test may improve both the agreement between observers and the diagnostic accuracy of the dobutamine test. We have previously shown that interobserver agreement is higher during pharmacologic stress echocardiography with dipyridamole infusion than with bicycle stress echocardiography (92% versus 81%)[24] and have suggested that this difference may be due to the more difficult interpretation of tests associated with significant tachycardia and an altered hemodynamic situation. Like dynamic stress testing, dobutamine infusion increases the heart rate in the doses used for stress testing.[8,9]

In this study the sensitivity for the detection of myocardial ischemia in patients with coronary artery stenosis was low, because only 50% of patients with one or more significant lesions at coronary angiography were found to have positive test results by at least one observer. A probable explanation is that the majority of our patients had previous myocardial infarctions with baseline wall motion abnormalities in the coronary distribution supplied by the stenosed coronary artery. The stenotic lesion may thus represent a partially revascularized vessel supplying infarcted, nonviable myocardium, whereas inducible ischemia occurs only in myocardium with preserved viability. Furthermore, evaluation of ischemia in patients with baseline wall motion abnormalities may be difficult if the ischemic myocardium is restricted to the infarct-related distribution.[25] Atropine was not used in our study but has been shown to increase sensitivity of dobutamine stress echocardiography for identification of coronary artery stenosis.[26]

Semiquantitative Wall Motion Scoring

WMSI is an easily applicable method for describing regional left ventricular systolic function and has been shown to be valuable for risk stratification after myocardial infarction.[27,28] The results of our study show that the mean interobserver and intraobserver differences for WMSI were small and clinically insignificant throughout the stress test. Individual patient data show that, on average, only one of the 16 myocardial segments was interpreted differently by the two observers. However, in a few patients, WMSI showed greater interobserver discrepancies, the extreme being 0.63, underlining the subjectivity of this index. The large discrepancies (>0.50) found in two patients could not be explained by poor image quality. In one of these cases (patient 17) the discrepancy was caused by interpretation of ischemia in the RCA distribution at high doses by observer B1. The other patient (No. 25) was found to have baseline wall motion abnormalities in both the RCA and LCX distributions by observer A, whereas observer B1 evaluated the wall motion in the RCA distribution as normal.

The mean interobserver differences in WMSI, although small, were statistically significant at all three stress levels, a result of the almost consistently higher values scored by observer A than by observer B. Intraobserver variations were smaller than interobserver variations and did not reach statistical significance at any level of the test. These results indicate that serial wall motion scoring for follow-up purposes preferably should be performed by the same observer.

Conclusion

The results of this study underline the role of observer dependency in the assessment of myocardial viability and ischemia during dobutamine stress echocardiography. WMSI assessment generally shows good agreement between observers, but in a few patients the discrepancy may be clinically significant. Evaluation by the same observer may reduce the WMSI variability.

Although visual wall motion interpretation has satisfactory reproducibility, more accurate methods should be searched to assess the changes in regional left ventricular function during stress echocardiographic testing and to describe serial changes in the extent and severity of left ventricular dysfunction after coronary interventional procedures.

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Paper VI

QUANTITATIVE COMPUTERIZED ANALYSIS OF LEFT VENTRICULAR WALL MOTION

K. Bjoernstad, M.D., J. Maehle, M.Sc., S. Aakhus M.D.

Introduction

Two-dimensional echocardiographic imaging is a widely used technique for noninvasive identification of coronary artery disease by analysis of left ventricular (LV) wall motion analysis. In patients admitted to the coronary care unit, a wall motion abnormality is more sensitive and specific for acute myocardial infarction than electrocardiographic changes[1]. During cardiac stress testing, detection of a new wall motion abnormality strongly indicates the presence of significant coronary artery stenosis[2, 3]. During ischemia, regional systolic dysfunction can be observed with echocardiography before electrocardiographic ST-depression and anginal pain occur[4], and stress echocardiography is more sensitive for the diagnosis of significant coronary artery stenosis than stress electrocardiography [3, 5].

Computer technology has greatly influenced the diagnostic value of stress echocardiography. Images of the LV at rest and during stress can be compared side-by-side, and facilitates detection of subtle changes in regional wall motion. However, stress echocardiography is still regarded as a qualitative test, analyzed by visual interpretation of wall motion. The position of the heart in the chest changes with respiration and ventricular contraction. In addition, assessment of systolic LV wall motion involves evaluation of both endocardial motion, myocardial

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thickening, and of the time sequence of contraction. The visual interpretation is superior to computerized analysis in the integration of all these factors. However, recent improvements in computer software and image quality have encouraged new computerized methods for quantitative LV wall motion analysis.

In this presentation, we review different methods for quantitative regional wall motion analysis. We also present a method for 3-dimensional wall motion analysis with reconstruction of the LV endocardium based on transthoracic 2-dimensional apical images. Our data were obtained with an ultrasound scanner (CFM 750, Vingmed Sound, Norway) interfaced to a computer (Macintosh II series, Apple Inc., USA). Digital cineloops were transferred from the scanner to the computer as scanline data, providing cineloops with the same high framerate as the scanner. The algorithm used for 3-dimensional reconstruction was developed and computer implemented at the Department of Biomedical Engineering, Trondheim, and operates with a commercially available computer software (Echo-Loops/Echo-Disp version 3.0, Vingmed Sound, Norway.)

Two-dimensional wall motion analysis

With 2-dimensional echocardiography, wall motion abnormalities can be assigned to the distribution of specific coronary arteries, and the presence of multivessel disease may be identified. The common distribution of the coronary arteries in relation to the different segments of the standard apical echocardiographic views are shown in figure 1. Several semiquantitative and quantitative methods have been proposed.

Wall motion score index (WMSI): WMSI is a simple yet clinically useful method for semiquantitative description of LV wall motion. We have used the 16-segment model of the left ventricle as recommended by the American Society of Echocardiography, with 6 basal, 6 mid-ventricular and 4 apical segment [6]. Segmental wall motion is assessed by visual interpretation of individual apical or parasternal cineloops. Segments with normal wall motion are assigned a score of 1, hypokinesia = 2, akinesia = 3, dyskinesia = 4, and aneurysmatic segments = 5. Segments that are not adequately visualized are not scored. WMSI is calculated as the ratio between the sum of all segmental scores and the number of visualized segments.

Segmental scoring can be displayed as a "bull's eye plot" as shown in figure 2. This plot illustrates the location, the extent, and the severity of wall motion abnormality. In stress echocardiography, bull's eye plots can be used to compare regional wall motion at rest and during stress (Fig. 3).

WMSI is a widely used method for description of LV regional wall motion in the clinical situation. It is useful for prognostic stratification of patients with recent

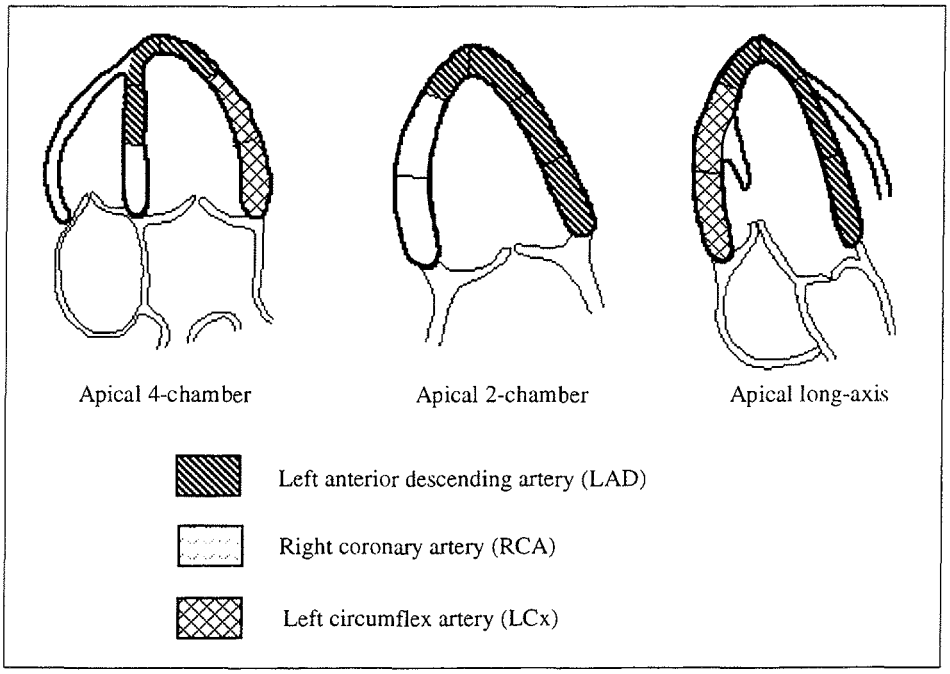

Figure 1 – The common distribution of coronary flow as related to the 3 standard apical echocardiographic image planes.

