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Infra-low dose dipyridamole test

A novel dose regimen for selective assessment of myocardial viability by vasodilator stress echocardiography

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Low (0·56 mg . kg^{-1} over 4 min) and high (0·84 mg . kg^{-1} over 10 min) doses of dipyridamole can identify viable myocardium through the contractile recovery of basally dyssynergic regions; however, it also induces ischaemia in susceptible patients. The aim of this study was to assess the potential of an 'infra-low' dose of dipyridamole to selectively identify myocardial viability, independently evaluated by low dose dobutamine. Forty patients with resting dyssynergy and angiographically assessed coronary artery disease (1-vessel in 18, 2-vessel in 12, and 3-vessel in 10 patients) separately underwent a low dose dobutamine (5–10 μg . kg^{-1} . min^{-1} for 3 min) echo test and an infra-low dose (0·28 mg . kg^{-1} over 4 min) dipyridamole echo test. Systolic blood pressure (rest: 131 ± 19 mmHg) changed slightly after dobutamine (137 ± 21, $P<0·05$ vs rest) and remained stable after dipyridamole (130 ± 17, P=ns vs rest). Heart rate (rest: 68 ± 13 beats . min^{-1}) was also unchanged after dipyridamole (69 ± 12, P=ns vs rest) and increased slightly after dobutamine (71 ± 15, $P<0·05$ vs rest and vs dipyridamole). No patient developed echocardiographic or electrocardiographic signs of ischaemia after either dipyridamole or dobutamine. Of the 243 segments with baseline dyssynergy, 70 were responders (i.e. they showed an improvement of 1 grade or more, from 1=normal/hyperkinetic to 4=dyskinetic in a 16-segment model of the left ventricle) by both dipyridamole and dobutamine, 157 were non-responders (i.e. they showed no change) by both dipyridamole and dobutamine, and 16 showed discordant results (five responders by dipyridamole only; 11 by dobutamine only). The overall concordance of dipyridamole and dobutamine was 93%. An echocardiographic follow-up could be obtained >6 weeks after successful revascularization (achieved with angioplasty in 17, with by pass surgery in 3) in 19 patients and showed an improvement of one grade or more in 50 segments (viable) and no improvement in 50 segments (necrotic). The sensitivity of dobutamine and dipyridamole for predicting recovery was 76 and 78% respectively (P=ns); the specificity of both tests was 94%.

In conclusion, infra-low dose dipyridamole is a haemodynamically neutral stress test which does not affect either heart rate or systolic blood pressure; it allows myocardial viability to be explored selectively, without eliciting ischaemia; it shows excellent overall concordance with low dose dobutamine and has good sensitivity and excellent specificity for predicting functional recovery following successful revascularization.

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Key Words: Dipyridamole, dobutamine, viability.

Introduction

In a large subset of patients with chronic coronary artery disease and left ventricular dysfunction, left ventricular performance is reduced because the myocardium is regionally stunned or hibernating rather than irreversibly infarcted or fibrotic. The detection of reversible dysfunctional myocardium is clinically relevant, as regional or global left ventricular function will improve after revascularization[1,2]. To date, nuclear medicine, with positron emission tomography or thallium imaging, remains the accepted definitive method for clinical assessment of myocardial viability[3]. However, nuclear medicine is not always easily accessible and is expensive. Several alternative methods have been recently proposed for the clinical assessment of myocardial viability, such as pharmacological stress echocardiography, with either

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dobutamine[4–9] or dipyridamole[10,11]. With pharmacological stress, the principle (i.e. the underlying physiological marker) of the test relies on the demonstration of residual contractile reserve in a basally dysfunctional region: improved myocardial thickening of segments that are dyssynergic in resting conditions is a sign of viability, whereas necrotic segments show no functional improvement. Such reserve can be elicited either by direct stimulation of β1 adrenoreceptors with low doses of dobutamine or through a flow-mediated increase in contractile function linked to endogenous adenosine accumulation achieved by intravenous infusion of dipyridamole[12]. An advantage of dobutamine over dipyridamole for viability assessment is the possibility of offsetting the inotropic dose for viability (up to 10 μg) from the higher ischaemic dose (up to 40 μg)[12]. The usefulness of dipyridamole stress as a stimulus for viability would increase if a dose regimen could be identified, capable of selectively exploring viability without eliciting ischaemia — similar to the way in which dobutamine works. Experimental data suggest that even very low doses of dipyridamole can improve function in stunned myocardium[13]. The aims of this study were: (1) to compare the accuracy of infra-low (0·28 mg . kg^{-1} over 4 min) dose dipyridamole, in identifying myocardial viability, with that of low (up to 10 μg) dose dobutamine — the most widely used of the pharmacological stress echocardiographic stimuli for viability recognition; and (2) to assess the systemic, haemodynamic and left ventricular function correlates of an infra-low dose of dipyridamole, substantially lower than the high dose regimen (0·84 mg . kg^{-1} over 10–min) usually employed for echocardiographic imaging, and also lower than the regular or low dose regimen (0·56 mg . kg^{-1} over 4 min) usually employed for perfusion imaging[14]. Therefore both tests were performed in 40 patients with coronary artery disease; of these 40 patients, 22 underwent a revascularization procedure, and echocardiographic follow-up after successful revascularization could be obtained in 19 patients.

Methods

Study population

Forty patients (33 men and seven women, age range 35 to 74 years, mean ± SD = 58 ± 10) with history of myocardial infarction, angiographically proven coronary artery disease, technically satisfactory acoustic windows and resting wall motion dyssynergy of the left ventricle were enrolled in the study. Thirty-eight patients had evidence of previous (>3 month) myocardial infarction, whereas two were examined early (within 3 weeks) after an acute myocardial infarction; 32 patients had a Q wave, and eight a non-Q wave infarction on the resting electrocardiogram. The site of myocardial infarction was anterior in 19 and inferior in 21 cases. Medical therapy was discontinued at least 48 h before the stress–echocardiographic examination in 26 subjects, while 14 patients received antianginal therapy: nitrates in two cases and combined therapy in 12 cases (nitrates and calcium antagonists in seven, calcium antagonists and beta blockers in five). Coronary angiography demonstrated significant stenosis (≥ 50% diameter reduction by quantitative coronary angiography) of one vessel in 18, two vessels in 12 and three vessels in 10 patients. The average left ventricular ejection fraction calculated from the apical 4-chamber view by 2-D echocardiography (single plane area-length method) was 41 ± 14%. Follow-up echocardiograms were obtained in baseline conditions in 19 patients at least 6 (9 ± 1) weeks after successful coronary revascularization.