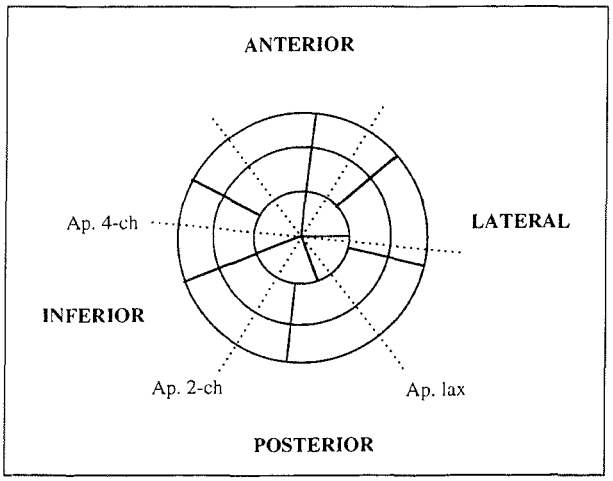

Figure 2 – Bull's eye plot of LV wall motion represented by 16 myocardial segments generated from the 3 apical views. Ap. 4-ch = apical 4-chamber; Ap. 2-ch = apical 2-chamber; Ap. lax = apical long-axis.

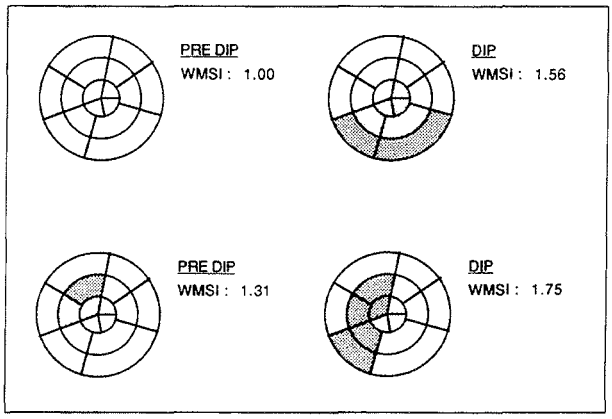

Figure 3 – Bull's eye plots with wall motion score index (WMSI) during stress echocardiography. The *upper panel* shows a patient with normal wall motion at rest (*left*), who developes infero-posterior wall motion abnormality during stress (*right*). The *lower panel* shows a patient with anteroseptal wall motion abnormality at rest (*left*), who developes inferior wall akinesia during stress (*right*), indicating multivessel-disease. WMSI is shown for each level.

myocardial infarction. For instance, a high score index in patients admitted to the coronary care unit indicates an increased risk for early complications[7], and a high WMSI shortly after myocardial infarction is associated with increased mortality on follow-up[8].

WMSI has, however, limitations as a tool for accurate determination of regional myocardial function. It is a semiquantitative calculation based on visual interpretation of wall motion. Even though all segments count equally in the score index, the endocardial areas represented by the different segments vary in size. Furthermore, the distributions of the 3 major coronary arteries are not absolute. For instance, the infero-posterior part of the ventricle may be perfused by either the right coronary or the left circumflex artery[9].

Single plane wall motion: These methods are based on the tracing of endocardial contours at end-diastole and end-systole. The two contours are superimposed and a common reference system is chosen for analysis of regional wall motion[10, 11]. A fixed reference system does not compensate for the translational and rotational movement of the heart during contraction, whereas a floating reference system does so by alignment of the contours with a defined common center and parallel ventricular long axis. Either the midpoint of the mitral plane, the ventricular long axis, or the center of area inside the contour can be used for alignment.

Regional wall motion is commonly assessed by the centerline or the radial wall motion method[12, 13]. With the centerline method, wall motion is defined as the distance

between end-diastolic and end-systolic endocardial contours along lines drawn perpendicular to the centerline, which is the line midway between the two superimposed contours. The two contours are aligned by the center of the mitral plane and the ventricular long axis. Myocardial regions with ischemia or fibrotic scar after myocardial infarction show reduced systolic movement, and thus, the end-diastolic and end-systolic contours will be close (Fig. 4). The radial wall motion method has the center of area, defined by the end-diastolic and end-systolic contours, as reference for wall motion. Regional wall motion is determined as the shortening along 50 radii drawn from this common center to the outer contour as

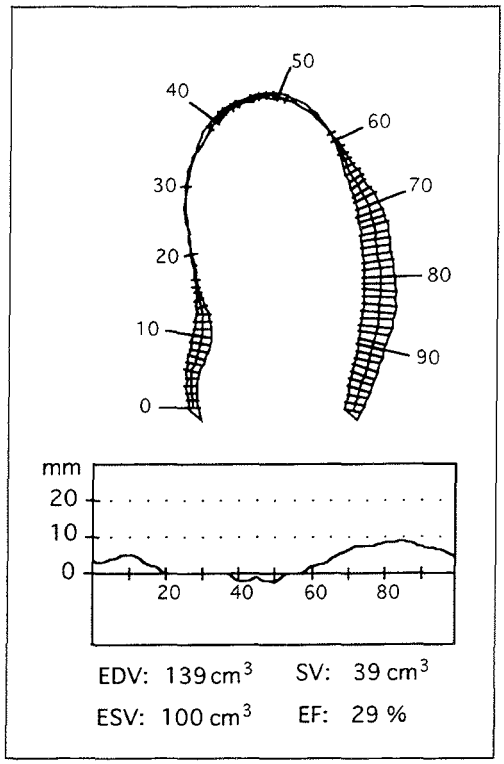

Figure 4 – The centerline method. *Upper panel*: The endocardium from apical 4-chamber view is traced in end-systole (inner contour) and end-diastole (outer contour). Wall motion is calculated in mm along the lines drawn perpendicular to the centerline (the line midway between the two contours). The figure shows an example of akinesia in apex and apical septum. *Lower panel*: A diagram of the regional wall motion is displayed. The numbers along the horizontal line correspond to the numbers of the perpendicular lines of the endocardial contours. EDV = End-diastolic volume; ESV = end-systolic volume; EF = ejection fraction; SV = stroke volume.

shown in figure 5. Wall motion is displayed as the percent shortening of the radius to the outer end-diastolic contour.

Delayed contraction (tardokinesia) or delayed relaxation are early markers of ischemia, and may be the only echocardiographic findings in patients with mild ischemia. Single plane methods can be used to show the temporal sequence of contraction and relaxation in the different regions of the ventricle[14]. This requires tracing of endocardial contours in every frame through the heart cycle.

Impaired myocardial thickening is also a sensitive marker of ischemia[15]. Systolic wall thickening in the various regions of the left ventricle may be displayed if both endocardial and epicardial borders are identified and traced (Fig. 6). However, the

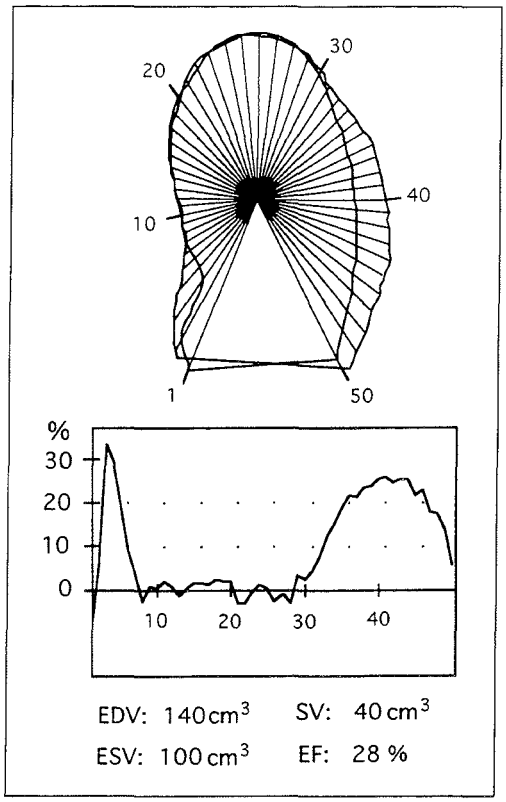

Figure 5 – The radial wall motion method. This example is from the same heart as shown in figure 4. *Upper panel*: The end-diastolic and the end-systolic endocardial contours are aligned by a common surface center and common direction of the major axes. Wall motion is calculated along radii drawn from the common center to 50 equally spaced points on the end-diastolic contour. *Lower panel*: Radial shortening displayed as % of the distance in end-diastole. The numbers on the horizontal line correspond to the numbers of the radii on the end-diastolic contour.

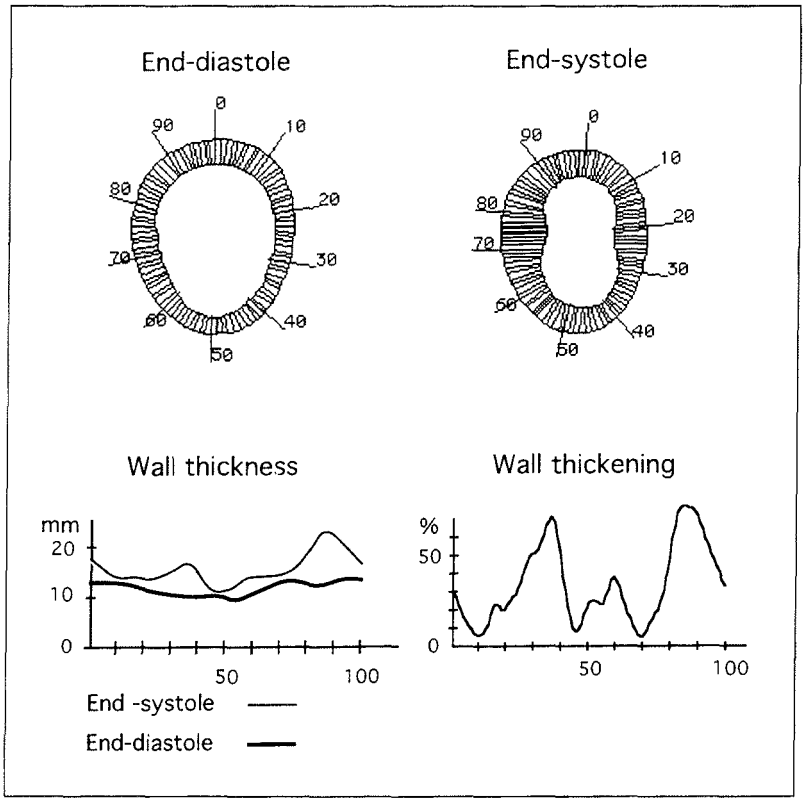

Figure 6 – Example of systolic wall thickening. *Upper panel*: Epicardial and endocardial borders of parasternal short axis images are traced in end-diastole and end-systole. The figure shows an example of reduced wall thickening in the anterior and posterolateral LV wall. *Lower panel*: Regional wall thickness in end-diastole and end-systole is displayed in mm (*left*), and regional systolic wall thickening as % of end-diastolic wall thickness (*right*). This figure illustrates impaired wall thickening in the anterior and posterolateral LV wall.

epicardial contour may be difficult to define accurately during transthoracic apical imaging.

Single plane methods for wall motion assessment have limited clinical value, but are useful for the purpose of description and illustration. Reproducible LV volumes can be obtained with computerized analysis of 2-dimensional apical images[6, 16, 17], and the stroke volume and ejection fraction may thus be determined. The single plane method of discs is used for these calculations. Ventricular dilatation during cardiac stress is a specific finding in patients with multivessel coronary disease, and suggests a severe impairment of global systolic function[18]. However, patients with less extensive coronary artery disease may have normal ventricular volumes

and ejection fraction during stress, due to compensatory hyperkinesia in regions with normal coronary perfusion.

Three-dimensional wall motion analysis

Three-dimensional reconstruction of LV chamber should ideally provide reproducible data on chamber volume, shape, and regional wall motion. Several methods have been proposed: 1) rotation of the imaging plane from the apical position during transthoracic imaging[19, 20]; 2) tilting of the image plane from the parasternal position[21, 22]; and, recently, 3) parallel short axis images of the left ventricle obtained with transesophageal echocardiography[23].

We have used an algorithm for 3-dimensional reconstruction of the left ventricle from multiple 2-dimensional transthoracic apical views. The images are obtained by rotation of the transducer starting with the standard apical 4-chamber view (Fig. 7). Endocardial contours are automatically traced by a computer algorithm and

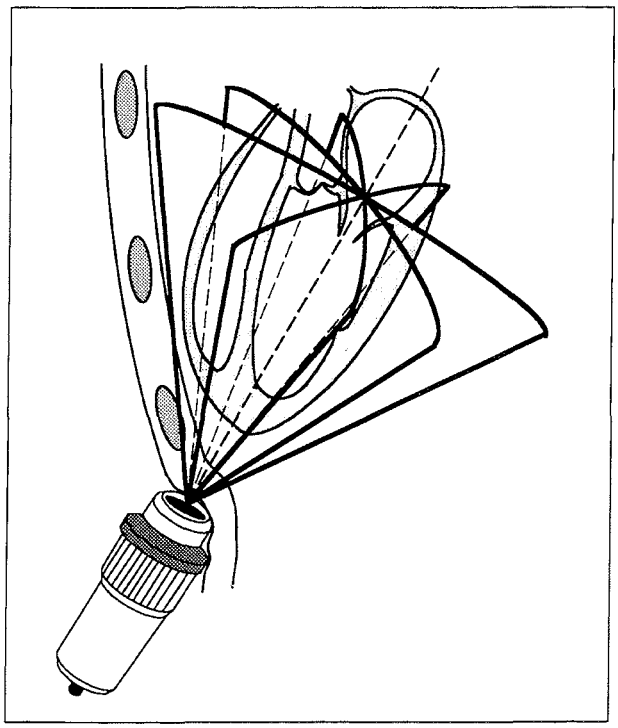

Figure 7 – Three-dimensional reconstruction of the LV is performed from apical images obtained by rotation of the image plane around the major axis of the ventricle.

manually adjusted by the investigator. All frames are traced, allowing reconstruction of the ventricular endocardium during the entire cardiac cycle. The endocardium is reconstructed by a surface through the tracings of the apical images in 3-dimensional space. The surface is generated using bicubic spline interpolation in order to obtain a surface with minimal variation in curvature. The tracings are positioned in 3-dimensional space with respect to the relative angles between the image planes, and by alignment of the ventricular apex and the LV long axis. The apex is determined by the computer as the point of the tracings most distant from the midpoint of the mitral plane. Skewed or foreshortened image planes will cause underestimation of volumes and error in the reconstructed endocardial surface. To avoid this, the contours are stretched in the direction of the major axis, so that all major axes equal the longest axis obtained. The endocardial surface area, the cavity volume, and the position of the center of mass of the cavity are automatically calculated.

Accurate and reproducible LV volumes can be obtained with this 3-dimensional reconstruction by using 3 standard apical image views: apical 4-chamber, 2-chamber and long-axis views (Fig. 8). In our laboratory, this method has been found to determine accurately shapes and volumes of deformed and normal balloons over a large range of sizes. Interobserver variation on volumes determined with 3-dimensional reconstruction are in the range of 5-7%, when the edges are traced manually.

Regional wall motion: Three-dimensional reconstruction of the LV may also be used for assessment of regional wall motion abnormalities in patients with myocardial infarctions or undergoing stress echocardiography. The endocardial surface is represented by 1024 numbered points in 3-dimensional space. The reconstructed surface is divided into small regions surrounding each point, and the area of each of these regions is calculated. By summation of these areas the total surface area can be calculated. Our algorithm determines systolic wall motion in each point from the end-diastolic and end-systolic surface reconstructions. Thereby, the endocardial area with reduced wall motion can be described as a percentage of the total end-diastolic endocardial area. The location and extent of the wall motion abnormality is displayed in a bull´s eye plot similar to the one used with WMSI (Fig. 9). The total end-diastolic and end-systolic endocardial areas are calculated in cm^2, thus, the absolute endocardial area with reduced systolic motion can be determined.