Baseline echocardiographic examination

Two-dimensional echocardiograms were obtained using commercially available imaging systems (Hewlett-Packard 77020, 77025 or Diasonics, 2·5 and 3·5 MHz transducers). Echocardiographic images were recorded on VHS videotape for subsequent playback and analysis. Regional wall motion was assessed according to the recommendations of the American Society of Echocardiography with a 16-segment model[15]. In all studies, segmental wall motion was semiquantitatively graded as follows: Normal=1; hypokinetic, marked reduction in endocardial motion and thickening=2; akinetic, virtual absence of inward motion and thickening=3; and dyskinetic, paradoxic wall motion away from the centre of the left ventricle in systole=4. Baseline echocardiography was obtained before coronary angioplasty or coronary artery bypass surgery. Inadequately visualized segments were not scored.

Pharmacological stress echocardiography

All patients underwent, on separate sessions, and before coronary revascularization, low dose dobutamine infusion (5 μg . kg^{-1} . min^{-1} followed by 10 μg . kg^{-1} . min^{-1}, each step lasting 3 min) and an infra-low dose dipyridamole (0·28 mg . kg^{-1} over 4 min) echocardiography. Two-dimensional echocardiograms were continuously obtained and intermittently recorded during drug administration. In the baseline studies as well as during stress, all standard echocardiographic views were obtained when possible. During the procedure, the blood pressure and the electrocardiogram were recorded each minute. The videotapes were analysed by two independent cardiologist–echocardiographers, who were blind to the clinical and angiographic data. Digital acquisition of images of interest were obtained with a side-by-side display of rest and peak stress images in a cine-loop mode. A wall motion score index was derived for rest and peak stress (0 to 1 min after the end of each infusion) echocardiograms in all patients, as previously described for the baseline echocardiographic examination. A segment was considered to show signs of viability when it improved

by 1 grade or more at peak stress (for instance, a hypokinetic segment becoming normal, or an akinetic segment becoming hypokinetic). The level of inter-observer and intra-observer reproducibility of stress echo readings was >90% between the two echo laboratories participating in the study, as previously reported[16].

Echocardiographic follow-up

Coronary revascularization was performed in 22 patients: either by coronary artery bypass surgery (n=4) or by percutaneous transluminal coronary angioplasty (n=18). One patient died immediately after the procedure of acute heart failure, one patient had acute heart failure and ventricular fibrillation after the surgical intervention and needed a reoperation and in one patient early restenosis (within one month) occurred. In 19 patients a baseline follow-up echocardiogram was obtained at least 6 (9 ± 1) weeks after revascularization. None of these patients showed clinical, enzymatic, electrocardiographic or echocardiographic evidence of perioperative myocardial infarction, and all were thought to have had successful revascularization. Postoperative resting wall motion scores were determined as previously described by an experienced echocardiographer who was blind to stress echo results. Digital acquisition of images was obtained with a side-by-side display of baseline (pre-revascularization) and follow-up (post-revascularization) echocardiograms. Improved segmental wall motion at follow-up was defined as either endocardial excursion and wall thickening (score 1 or 2) in areas of akinesis or dyskinesis (score 3 or 4) at baseline, or normalization (score 1) of reduced endocardial excursion and wall thickening (score 2) at baseline.

Statistical analysis

Values are expressed as mean ± standard deviation. Differences in haemodynamic values before and after the infusions and in the wall motion score index under different conditions were tested for significance by analysis of variance and subgroup analysis by the Scheffé F test. Calculations of sensitivity, specificity and accuracy were performed according to standard definitions[17]. A P value <0·05 was considered statistically significant.

Results

Baseline echo findings

By inclusion criteria, all patients had regional dyssynergy in the resting echocardiogram. There were 243 segments with baseline dyssynergy: dyskinesis in 10, akinesis in 137, and marked hypokinesis in 96 segments.

Clinical and haemodynamic findings during pharmacological stress

None of the 40 patients had significant side effects or developed echocardiographic or electrocardiographic signs of ischaemia after either dipyridamole or dobutamine. In comparison with baseline, systolic blood pressure (rest=131 ± 19 mmHg) increased slightly after dobutamine (137 ± 21 mmHg, P<0·05 vs rest), whereas it did not change significantly after dipyridamole (130 ± 17 mmHg; P=ns vs rest; P<0·05 vs dobutamine). Heart rate (rest=68 ± 13 beats . min^{-1}) was also unchanged after dipyridamole (69 ± 12; P=nsvs rest), while a very mild increase was observed after dobutamine (71 ± 15, P<0·05 vs rest and vs dipyridamole).

Echocardiographic findings

Wall motion score index was 1·64 ± 0·32 at rest and improved significantly after dobutamine (1·51 ± 0·38 P<0·05 vs rest) and after dipyridamole (1·52 ± 0·39 P<0·05 vs rest, P=ns vs dobutamine). Of the 243 segments with baseline dyssynergy, 70 were responders (i.e. improved by one grade or more) with both dipyridamole and dobutamine, 157 were non-responders with both dipyridamole and dobutamine; and 16 showed discordant results (five responders by dipyridamole only, and 11 responders by dobutamine only). The overall concordance of dipyridamole and dobutamine in the 243 dyssynergic segments at baseline was 93%.

Follow-up resting echo

Follow-up echocardiography was available in 19 patients after successful coronary revascularization. Assuming as a viability criterion improved systolic wall thickening after dipyridamole in at least two adjacent abnormal segments, contractile reserve following dipyridamole was present in 11 (58%) of the 19 patients undergoing revascularization. Ten of the 11 patients with contractile reserve had improved systolic wall thickening after revascularization, whereas three of the eight patients without contractile reserve improved (91% vs 38%, P<0·05). At baseline echo at study entry, these 19 patients showed a total of 100 dyssynergic segments. Regional wall motion improved in time by one grade or more in 50 segments (viable) while in the remaining 50 (necrotic) no improvement could be observed. Of the 50 viable segments, dobutamine and dipyridamole correctly identified 37 and 38, respectively. Of the 50 necrotic segments, dobutamine and dipyridamole correctly identified 47 and 47, respectively (Fig. 1). The sensitivity of dobutamine and dipyridamole was 76% and 78% (P=ns), respectively. The specificity of both tests was 94%. Of the 40 segments identified as viable by dobutamine, 37 were also viable by dipyridamole; of the 60 segments necrotic by dobutamine, 56 were also necrotic

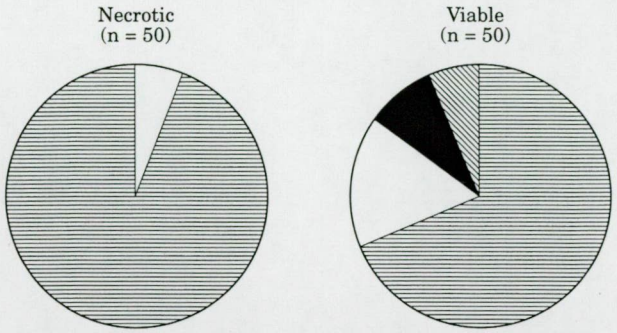

Figure 1 **Pie graph showing the sensitivity and specificity of dipyridamole (DIP) and dobutamine (DOB) in predicting functional recovery following revascularization. The two tests have comparable excellent specificity and good sensitivity. The numbers in parenthesis indicate segments. ▤=identified by DOB and DIP; ▧=identified by DOB only; ■=identified by DIP only; □=missed by DOB and DIP.**

by dipyridamole. The overall concordance of dipyridamole and dobutamine in the 100 dyssynergic segments at baseline was 93%

Discussion

Our results are in agreement with previous experimental and clinical studies demonstrating that ventricular dysfunction of viable tissue — due to either myocardial hibernation or stunning — can be improved by an inotropic stimulus with an accuracy of about 80% in predicting either spontaneous or revascularization-induced functional recovery[7–14]. Our study also showed that dobutamine and dipyridamole were similarly accurate in predicting recovery. This is consistent with preliminary reports showing comparable accuracy by high dose dipyridamole and low dose dobutamine in assessing myocardial viability[11,18]. In addition, the present study demonstrates for the first time, the feasibility, tolerability and accuracy of a very low dose dipyridamole regimen, especially designed as a coronary vasodilatory stimulus to selectively explore myocardial viability. This finding has potential clinical and pathophysiological relevance. From the clinical viewpoint, a low dose vasodilatory stress echo might be a suitable alternative to dobutamine stress echo for the selective assessment of myocardial viability, especially in patients with a history of malignant arrhythmias, or in those showing limiting side effects with low dose dobutamine[19].

From the pathophysiological viewpoint, the present data provide indirect support, in a clinical setting, for the concept that flow and function remain 'matched' in the hibernating heart[20,21], and that contractile reserve can be elicited in an equally effective way with a mild inotropic stimulus, increasing flow secondarily (as with dobutamine), or with a mild vasodilatory stimulus, increasing function secondarily (as with low dose dipyridamole).

The mechanism of viability recognition by infra-low dose dipyridamole

In this study myocardial viability was achieved with very low doses of dipyridamole, and with an accuracy similar to that reported with high dose dipyridamole[10]. In a dog model of stunned myocardium, Jeremy *et al.* showed that a significant improvement in % systolic thickening in the stunned area was achieved with very low adenosine doses, and the same improvement was obtained with adenosine doses up to 100 times higher[22]. This might explain why inotropic reserve can be recruited with similar efficacy by infra-low and high doses of dipyridamole. This differs from the ischaemic effect, which rises sharply with increasing doses[14].

Infra-low dose dipyridamole recruits inotropic reserve through two possible mechanisms: haemodynamic (linked to increased coronary flow) or metabolic (due to accumulation of endogenous adenosine).

Dipyridamole may increase post-ischaemic function by increasing flow through the Gregg phenomenon[23]: changes in vascular distension affect sarcomere length and thereby influence contractile function. This interpretation is consistent with experimental[24–27] and clinical[28] studies, demonstrating that residual flow reserve can be elicited in the presence of a severe coronary stenosis and depressed baseline function. In addition, myocardial contrast echocardiography[29] and positron emission tomography[30] studies have recently shown that the presence of residual coronary reserve following dipyridamole infusion identifies segmental viability in patients with wall motion abnormalities.

The second, and probably more likely, mechanism does not need the increase in coronary flow to improve function. In an experimental study on the dog model of stunned myocardium, Zughaib *et al.* showed that the augmentation of endogenous adenosine attenuates myocardial stunning independent of coronary flow or haemodynamic effects[31]. This conclusion is corroborated by the study of Ely *et al.*, who reported beneficial effects of adenosine on ischaemia–reperfusion injury in isolated hearts at constant coronary flow[32]. Several flow-independent beneficial effects of endogenous adenosine have been hypothesised including: blocking of slow calcium channels (with reduction of cytosolic accumulation of calcium); glycolysis stimulation; inhibition of free radical generation[21,31].

Study limitations

The echocardiographically documented improvement of wall motion at follow-up was used as the definitive method for judging the accuracy of stress-induced functional improvement. We did not use an independent standard such as fluorodeoxyglucose or Thallium uptake.

About one half of the patients enrolled in this study did not undergo coronary revascularization and therefore did not enter the echocardiographic follow-up

programme. Some of these patients had no evidence of viable myocardium by either test; others had evidence of viable myocardium but no clinical indication for revascularization. Indeed, at present, the identification of viable myocardium is not in and of itself an indication for revascularization. As in any other patient with coronary artery disease, this decision should be based on clinical presentation, coronary anatomy, left ventricular function, and evidence of inducible ischaemia[3].

The main results of the study concerning the diagnosis of viability were based on 19 patients only, i.e. those who had an echocardiographic examination at follow-up. Therefore, the results should be considered preliminary, and need to be confirmed with larger series.