Different reference systems for quantitative wall motion analysis in 3 dimensions are available. We have implemented six different methods in the computer software. Three of these methods may be regarded as extentions of the 2-dimensional radial wall motion method to 3 dimensions. In these methods, regional wall motion is measured as the percent shortening of the distance from the points in the reconstructed

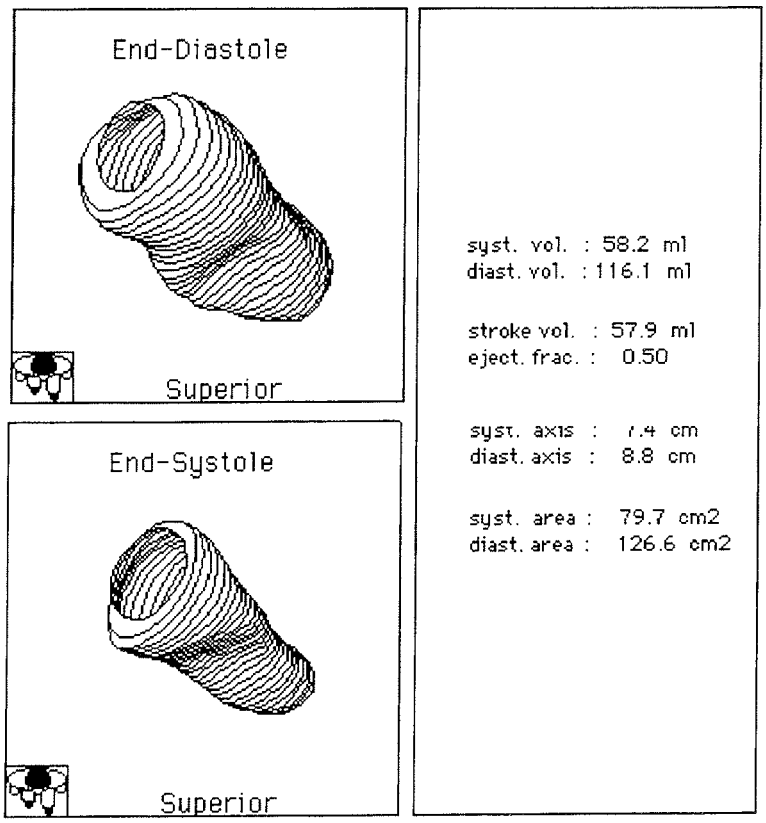

Figure 8 – Plot of the left endocardial surface in end-diastole and end-systole., generated from 3-dimensional reconstruction. The figure shows a ventricle with normal contraction, displayed from the superior view. Corresponding volumes, stroke volume, ejection fraction, endocardial long axes and surface areas are calculated by the computer algorithm.

endocardial surface to a chosen center or axis. The LV major axis, the center of the major axis, or the center of mass are used, respectively. The other methods may be regarded as extentions of the 2-dimensional centerline method to 3 dimensions and regional wall motion is calculated in millimeters as the actual displacement of the point during systole.These methods differ in the way the contours are aligned. The center of mass, the center of the mitral plane, or the center of the major axis are used, respectively. The implementation of the methods is simplified as compared to the 2-dimensional centerline method originally described[24] as our algorithm measures distances along normals to the end-systolic surface.

Knowledge of the benefits and limitations of each reference system is important in order to select an appropriate method and to avoid misinterpretations in wall

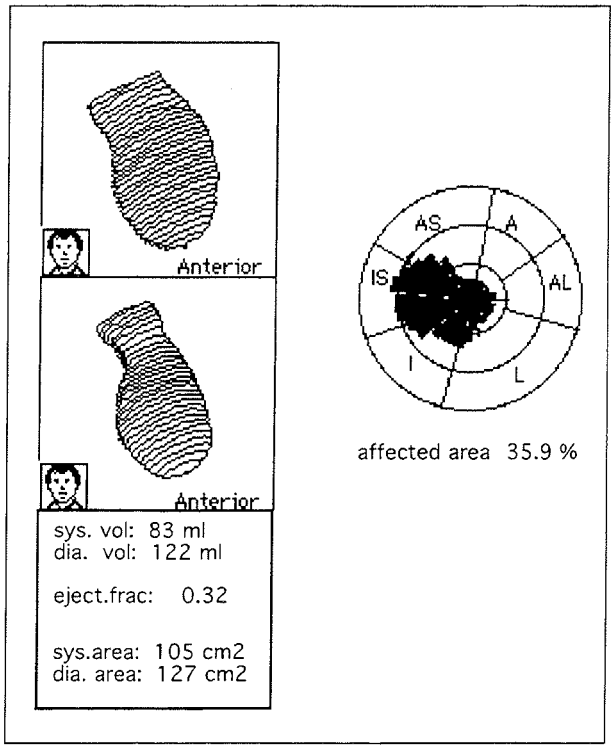

Figure 9 – Three-dimensional reconstruction of a left ventricle with regional wall motion abnormality. *Left panel*: The reconstructed end-diastolic and end-systolic LV endocardial surface shapes and dimensions are displayed from the anterior view. *Right panel*: Bull's eye plot of the regional wall motion abnormality, located in the septal and apical part of the left ventricle. The darkened area of the bull's eye plot is defined by the endocardial area with wall motion <50% of the mean endocardial motion. A = anterior; AL = antero-lateral; AS = anteroseptal; I = inferior; IS = infero-septal; L = lateral.

motion analysis. For example, the center of mass method will be misleading if used for wall motion analysis in a patient with apical dyskinesia: i.e. during systole, the ventricular center of mass will move towards the apex due to the paradoxical movement of the dyskinetic portion of the ventricle and the normal contraction of the basal segments. If the two centers of mass are superimposed and used as reference point for wall motion analysis, the distance from the center of mass to the mitral plane will be increased during end-systole. This will give the false impression of dyskinesia of the basal LV segments. We have found the LV major axis method to be the most reliable reference system for 3-dimensional reconstruction, and are currently using this method as the standard, irrespective of the location of the wall motion abnormality.

The wall motion in each endocardial point is calculated by the computer algorithm and may be displayed as a bull's eye plot. The investigator decides a threshold value to discriminate between normal and abnormal wall motion. Normal LV function exhibits a narrow range of wall motion, whereas patients with regional dysfunction will show a greater range. We have used a threshold value of 50% of the mean wall motion for detection of regional dysfunction. A lower threshold value will increase the specificity, but tends to underestimate the area of dysfunction as compared to visual analysis.

We have found that reconstruction from 3 apical image planes can localize myocardial infarctions of medium and large size. Detection of smaller infarctions, and more accurate area quantitation, may require more than 3 imaging planes. For this purpose, we have used an electrical prototype for probe rotation. This device rotates the transducer in preset steps from 2 to 180 degrees, and thus facilitates standardized rotational steps and accurate LV reconstruction.

Quantitative wall motion analysis can be applied to stress echocardiographic examinations. By tracing the endocardial contours of the 3 standard apical images in end-diastole and end-systole at rest and during stress, regional wall motion of the corresponding 3-dimensional reconstructions can be displayed as bull's eye plots.

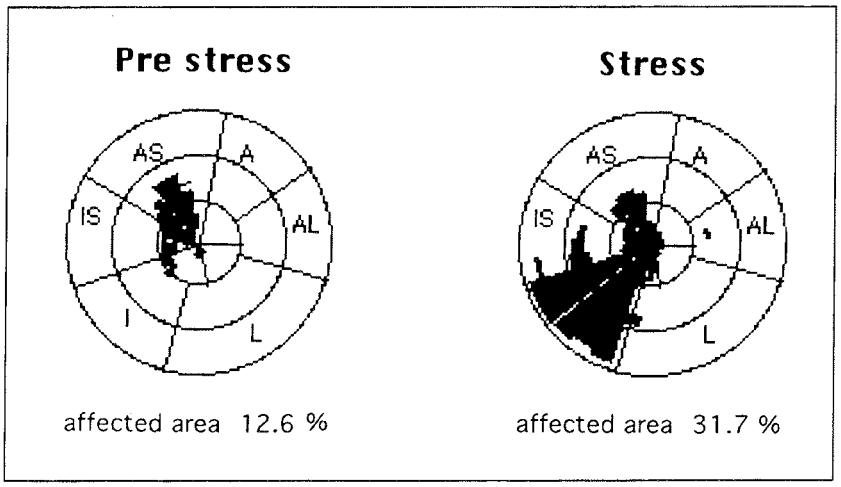

Figure 10 – Bull's eye plots for 3-dimensional quantitation of wall motion abnormalities during stress echocardiography. This example corresponds to the patient illustrated in figure 3., lower panel. *Left panel*: At rest, a wall motion abnormality in the anterior part of the septum and apex is shown. *Right panel*: During stress., the patient developes a new wall motion abnormality in the inferior region of the LV, indicating the presence of multivessel coronary artery disease.

The two plots identify the location and extent of wall motion abnormalities at rest and during stress (Fig. 10), and the change associated with stress can be displayed.

If all frames through the entire cardiac cycle are traced, more comprehensive studies of regional wall motion can be performed. The regional contribution to LV volume change can be displayed with phase analysis. We have implemented this method in our computer software with colour coding in a bull's eye plot. Accordingly, LV regions with different degrees of wall motion are displayed in different colours. An aneurysmatic region with systolic bulging will give a negative contribution to the reduction in LV volume during systole, and will thus be easily identified by this method.

Methodological limitations: Quantitative wall motion analysis has important methodological limitations. It depends heavily on image quality, and blurred or invisible endocardial borders may result in erroneous interpretations. Three-dimensional reconstruction is more difficult to perform during cardiac arhythmias. This is due to the variation of systolic duration, and to the variability in the dynamics of LV filling and ejection. Furthermore, respiratory movement of the heart should be eliminated by recording the cineloops at the same stage of the respiratory cycle.

Time for postprocessing of data for 3-dimensional reconstruction requires 15-30 minutes, depending on image quality and the amount of manual edge tracing necessary.

Conclusions

Accurate assessment of LV global and regional performance is valuable in several clinical situations, and will become even more important as the indications for cardiac interventional procedures are expanding. Computerized analysis of echocardiographic data has a great potential in this field, and relevant software for wall motion analysis and 3-dimensional reconstruction of the cardiac chambers is now available. At present, the major limitations for quantitative wall motion analysis are suboptimal image quality in some patients, and the time necessary for data recording and processing. However, during the last years, great improvements have been achieved in image quality and computer algorithms. Quantitative wall motion analysis may thus become a valuable clinical tool in the near future.

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Paper VII

ORIGINAL ARTICLE

Evaluation of Reference Systems for Quantitative Wall Motion Analysis From Three-Dimensional Endocardial Surface Reconstruction: An Echocardiographic Study in Subjects With and Without Myocardial Infarction

Knut Bjørnstad, Jørgen Mæhle, Svend Aakhus, Hans G. Torp, Liv K. Hatle, and Bjørn A.J. Angelsen

Six relevant computer-implemented reference systems for three-dimensional quantitative assessment of left ventricular wall motion abnormalities were compared with visual wall motion analysis of two-dimensional images. Endocardial borders were traced in three apical echocardiographic views at end-diastole and end-systole in 10 patients with myocardial infarction and 5 healthy subjects, and three-dimensional reconstruction of endocardial surfaces was performed. End-diastolic and end-systolic surfaces were aligned in a common axis system depending on the reference system, and systolic wall motion was assessed at 1,024 points on the endocardial surface. The localization of abnormal wall motion was displayed in bull's-eye maps, and the area was determined as a percentage of total endocardial area. For each reference system, the segmental concordance between three-dimensional computerized and visual assessment was determined. The best agreement between computerized and visual analysis was obtained with a reference system based on wall motion towards the major ventricular axis, whereas the poorest result was obtained using the center of left ventricular cavity as reference. Correlation between the estimated area of wall motion abnormality and visually determined wall motion score index was best using the aligned center of mitral valve plane as reference (r = .92).

TWO-DIMENSIONAL echocardiography is commonly used for evaluation of left ventricular systolic function in patients with coronary artery disease. Chamber dimensions, volumes, ejection fraction, and the presence and location of regional wall motion abnormalities can be assessed.[1-3] The extent of myocardial damage has been shown to be a major prognostic determinator after myocardial infarction.[4,5] Clinical evidence of left ventricular failure may present when 20% to 25% of the myocardium is injured, and cardiogenic shock may result if more than 40% is affected.[6,7] Unfortunately, conventional echocardiographic methods for quantitative left ventricular wall motion analysis are not sufficiently accurate for serial assessment of regional function. Single plane methods have been described for comparison of end-diastolic and end-systolic endocardial borders,[8-12] but have not been adapted for clinical use. Wall motion score index,[13] although based on subjective interpretation, is at present the most commonly used method for describing the severity of left ventricular dysfunction.

Advances in computer processing of image data have facilitated the search for more accurate quantitative wall motion analysis. In former studies, visual analysis combined with computer processing have been used to obtain estimates of the extent of myocardial infarction.[14-17] In the present study, quantitative wall motion analysis was performed with three-dimensional (3-D) reconstruction of endocardial surfaces from apical two-dimensional (2-D) views.[18] The reconstruction algorithm has been presented previously and shown to reproduce volumes in vitro with high accuracy.[19] In this study, the algorithm was used to describe regional wall motion in subjects with and without myocardial infarction.

METHODS

Patient Selection

Fifteen subjects were studied, 10 with recent myocardial infarction (less than 2 weeks, group A), and five healthy subjects without evidence of coronary artery disease (group B). In group A, myocardial infarction was documented by at least two of the following criteria: (1) typical chest pain lasting at least 30 minutes; (2) typical serial electrocardiographic changes; and (3) rise in serum cardiac enzymes to more than twice the normal values. Patients with unacceptable echocardiographic image quality, previous myocardial

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infarction, unstable angina pectoris, or atrial fibrillation were not included. Group A patients had 12-lead electrocardiography and cardiac enzymes taken at admission for the acute infarction and thereafter at 12 hour intervals for 48 hours. Individual data for group A and B subjects are presented in Table 1. All gave informed consent to participate in the study.

Echocardiographic Data Acquisition

The subjects were examined in the left lateral decubitus position, using an ultrasound scanner (Vingmed CFM 750, Vingmed Sound A/S, Horten, Norway) with a 3.25 MHz annular array transducer. All images were obtained at held end-expiration. Care was taken to position the transducer over the cardiac apex, as defined by minimal displacement of apex during systole and by alignment with the left ventricular major axis and the midpoint of the mitral valve plane. Input data to the computer consisted of cineloops of standard apical four-chamber, two-chamber, and long-axis left ventricular views, obtained by apical rotation of the transducer with adjustment to maintain the imaging plane in the ventricular major axis. Images were transferred to a personal computer (Macintosh II series, Apple Computer, Cupertino, CA), and subsequent analysis was performed using specifically designed software operating under a general program for handling of digital ultrasound data (EchoDisp 3.0, Vingmed Sound A/S, Horten, Norway). Cineloops were transferred as digital scanline data with a frame rate of 47 frames per second using a sector angle of 60° and depth of 16 cm. An electrocardiographic tracing was transferred simultaneously with the cineloop.

Endocardial Surface Reconstruction

End-diastole was defined as the frame corresponding to the peak of the R-wave of the electrocardiogram, and end-systole as the last frame before mitral valve opening. On these two frames, left ventricular endocardial border was traced in each of the apical views, using an automatic edge detection program (EdgeFinder, Vingmed Sound)[20] with manual correction of the detected edge as necessary. The endocardium was traced at the echogenic transition zone between left ventricular cavity and myocardial wall, excluding the papillary muscles, and including the left ventricular outflow tract up to the aortic valve level in apical long-axis view (Fig 1). The mitral valve plane was defined as the straight line between the mitral annulus echo boundaries, ie, at the ventricular aspect of the insertion of the mitral valve leaflets. The endocardial traces were assigned an angle corresponding to the respective rotation of the transducer around its center axis, starting at zero degrees for the apical four-chamber view. Apical two-chamber and apical long-axis views were assumed to be at 62° and 101° counter-clockwise rotation, respectively.[21] The endocardium was automatically reconstructed as a smooth bicubic spline surface (Fig 1). The reconstruction algorithm has previously been described in detail.[18]

Table 1. Baseline Patient Characteristics

Patient No.	Age (yrs)	Sex	AMI	AMI Region (ECG)	ASAT (mmol/L)	CK (μmol/L)	WMSI
1	66	M	+	Anterior	278	1786	1,81
2	68	M	+	Inferior	685	3607	1,75
3	73	M	+	Anterior	545	2201	1,81
4	70	M	+	Anterior	707	4884	2,00
5	65	M	+	Lateral	323	2350	1,25
6	68	M	+	Anterior	366	2079	1,56
7	58	M	+	Anterior	215	1558	1,06
8	53	M	+	Anterior	357	2142	1,50
9	66	M	+	Anterior	143	602	2,06
10	71	M	+	Anterior	485	1524	1,56
11	36	M	–	Normal	—	—	1,00
12	62	M	–	Normal	—	—	1,00
13	35	F	–	Normal	—	—	1,00
14	29	M	–	Normal	—	—	1,00
15	26	M	–	Normal	—	—	1,00

ABBREVIATIONS: AMI, acute myocardial infarction; ECG, electrocardiography; WMSI, wall motion score index.