The study population involved a substantial number of individuals who had only mild left ventricular impairment, as the average ejection fraction was 41 ± 14%. After the present initial feasibility study, the infra-low dose test should be assessed in patients with severe left ventricular dysfunction, in whom the clinical question regarding the extent of viable tissue is more important[3]. This validation is currently ongoing, on a multicentre basis, with the VIDA (Viability Identification with Dipyridamole–Dobutamine Administration) project.

Infra-low dose dipyridamole: a haemodynamically neutral stress

Regional function can be modulated by extrinsic conditions such as systolic ventricular pressure, tethering by adjacent segments, preload changes, heart rate modifications[33]. At high (ischaemic) dipyridamole or dobutamine dosages, the effect on heart rate and blood pressure and the tethering effect from neighbouring segments and from the epicardial rim of muscle ('transmural tethering') make the increment of regional function more evident but less predictive of the real status of myocardium and of the subsequent functional recovery. Therefore, the ideal stress for viability should only minimally affect all these factors, since manipulation of haemodynamic variables can induce variations in wall motion and thickening independent of the local inotropic effect. Both low dose dobutamine and infra-low dose dipyridamole fulfil these requirements. Heart rate and systolic blood pressure were only minimally affected by dobutamine, were not affected at all by dipyridamole and neither stress induced ischaemia in any patient.

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The flow-function relationship in patients with chronic coronary artery disease and reduced regional function: a Doppler transesophageal and bidimensional transthoracic echocardiography study

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Key words: dipyridamole, Doppler, myocardial viability, transesophageal echocardiography

Abstract

Background: Infra-low dose dipyridamole allows one to selectively explore myocardial viability. Transesophageal echocardiography Doppler measurement of left anterior descending coronary artery flow at baseline and following dipyridamole is an efficient tool to assess coronary flow response. Aim of this study was to determine the flow-function relationship during coronary vasodilatory stress in patients with coronary artery disease and baseline dysfunction. *Methods and results*: Twelve patients with resting dyssynergies and 6 controls underwent assessment of regional function and of left anterior descending blood flow velocity. Flow and function were evaluated at rest and following infra-low dose dipyridamole (0.28 mg/Kg over 4 min). Controls showed a normal function at rest and after dipyridamole. Six patients ('Responders') with resting dyssynergies showed an improvement in segments of left anterior descending artery territory, whereas the other six ones ('Non-responders') showed no functional change. Controls and 'Responders' had similar values of resting peak diastolic left anterior descending artery flow velocity both at rest and after dipyridamole, whereas 'Non-responders' showed a blunted flow response to dipyridamole. *Conclusion*: Myocardial segments with a resting dysfunction and a contractile reserve more often exhibit a residual flow response, whereas segments with fixed pattern show a flat flow response during coronary vasodilator stress.

Introduction

Left ventricular dysfunction of viable tissue can be improved by an adenosinergic stimulus [1], such as dipyridamole, which acts as an inhibitor of adenosine cellular reuptake determining endogenous adenosine accumulation [2]. Dipyridamole-induced contractile response has an accuracy similar to dobutamine in predicting spontaneous [3] or revascularization induced [4] functional recovery.

It has been recently shown that an 'infra-low' (0.28 mg/Kg over 4 min) dipyridamole dose allows one to explore myocardial viability selectively, without eliciting ischemia [5]. It increases function in the majority of viable segments and potentiates the effect of dobutamine infusion [4], eliciting a contractile response in segments destined to recover following revascularization, which did not respond to either dipyridamole or dobutamine separately, administered. This dose regimen is neutral on systemic hemodynamics, determining no significant change on heart rate or blood pressure [5], but its effects on coronary flow

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response remain unknown. In fact, no data are available of flow-function correlation during low dose coronary vasodilation in patients with chronic artery disease and reduced regional function. Such data are crucial for the understanding of clinical findings in the context of defined pathophysiological principles, since diagnosis without physiology is merely phenomenology [6].

Transesophageal echocardiography Doppler measurement of left anterior descending coronary artery flow velocity at baseline and following dipyridamole is an efficient and reproducible tool to assess coronary flow reserve [7–9], which correlates well with that obtained by positron emission tomography [10].

The aim of this study was to assess whether infra-low dose dipyridamole can evoke a significant hyperemic coronary response in the left anterior descending artery flow, evaluated by pulsed wave Doppler obtained by transesophageal echocardiography. In each patient, the myocardial contractile response was independently assessed by transthoracic echocardiography. We therefore studied 18 patients with transthoracic echocardiography, for assessment of myocardial function, and with transesophageal echocardiography, for evaluation of coronary flow reserve: 6 patients had normal baseline function, and 12 a resting dysfunction in left anterior descending artery territory.

Methods

Subject selection

Twenty-three in-hospital patients admitted to the hospital for known or suspected coronary artery disease were initially considered for the study. Of these, five were subsequently not eligible for either refusal to give the informed consent ($n = 2$) or for transesophageal echocardiography Doppler tracings of suboptimal quality ($n = 3$). The remaining 18 patients (11 men and 7 women, age range to 27–70 years, mean ± SD 57.9 ± 11.1) completed the study.

Of these 18 patients, 6 ones had normal left ventricular function; 12 ones had a previous anterior myocardial infarction. Coronary angiography showed significant stenosis (> 50% diameter reduction by a visual, semi-quantitative evaluation) of 1 vessel in 3, 2 vessels in 5 and 3 vessels in 4 patients.

All patients underwent, on separate session on different days and in random order, a baseline and infra-low (0.28 mg/Kg over 4 min) dipyridamole study with transthoracic echocardiography for wall motion analysis, and with transesophageal echocardiography for coronary blood flow assessment.

Transthoracic and transesophageal studies were performed and interpreted by cardiologist blinded to the results of the other test.

Transthoracic echocardiographic examination

Two dimensional echocardiograms were obtained by using commercially available imaging systems. Echocardiographic images were digitally acquired as well as recorded on VHS videotape for subsequent playback and analysis. According to the recommendation of the American Society of Echocardiography [11], segmental wall motion was semiquantitatively graded as follows: normal = 1; hypokinetic, marked reduction of endocardial motion and thickening = 2; akinetic, virtual absence of inward motion and thickening = 3; and dyskinetic, paradoxical wall motion away from the center of the left ventricle in systole = 4. Wall Motion Score Index (WMSI) was derived by dividing the sum of individual segment scores by the number of interpretable segments. Inadequately visualized segments were not scored.