Quantitative Wall Motion Analysis

The reconstructed end-diastolic and end-systolic endocardial surfaces were represented by 1,024 numbered points. To determine regional wall motion, end-diastolic, and end-systolic surfaces were aligned in common coordinate systems, and wall motion was calculated at each point. Six different reference systems (a to f) were evaluated for quantitative wall motion analysis. In reference systems a, b, and c, systolic wall motion is determined as fractional change in distance to a selected point or axis (Fig 2). This reference point, or axis was: (a) center of ventricular cavity; (b) major ventricular axis, along lines perpendicular to the axis; and (c) center of major axis. With reference systems d, e, and f, regional wall motion was determined as the shortest distance from the end-diastolic to the end-systolic surface in millimeters (Fig 2). The surfaces were aligned by a common direction of the major axis and by a common position of the: (d) center of ventricular cavity; (e) midpoint of the mitral valve plane; and (f) center of major axis.

Regional wall motion was displayed in bull's-eye maps for visualization of the extension and location of wall motion abnormalities as determined by each reference method. A pattern code was applied to illustrate variation in regional wall motion (Fig 3). Mean wall motion was calculated for each subject and each reference system (see Appendix), and a threshold value of 50% of mean wall motion was used to distinguish between normal and abnormal motion. The endocardial area representing a wall motion abnormality was determined as a percentage of total end-diastolic endocardial surface area, and the location was graphically displayed within the bull's-eye maps.

Visual Wall Motion Scoring

The three apical left ventricular cineloops used for endocardial tracing were also analysed visually on the computer monitor, using a specific software for wall motion display and analysis (EchoLoops version 3.0, Vingmed Sound). A 16-segment model of the left ventricle was used.[13] Each segment was assigned a score based on wall motion and myocardial thickening: normal = 1, hypo-

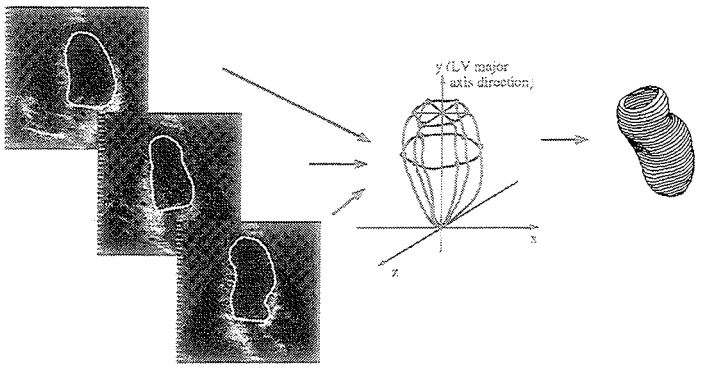

Fig 1. Three-dimensional reconstruction of endocardial surface from three apical views of the left ventricle. The endocardium is reconstructed as a smooth bicubic spline surface, the apical borders are described by cubic spline curves, and cross sections are reconstructed by a closed cubic spline curve interpolating the apical borders.

kinetic = 2, akinetic = 3, dyskinetic = 4, or aneurysmal = 5. Wall motion score index (WMSI) was calculated as the sum of the segmental scores, divided by number of observed segments, and expressed a semiquantitative index of the severity of wall motion abnormality. The location and extent of abnormal wall motion was displayed within the bull's-eye maps (Fig 4).

Analysis

The individual results of the 3-D computerized wall motion analysis for each of the six reference systems were compared with visually determined wall motion on a segmental basis. Using bull's-eye maps from the computerized analysis, each of the 16 segments was classified as normal or abnormal. Segments partially or completely affected by wall motion abnormality were defined as abnormal. By visual assessment of 2-D images, segments scored as hypokinetic or worse were defined as abnormal. The number of the segments classified equally by computerized analysis and visual analysis as normal or abnormal was expressed as a percentage of the total 16 segments. As an example: in an individual patient, a particular reference system and visual wall motion scoring showed equal results in 12 of the 16 segments (normal or abnormal wall motion). The concordance is calculated as 12 divided by 16 equaling 75%. When all 15 subjects are analyzed, mean ± standard deviation of the concordance for that reference system can be calculated. The range states the minimal and maximal concordance among the 15 subjects. The percentage of the endocardial surface area representing abnormal wall motion by each reference system was compared to wall motion score index using correlation coefficient (r-value).

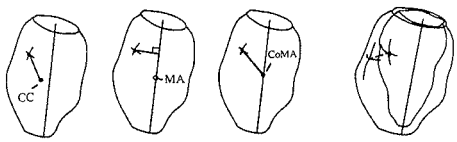

Fig 2. Reference systems for wall motion calculations from end-diastolic and end-systolic endocardial surfaces. From left to right, reference systems a, b, c, and e are illustrated. CC, center of left ventricular cavity; CoMA, center of major axis; MA, major axis.

RESULTS

The agreement between computerized wall motion analysis by each of the reference systems and visual analysis is shown in Table 2, comprising segmental agreement as well as the correlation between percentage area of abnormal wall motion and wall motion score index. Individual patient bull's-eye maps as determined by computerized wall motion analysis for the different reference systems, and visual wall motion scoring are shown in Fig 5.

All reference systems differentiated well between healthy subjects and patients with myocardial infarctions. Minor differences were found between the reference systems based on major ventricular axis (system b), center of major axis (system c), fixed center of mitral valve plane (system e), and fixed center of major axis (system f), with segmental agreement varying

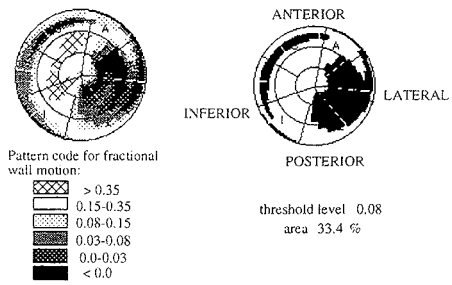

Fig 3. Example of computerized wall motion analysis (patient no. 5, analyzed with reference system b).

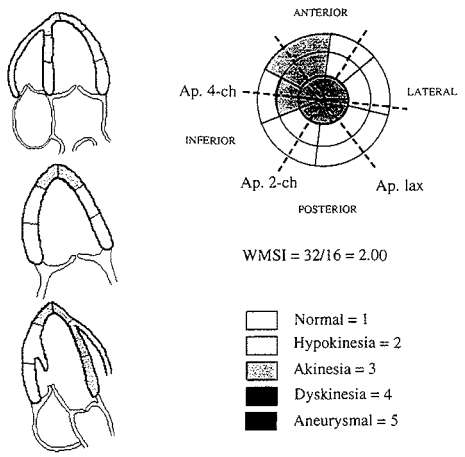

Fig 4. Example of visual wall motion analysis with wall motion score index calculation. See text for explanation.

from 77 ± 17% to 78 ± 13%. Poorest results were obtained with reference system a, based on the center of ventricular cavity as reference. Using reference system c, which showed the optimal specificity, none of the healthy subjects were found to have abnormal wall motion involving more than 5% of the endocardial surface (Figs 5 and 6).

Regression plots for percentage area calculations and wall motion score index for each reference method are shown in Fig 6. The % endocardial area of abnormal wall motion correlated best with wall motion score index when reference systems c, e, or f were applied, with *r*-values in the range of .87 to .92.

Table 2. Comparision Between Computerized and Visual Wall Motion Analysis

Reference System	Segmental Agreement (%) Mean ± SD	Range	Correlation Percentage Area/WMSI *r* Value
a Center of left ventricular cavity	58 ± 20	31-88	.77
b Major left ventricular axis	78 ± 13	56-94	.79
c Center of major left ventricular axis	76 ± 15	50-100	.87
d Aligned center of cavity	69 ± 18	38-94	.82
e Aligned center of mitral valve plane	77 ± 13	56-94	.92
f Aligned center of major axis	77 ± 17	31-100	.87

NOTE: Confer text (Method section) for explanation of calculated segmental agreement and correlation of %area and wall motion score index (WMSI).

DISCUSSION

Single plane methods are traditionally classified as using a fixed or a floating reference. With a fixed reference system, no correction for translatory and rotational cardiac motion is applied, whereas a floating reference system is based on realignment of the edges by geometrically defined landmarks. The present study investigated six different floating reference systems for quantitative left ventricular wall motion analysis. Wall motion analysis based on 3-D geometry can be considered as extensions of conventional 2-D single plane methods, but has the important advantage that regions with abnormal wall motion as well as the total endocardial surface area can be quantitated (see Appendix).