Transesophageal echocardiography

The procedure was performed in accordance with a standard protocol, which included pharyngeal topical anesthesia. Vital signs were monitored throughout the study using an automated blood pressure monitor and 12-lead ECG display; the timing of measurements was synchronized to the timing on the echocardiogram [12]. The bifurcation of the left main coronary artery was

visualized after flexion and rotation of the probe in the esophageal transverse view, and flow velocity profiles in the proximal left anterior descending coronary artery were recorded on videotape. Because of translational cardiac movement, measurement of systolic flow would have required the Doppler sample volume to be adjusted to a position distal from that used for diastolic measurement. No angle correction of the Doppler beam was performed. Basal flow data were obtained after the development of stable resting hemodynamics, at which time flow measurements were reproducible. After obtaining resting flows, since diastolic flow allows more reproducible and meaningful index measurements of coronary flow reserve than systolic flows, we elected to assess only diastolic flow. Flow velocities were continually measured throughout the study at minute intervals (where possible) from the start of the injection, for a minimum of 10 min, and particular attention was paid to record resting flow, flow at 6 min after the injection of dipyridamole, and the maximum recorded flow (and the time at which this occurred). The total duration of the procedure was 15–20 min.

Flow parameters were analyzed off-line by two experienced observers. At each time-point, the two or three optimal diastolic Doppler flow profiles were measured, and the results averaged. These parameters measured included peak flow velocity for each diastolic Doppler flow profile – the parameter easiest to be measured and with the highest reproducibility [10]. Coronary blood flow velocity reserve (flow reserve using transesophageal echocardiography) was expressed as the ratio of the index of flow recorded at minute intervals following dipyridamole divided by the mean of the corrected resting values [10].

Interobserver variability was determined by having a second independent echocardiographer measure Doppler velocity readings in 10 consecutive patients. Intraobserver variability was determined by having one observer measuring Doppler velocity recordings obtained in 10 patients at 10 min interval, after >1 month from the first assessment.

Intra and interobserver variability in our lab were 12% and 9% respectively.

Infra-low dose dipyridamole stress echocardiography test

Two-dimensional echocardiographic and 12-lead ECG monitoring were performed in combination with dipyridamole (Persantin) infusion, given at a dose of 0.28 mg/Kg i.v. over four minutes [4]. In the baseline studies as well as during stress, all standard echocardiographic views were obtained when possible. During the procedure, the blood pressure and the electrocardiogram were recorded each minute. The videotapes and digital images were analyzed by a cardiologist-echocardiographer, who was blind to the clinical and angiographic and transesophageal echocardiography data.

A digital acquisition of images of interest was obtained with a side by side display of rest and peak stress images in a cine-loop mode (either on-line or off-line). A WMSI was derived for rest and peak stress (0–1 min after the end of infusion) echocardiograms in all patients, as previously described for the baseline echocardiographic examination. Each patient was allocated to only one of the following pre-defined subsets: (1) Normal (WMSI rest = 1; WMSI dipyridamole = 1); (2) 'Responder' (WMSI rest > 1; WMSI dipyridamole < rest); (3) 'Non-responder' (WMSI rest = > 1; WMSI dipyridamole = rest). A segment was considered to show signs of viability when it improved of 1 grade or more at peak stress (for instance, a hypokinetic segment becoming normal, or an akinetic segment becoming hypokinetic).

The previously assessed low level (< 10%) on inter- and intraobserver variability between experienced observers in our laboratory has been documented [13] and is probably linked to previous extensive experience in joint reading and development of a priori reading criteria, thus overcoming the otherwise more substantial variability between independent 'expert' readers [14].

Statistical analysis

Mean values and standard deviations of the data were calculated. Intergroup comparisons were performed by the unpaired *t* test. Intragroup

comparisons were performed by the paired t test. Multiple group comparisons were performed with ANOVA and the Newmann–Keuls test for individual comparisons within groups were applied. A value of $p < 0.05$ was considered significant.

Results

Individual, demographic, resting echocardiographic and angiographic data of the study are summarized in Table 1.

Baseline echocardiographic findings

Six patients had a completely normal regional and global left ventricular function in the resting echocardiogram, with angiographically normal coronary arteries.

Twelve patients had a resting dysfunction with angiographically assessed coronary artery; the resting dysfunction involved the left anterior descending artery territory in all 12 patients.

Hemodynamic response to dipyridamole infusion

The systemic hemodynamic response to dipyridamole infusion is reported in Table 2. The data are reported for both the transesophageal echocardiography and the transthoracic echocardiography study. There were no significant changes in blood pressure and heart rate values following stress, although heart rate values tended to be higher, both at rest and following dipyridamole, with transesophageal echocardiography.

Stress echocardiographic findings

Six patients had normal function both at rest and following dipyridamole: 'Control group'. Six patients had a resting dysfunction at rest improving in at least 2 contiguous segments after stress: 'Responder group'. Their Wall Motion Score Index was 1.29 ± 0.18 at rest and 1.1 ± 0.09 during stress.

Six patients had a resting dysfunction at rest, which remained fixed after stress: 'Non-responder group'. Their Wall Motion Score Index was 1.33 ± 0.14 at rest and 1.3 ± 0.11 during stress.

Table 1. Clinical, echocardiographic and angiographic features of the study population.

Patient	Sex	Age	Previous infarction	Coronary angiography			
				LAD	LCX	RCA	EF%
15	F	58	no	0	0	0	65
16	F	47	no	0	0	0	63
18	F	27	no	0	0	0	65
12	M	59	no	0	0	0	36
8	F	69	no	0	0	0	65
9	F	42	no	0	0	0	70
1	M	64	Ant/Lat	75	99	100	30
2	M	70	Ant	90	75	0	60
3	F	63	Ant	0	90	75	32
4	M	68	Ant	100	90	75	48
5	M	61	Ant	90	0	90	58
6	M	67	Ant	50	100	100	50
7	F	66	Ant	90	75	50	45
10	M	63	Ant	90	0	0	70
11	M	48	Ant	75	0	0	55
13	M	52	Ant	99	75	0	50
14	M	58	Ant	100	0	0	61
17	M	61	Ant/Inf	80	0	100	45

EF% = Ejection Fraction; F = Female; LAD = Left Anterior Descending Coronary Artery; LCX = Left Circumflex; M = male; RCA = Right Coronary Artery.

Table 2. Hemodynamic changes during stress echocardiographic testing.

	Baseline		DIP	
	TTE	TEE	TTE	TEE
SBP (mmHg)	142.1 ± 20.4	145.2 ± 23.1	141.3 ± 19.7	146.1 ± 26.1
DBP (mmHg)	84.3 ± 11.5	87 ± 15.6	80.8 ± 10.9	83.6 ± 14.2
HR (beats/min)	78.8 ± 6.8	85.3 ± 10.9	82.1 ± 7	89.6 ± 15.5
RPP (mmHg × beats/min)	11214 ± 2165	12395 ± 1350	11619 ± 2168	12425 ± 7627

DBP = Diastolic Blood Pressure; DIP = Dipyridamole; HR = Heart Rate; RPP = Rate Pressure Product; SBP = Systolic Blood Pressure; p = NS.

Transesophageal echocardiography coronary flow findings

The transesophageal echocardiography peak diastolic flow velocity went from 50.5 ± 7.77 at rest to 64 ± 22.62 cm/s following dipyridamole ($p < 0.05$), with an average increment of 24.7%.

In 5 patients the diameter of proximal portion of left anterior descending artery was measured: no significant change was found between mean values obtained at rest and after dipyridamole (rest = 3.03 ± 0.6 mm vs dipyridamole = 2.97 ± 0.7 mm, p = NS).

Correlation between wall motion and coronary flow findings

Control patients had a resting flow velocity of 46 ± 14 cm/s and 60 ± 16 cm/s after dipyridamole ($p < 0.01$) yielding a coronary flow increase of 30%. The corresponding functional pattern was a normal contraction remaining unchanged during stress (Wall Motion Score Index rest = 1 vs dipyridamole = 1). Of the 12 patients with baseline dysfunction, 'Responders' showed an improvement of Wall Motion Score Index in segments of left anterior descending artery territory after dipyridamole (Wall Motion Score Index rest = 1.29 ± 0.18 vs dipyridamole = 1.1 ± 0.09, $p < 0.01$), whereas 'Non-responders' showed no functional change (Wall Motion Score Index rest = 1.33 ± 0.14 vs dipyridamole = 1.3 ± 0.11, p = NS). Controls, and 'Responders' had similar values of resting peak diastolic flow velocity both at rest (46 ± 14 and 57 ± 6 cm/s) and after dipyridamole (60 ± 16 and 76 ± 16 cm/s, $p < 0.01$ vs rest). A typical example of 'Responder' pattern is shown in Figure 1.

Left anterior descending artery resting flow velocity was similar in 'Responders' and 'Non-responders' patients (57 ± 6 vs 49 ± 8 cm/s, p = NS, whereas the peak dipyridamole flow velocity was higher in 'Responders' than in 'Non-responders' (76 ± 16 vs 53 ± 15 cm/s, $p < 0.05$): Figure 2. Segments with a 'Responder' pattern showed an upsloping flow-function curve during stress, with increased flow and function following dipyridamole. Segments with a 'Non-responder' pattern showed a flat flow-function curve during stress with no significant change in either flow velocity or function following dipyridamole.

Discussion

Our results confirm and expand previous evidences showing that:

- Transesophageal echocardiography is a technically demanding but suitable technique to measure variations in coronary flow [7–10], especially in the left anterior descending artery district and using each patient as his/her own control during short lasting pharmacological stimuli.
- Dipyridamole infusion, even at a very low infusion rate, can elicit an inotropic response in dysfunctioning, albeit viable, myocardium [4].
- The presence of an inotropic response elicitable by infra-low dose dipyridamole is mirrored by an increase in flow, as previously shown with the low or standard dose regimen employing myocardial contrast echocardiography [15] and positron emission tomography [16].