Regional Wall Motion Analysis

Reference systems a, b, and c assume that the ventricular contraction approximates a single center or axis, whereas reference systems d, e, and f measure the actual distance between the two surfaces. Each system has specific advantages and shortcomings, as illustrated by the results of this study:

Reference system a. This system is based on a common center of left ventricular cavity for wall motion analysis. In general, the center of cavity will be shifted toward an akinetic or dyskinetic region during systole and thus tends to average regional wall motion. Accordingly, both reduced wall motion and hyperkinesia may be masked. In the present study, the majority of patients had anterior or apical infarctions, however, the wall motion abnormality tended to be displayed in the basal left ventricular regions (Fig 5). This reference system showed the poorest overall results of those evaluated.

Reference system b. The best results in our study were obtained with this reference system, based on calculation of wall motion along lines perpendicular to the major left ventricular axis. This is the only reference system analyzing basal and apical contraction separately, and the dominant wall motion abnormality was correctly identified in all patients. However, axial shortening is not taken into account with this reference system, and this may explain the suboptimal

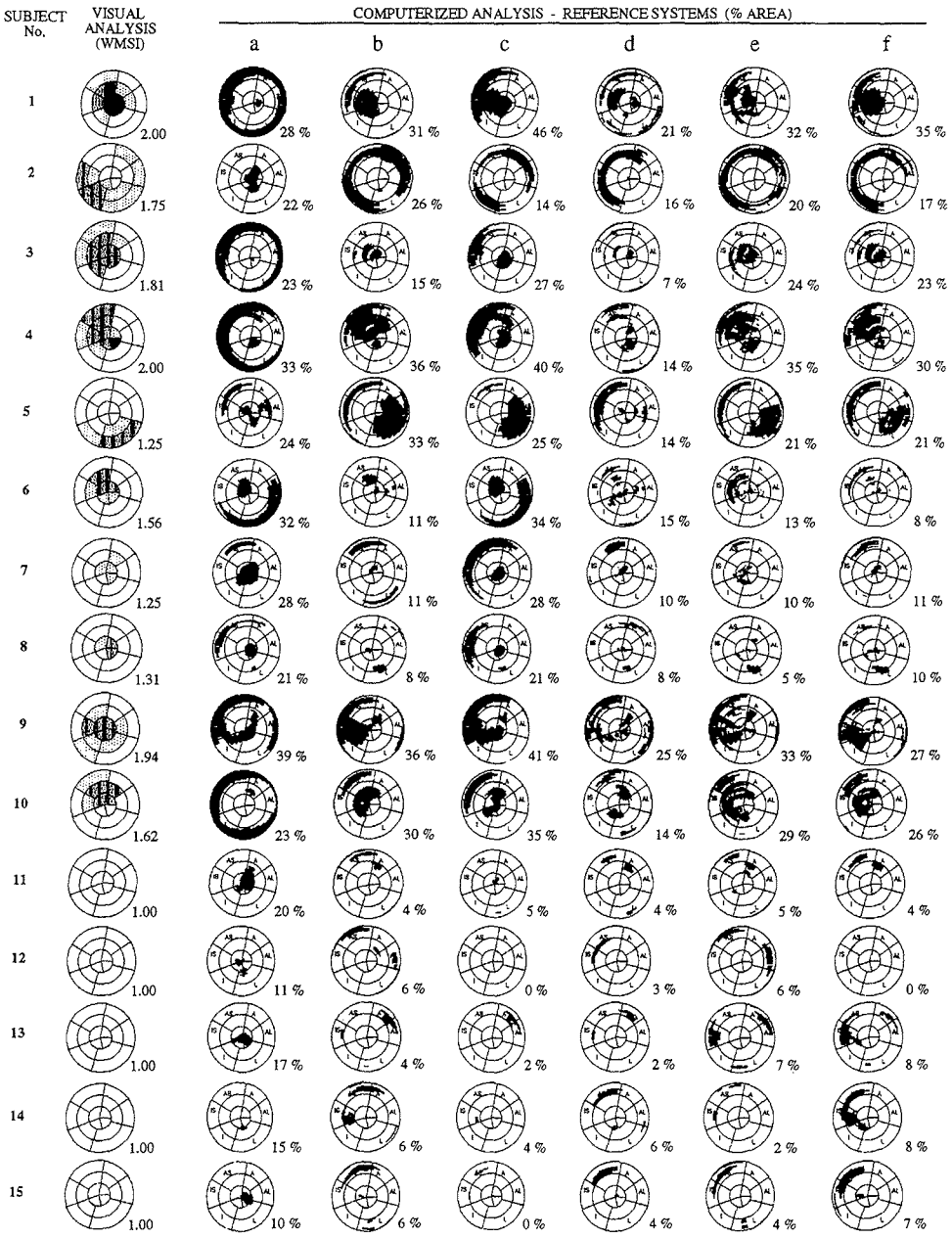

Fig 5. Bull's-eye maps from individual patients, with visual wall motion analysis (left column) and computerized wall motion analysis with different reference systems.

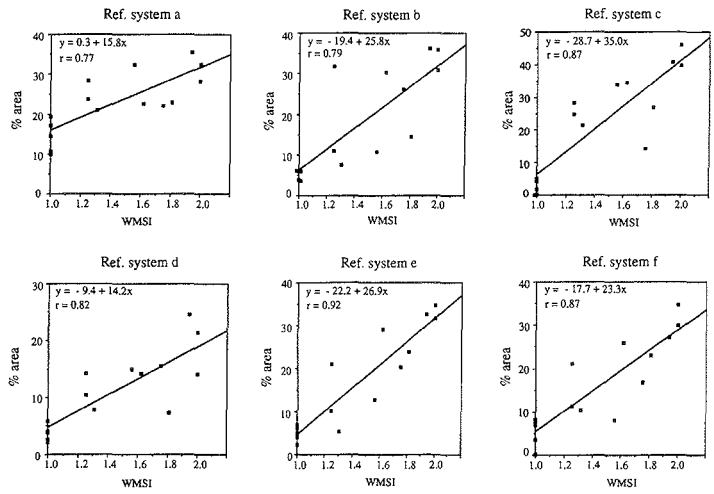

Fig 6. Regression plots for percentage area calculations and wall motion score index for the six different reference systems.

correlation between the percentage area calculation and wall motion score index.

Reference system c. This system is based on the center of major ventricular axis as reference. As illustrated by Figs 5 and 6, this reference system showed the best ability to differentiate between healthy subjects and patients with myocardial infarction. However, axial contraction may be distributed both to the basal and the apical regions. Accordingly, a severe apical wall motion abnormality will be underestimated and partly projected to the basal portion of the left ventricle. As illustrated by the bull's-eye maps in Fig 5, analysis with this reference system tended to display wall motion abnormalities in both the apical and basal left ventricular regions in patients with apical infarctions.

Reference system d. This reference system is based on the same method of endocardial surface alignment as reference system a, and differs only in the method of wall motion calculation. Reference system d has the same shortcomings as system a, and, accordingly, did not have a favorable outcome in our study patients.

Reference system e. This system aligns the reconstructed left ventricular surfaces by a common center of the mitral valve planes. Like reference system c, this system will be inaccurate in localizing abnormal contraction along the ventricular long axis, and apical hypokinesia may be masked in patients with axial shortening (eg, subject nos. 7 and 8, Fig 5). However, more severe apical wall motion abnormalities will be identified, and the results obtained with this system were almost as good as with reference b. This reference system had the best correlation between percentage area and wall motion score index.

Reference system f. Although the method of alignment was similar to reference system c, this system did not differentiate quite as well between patients with myocardial infarction and healthy subjects. In addition, reference system c is recommended because of better ability to localize the wall motion abnormality correctly.

Echocardiographic Surface Reconstruction

The results of wall motion analysis depend not only on the reference system, but also on the accuracy of the reconstructed endocardial surface. Important factors are correct endocardial visualization and tracing, correct spatial orientation of the edges from 2-D images in the 3-D coordinate system, as well as the validity of the assumptions and simplifications of the reconstruction algorithm. Correct endocardial tracing of the apical 2-D views depends on adequate visualization of the endocardial border in the end-diastolic and end-systolic frames. According to the recommendations of the American Society of Echocardiography,[13] endocardial trac-

ing is not recommended if less than 80% of the endocardial border is visualized. The high frame rate of the scanconverted cineloops (47 frames/sec) allows slow motion display for accurate edge detection. Advances in automatic edge detection may improve the reconstruction procedure by increasing the accuracy and reducing the time needed for edge tracing, as this is the most time-consuming part of the present technique.

The surface reconstruction is based on assumed angles between the different apical views. For volume estimates, deviations within 15 degrees from these angles have only minor impact on the results.[19] However, correct spatial orientation is likely to be more important for regional wall motion analysis. This problem can be solved by using a device for exact, predetermined steps of rotation, or by measuring the actual angle of imaging plane rotation.

The assumptions and simplifications of left ventricular geometry refer to the smoothing of the left ventricular outflow tract, which becomes a part of the reconstructed endocardial surface. Also, the mitral valve annulus is assumed to be planar, in contrast to the findings in echocardiographic studies.[22] These factors may cause errors in regional wall motion in the basal portion of the ventricle, whereas volumes and endocardial surface area calculations are less affected.

Methodological Considerations and Limitations

Three-dimensional reconstruction based on apical echocardiographic images with transducer rotation around the major ventricular axis has previously been used to assess left ventricular geometry.[23-25] A major advantage with the apical approach as compared with other 3-D techniques is the simplicity of obtaining images. In this study, no special instrumentation for measuring or controlling the position of the imaging planes was applied. The algorithm used for 3-D reconstruction provides accurate assessment of volumes in vitro, and interobserver and intraobserver repeatability for analysis of ventricular volumes in the clinical setting are good with coefficients of variation ranging from 3.5% to 6.2%.[19] The time needed to trace three cineloops at end-systole and end-diastole is 5 to 10 minutes, and the processing and display of quantitative wall motion data can be performed within a few seconds.

As shown by Fig 5, patients with myocardial infarctions commonly had several regions with abnormal wall motion, and the percentage area calculation summarized all areas. A threshold value served to make a crude distinction between normal and abnormal wall motion. Although pattern bull's-eye maps serve best for illustration of regional wall motion (Fig 3), a threshold value is necessary to quantitate the area extension of dysfunction. However, the threshold value does not take into account the variation in normal wall motion for different regions of the left ventricle with the exception of adjustments in the basal left ventricular region (see Appendix).

In the bull's-eye maps, the ratio between surface areas in different endocardial regions are distorted, eg, an area in the basal region appears larger than the same area in the apical region. Impaired basal wall motion will thus be visually overrepresented by the bull's-eye mapping technique.

Although three apical imaging views have been shown to give accurate volume determinations with the presently used algorithm,[19] a higher number of views may be required to detect more subtle wall motion abnormalities.

Future Directions

The shortcomings of the individual reference systems may be reduced by combining different reference systems. Although it was not investigated with the present study design, the software has been designed to allow this option. From theoretical considerations as well as from the data presented, combining reference system b and c and/or e may prove to be more accurate for assessment of wall motion abnormalities. To detect more subtle wall motion abnormalities, the number of imaging planes can be increased, and the angle between imaging planes can be standardized by using a device for transducer rotation. Furthermore, more powerful computers and improvements in the automatic edge detection algorithm will reduce the time needed for image processing and analysis.

APPENDIX

Mathematical Description of Reconstructed Endocardial Surfaces

With the present computer algorithm, the endocardium will be reconstructed as a smooth bicubic spline surface. Calculation of left ventricular wall motion is based on geometric data representing the endocardial surface at a selected number of points on this reconstructed smooth surface. The data used comprised a matrix of points $\{r_{i,j}\}$ on the reconstructed surface, and the points r_{apex} and r_{mm} positioned at the apex and at the mitral plane midpoint, respectively (Fig 7, upper panel). The ventricular major axis is defined as the straight line connecting r_{apex} and r_{mm}. Each point is given in Cartesian coordinates $r_{i,j} = (x_{i,j}, y_{i,j}, z_{i,j})$ positioned in space with the center of ventricular cavity fixed at the origin, and with left ventricular major axis along the y-axis. The range of indexes, i and j, was selected to be 32 both in axial and circumferential direction, with a total of 1,024 points representing the endocardial surface.

Calculation of Surface Areas

The reconstructed endocardial surface is divided into small areas $a_{i,j}$ surrounding each point $r_{i,j}$ of the surface. Each area $a_{i,j}$ includes the four parallellograms defined by the lines starting at the point $r_{i,j}$ and extending half the distance to the adjacent points. The results are stored in a matrix $\{a_{i,j}\}$ for further calculations. The endocardial surface area (ESA, cm^2) was calculated as the sum of the matrix elements by

$$ESA = \sum_{i,j} a_{i,j}$$

This estimate converges to the surface area of the smooth reconstructed endocardial surface as the resolution increases.

Three-Dimensional Wall Motion Analysis

Regional wall motion is calculated at each point of the geometric description of the endocardial surface and stored in a matrix $\{c_{i,j}\}$ (Fig 7, middle panel). The value of one $c_{i,j}$ expresses fractional shortening to a reference (reference

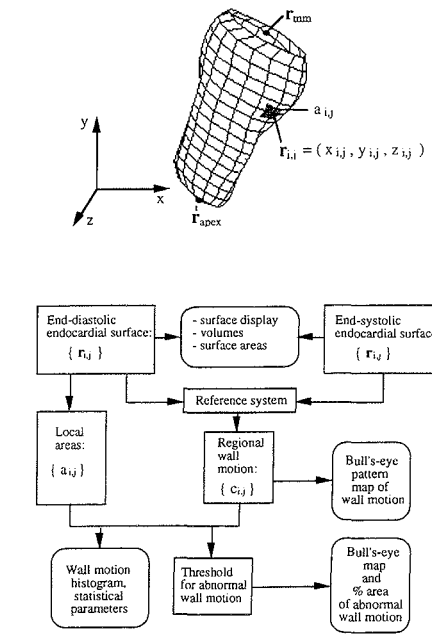

Fig 7. ***Upper panel:*** **Wire-frame display of the surface (low resolution for illustration) showing the mathematical description of the endocardial surface used for regional wall motion analysis; coordinates of the apex and the mitral midpoint, r_{apex} and r_{mm}, and the points $\{r_{i,j}\}$ at the mesh corners; $a_{i,j}$ refers to the portion of the subdivided endocardial surface area associated with point $r_{i,j}$. This area is composed of four parallelograms defined by half of the distance along the straight lines connecting the point to its adjacent points. Middle panel: Flow-chart illustrating the analysis of left ventricular function based on a mathematical description of the endocardial surface at end-diastole and end-systole. Lower panel: Wall motion histograms obtained by analysis using reference system b) (center of major axis). The histogram displays the portion of the endocardial surface (in % of the end-diastole endocardial surface area) as vertical bars at different levels of wall motion (relative systolic shortening) at the horizontal axis, the calculated mean value of wall motion is indicated with arrow. Left: Control subject no. 14, Table 1. Right: Patient with previous myocardial infarction, subject no. 1, Table 1.**

system a-c) or absolute displacement (reference system d-f) of the wall at position i,j from end-diastole to end-systole. The contents of the wall motion matrix $\{c_{i,j}\}$ is displayed in two dimensions in a bull's-eye map (Fig 3).

The calculated values of regional wall motion and end-diastolic endocardial area, $\{c_{i,j}\}$ and $\{a_{i,j}\}$, are combined for further calculations. A histogram displays the percent of the ventricle, in terms of end-diastolic endocardial surface area, at different levels of wall motion along the horizontal axis (Fig 7, lower panel). The calculated mean value and its variance of wall motion are expressed by

$$\hat{c} = \frac{1}{ESA}\sum_{i,j} c_{i,j}a_{i,j} \quad \Big| \quad \sigma^2 = \frac{1}{ESA}\sum_{i,j}(c_{i,j} - \hat{c})^2 a_{i,j}$$

The size of areas with abnormal wall motion (AMW) is estimated from the constant threshold level, t (50% of mean wall motion), by

$$AWM = \sum_{c_{i,j} < w_i t} a_{i,j} \quad (w_1 \ldots w_{28} = 1, w_{29} = 0.8, w_{30} = 0.5, w_{31} = 0.2, w_{32} = 0)$$

The estimated area with reduced wall motion is expressed as a percentage of the end-diastolic endocardial surface area, and its location is displayed in the bull's-eye map. The weight factors w_i are introduced to avoid relative low wall motion in the basal region to be detected as abnormal (numbers refer to the axial resolution of 32). The choice of a threshold level equal to 50% of the mean wall motion was motivated from the shape of histograms; healthy controls have narrow (low variance) histograms centered around a high mean value, whereas regional systolic dysfunction was reflected in a shift in the histogram towards zero combined with a higher variance.

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