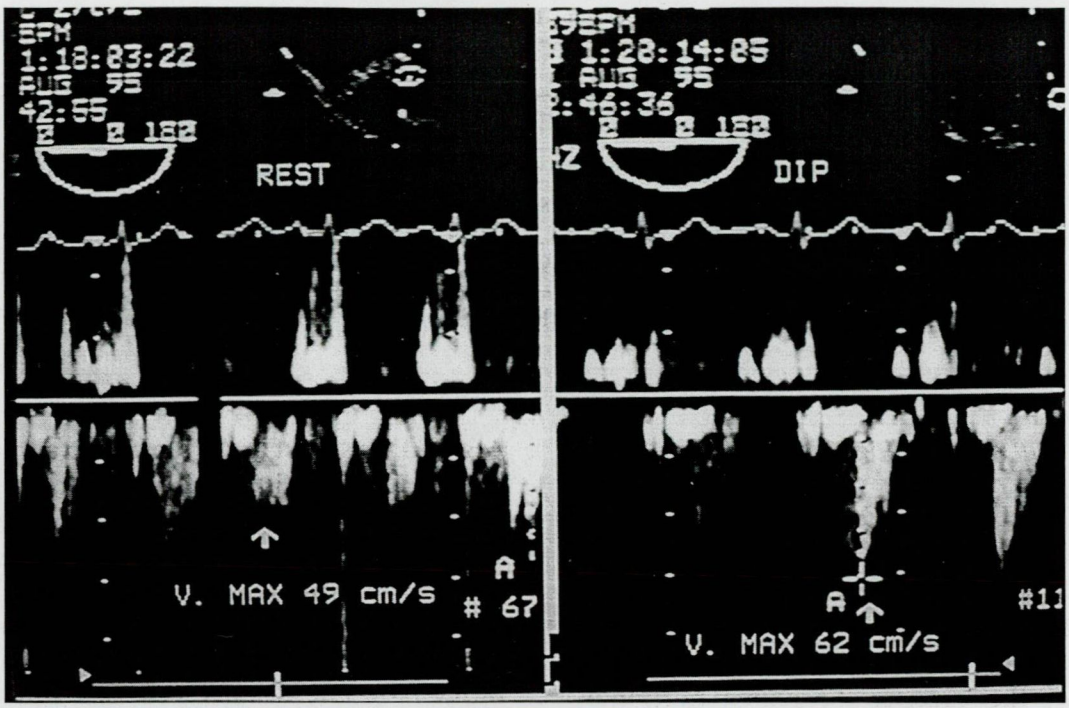

Figure 1. Measurement of regional flow reserve in a patient with dipyridamole-induced inotropic response in a region with baseline resting dysfunction. The pulsed Doppler flowmetry at baseline (REST, left panel) shows a normal bifasic, mostly diastolic, flow with a peak flow velocity of 49 cm/s. Following infra-low dose dipridamole (dipyridamole, right panel), there is an obvious increase in peak diastolic flow velocity, reaching 62 cm/s, with a 26% increment over baseline.

The pathophysiological mechanism of inotropic response to coronary vasolidation

The recruitment of an inotropic reserve by dipyridamole can occur by two possible mechanisms:

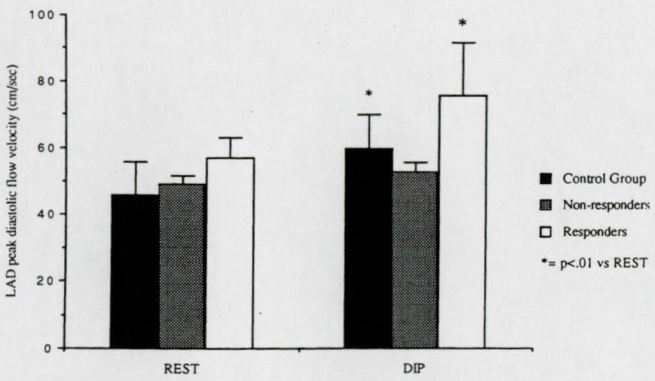

Figure 2. Bar graph histogram showing the dipyridamole-induced increase in left anterior descending artery flow velocity (*y* axis) in the subset of patients identified according to the wall motion response. The coronary blood flow response is comparable in 'Controls' and 'Responders', but significantly blunted in 'Non-responders'.

hemodynamic (linked to increased flow) or metabolic (due to accumulation of endogenous adenosine). The findings of the present study support the hemodynamic mechanism, since segments with mechanical improvement following dipyridamole had higher flow response values.

Even if the traditional concept is that coronary vasodilator reserve is exhausted in severe coronary narrowing, this does not necessarily imply exhaustion of pharmacological vasodilator reserve. The increase in function is expected following a vasodilator stress on the basis of the known relationship between myocardial contractility and coronary perfusion, as originally described by Gregg [17].

On the basis of our data, however, we cannot disprove a metabolic (non-flow mediated) mechanism for dipyridamole-induced mechanical recovery. It has been shown experimentally that several flow-independent effects of endogenous adenosine might account for a mechanical improvement on viable but dysfunctioning myocardium [18]. In fact, on the sole basis of the hemodynamic explanation,

it would be difficult to understand how the same inotropic response in dyssynergic, although viable, segments can be elicited by different dose regimens of dipyridamole evoking very different coronary flow responses. The infra-low dose increases of 20%, whereas standard and high doses of dipyridamole increase by 200–300% the left anterior descending artery coronary flow [19]. Experimental data show that a significant improvement in systolic thickening in the stunned area was achieved with very low adenosine doses, and the same improvement was obtained with adenosine doses up to 100 times higher [20].

Study limitations

In this study, transesophageal echocardiography and transthoracic echocardiography studies were performed on different days because of the technical and logistic problems posed by a simultaneous assessment of left anterior descending artery flow by transesophageal echocardiography and left ventricular function by transthoracic echocardiography. With transesophageal echocardiography, the more steady the imaging plane, the better and more reproducible is the coronary flow velocity signal. Therefore, although a simultaneous assessment of flow and left ventricular function is possible, we elected to focus only on blood flow monitoring during transesophageal echocardiography, and we assessed left ventricular function separately with a transthoracic echocardiography monitoring.

The completion of the two studies in different settings has the disadvantage of allowing possible differences in hemodynamic parameters between the two studies. Actually, we found only slightly higher values in resting heart rate in the transesophageal echocardiography study, but the other parameters – at rest and during stress – were comparable in the 2 settings.

For blood flow velocity measurements to correlate with flow reserve, it must be assumed that coronary dimensions remain unchanged despite administration of dipyridamole. Actually, this has been shown to be true with substantially higher doses of dipyridamole, with coronary lumen measured angiographically or echocardiographically [10]. The parallel orientation of the transesophageal transducer to the coronary artery is suboptimal for such measurements, although in the 5 patients in whom such evaluation could be performed there was virtually no change in left anterior descending coronary diameter.

Several parameters might have been measured from Doppler tracings of left anterior descending artery flow, including systolic flows, time-velocity integrals, and mean flows [7–10]. However, we chose to measure only the peak diastolic flow. This is not only the simplest parameter to be measured and the easiest to be obtained, but also the more reproducible and the one with the closest linear agreement with coronary perfusion reserve measured at positron emission tomography [10].

Conclusion

The present study confirm that, in skilled hands, transesophageal echocardiography is a suitable technique to measure variations in coronary blood flow velocity in the left anterior descending artery territory during pharmacological stimuli, using each patient as his/her own control.

Besides showing that also an infra-low dose dipyridamole is able to detect the presence of dysfunctioning, but still viable myocardium, our data have pointed out the flow-function link. Indeed myocardial segments with a resting dysfunction and a contractile reserve more often exhibit a residual flow response, whereas segments with fixed pattern show a flat flow response during coronary vasodilator stress.

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Combined Low Dose Dipyridamole-Dobutamine Stress Echocardiography to Identify Myocardial Viability

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Objectives. **We sought to evaluate the effects of combined administration of infra-low dose dipyridamole and low dose dobutamine on assessment of myocardial viability.**

Background. **Low dose pharmacologic stress echocardiography with either dobutamine or dipyridamole infusion has been proposed for the recognition of myocardial viability.**

Methods. **Thirty-four patients with rest wall motion dyssynergy by two-dimensional echocardiography and with angiographically proved coronary artery disease underwent in combination with two-dimensional echocardiographic monitoring: 1) low dose (5 to 10 μg/kg per min over 3 min) dobutamine infusion; 2) infra-low dose (0.28 mg/kg over 4 min) dipyridamole infusion; 3) combination of infra-low dose dipyridamole infusion immediately followed by low dose dobutamine infusion (combined dipyridamole-dobutamine).**

Results. **Follow-up rest echocardiography was available in 30 patients. After revascularization, 82 segments showed a contractile improvement of ≥1 grade, whereas 63 segments remained unchanged. The sensitivity of dobutamine, dipyridamole and combined dipyridamole-dobutamine for predicting recovery was 72% (95% confidence interval [CI] 60.9% to 81.3%), 67% (CI 55.8% to 77%) and 94% (CI 86.3% to 97.9%), respectively. The specificity of dipyridamole, dobutamine and combined dipyridamole-dobutamine was 95% (CI 86.7% to 99%), 92% (CI 82.4% to 97.3%) and 89% (CI 78.4% to 95.4%), respectively. The accuracy of the dobutamine, dipyridamole and combined dipyridamole-dobutamine test was 80%, 79% and 92%, respectively (combined dipyridamole-dobutamine vs. dobutamine, $p < 0.05$; combined dipyridamole-dobutamine vs. dipyridamole, $p < 0.01$).**

Conclusions. **Infra-low dose dipyridamole added to low dose dobutamine recruits an inotropic reserve in asynergic segments that were nonresponders after either dobutamine or dipyridamole alone and destined to recover after revascularization.**

(J Am Coll Cardiol 1996;27:1422–8)

The identification of viable myocardium has been recognized as an increasingly important goal in clinical cardiology (1–3). The potential reversibility of myocardial dysfunction in certain settings is now well established, but a remaining challenge is the development of an accurate means of reliably distinguishing reversible from irreversible dysfunction (4–7). Low dose dobutamine stress echocardiography is an attractive and increasingly used method of identifying viable myocardium based on its ability to respond to beta-adrenergic stimulation with an increase in myocardial thickening (8–14). The specificity of low dose dobutamine stress echocardiography for predicting functional recovery is excellent, but its sensitivity is less than ideal. Thus, a segment that shows improved wall motion with dobutamine, is likely to be viable and to recover with revascularization; but viability is still possible even if wall motion does not improve with dobutamine.

Experimental (15,16) and clinical (17,18) studies have shown that coronary vasodilator stress can recruit an inotropic reserve in viable segments. In particular, the infra-low dipyridamole dose regimen designates a dosage (0.28 mg/kg in 4 min) that selectively explores myocardial viability and has virtually no ischemic potential (18). This viability dose is called "infra-low" because it is 50% lower than the regular or low dose (0.56 mg/kg in 4 min), originally proposed by Gould (19) and currently employed in perfusion imaging, and 67% lower than the high dose (0.84 mg/kg in 10 min) most frequently used for echocardiographic imaging when myocardial ischemia is the diagnostic end point (20,21). Therefore, in patients with chronic coronary artery disease, a theoretically attractive way of increasing the sensitivity of pharmacologic stress echocardiography would be the addition of infra-low dose dipyridamole to low dose dobutamine. The two agents act through different, potentially synergic mechanisms: Dobutamine is a mild $beta_1$-adrenoreceptor–mediated inotropic stimulus on the myocardium, secondarily increasing coronary flow (22), whereas dipyridamole is an adenosine A_2-receptor–mediated mild vasodilator stimulus on the coronary arterioles, secondarily

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increasing myocardial function (15,16). The combined dipyridamole-dobutamine stress for viability should also be safe, because substantially higher doses of both dipyridamole and dobutamine have been used in a single combined test for the diagnosis of coronary artery disease (23), with excellent accuracy and tolerability.

We therefore separately performed infusions of low dose dobutamine alone, infra-low dose dipyridamole alone and combined infra-low dose dipyridamole and low dose dobutamine in 34 consecutive patients referred to the echocardiography laboratory for assessment of myocardial viability. All patients underwent a revascularization procedure; echocardiographic follow-up after a successful revascularization was obtained in 30 patients. Our working hypothesis was that the combined infra-low dose dipyridamole and low dose dobutamine stress would have greater sensitivity in identifying myocardial viability than would stress with either dipyridamole or dobutamine alone.

Methods

Study patients. Fifty-one consecutive patients with a history of myocardial infarction, angiographically proved coronary artery disease, a technically satisfactory acoustic window and wall motion dyssynergy of the left ventricle at rest were initially considered. Of these 51 patients, 17 underwent the stress echocardiographic study but did not enter the echocardiographic follow-up program because they did not undergo coronary revascularization on the basis of the independent decision of the referring physician. As in any other patient with coronary artery disease, this decision was based on clinical presentation, coronary anatomy and evidence of inducible ischemia in addition to assessment of myocardial viability, which was not in itself an indication for revascularization.

Of the initial group of 51 patients, 34 (30 men and 4 women, age range 31 to 73 years [mean ± SD 55 ± 11]) underwent revascularization and were enrolled in the study (Table 1). All 34 patients had evidence of previous (>3 months) myocardial infarction. Twenty-two patients had a Q wave infarction and 12 had a non-Q wave infarction. The site of the Q wave infarction was anterior in 12 patients and inferior in 10. Medical therapy was discontinued ≥48 h before the stress echocardiographic examination in 18 patients; the other 16 patients were examined while receiving antianginal therapy: nitrates in 1 patient beta-adrenergic blocking agents in 2 and combined therapy in 13 (nitrates and calcium antagonists in 9, nitrates and beta-blockers in 3 and triple therapy [nitrate plus calcium antagonist plus beta-blocker] in 1). Coronary angiography demonstrated significant stenosis (≥50% diameter reduction by quantitative coronary angiography) of one vessel in 18 patients, of two vessels in 10 and of three vessels in 6. Average left ventricular ejection fraction calculated from the apical four-chamber view by two-dimensional echocardiography (single-plane area-length method) was 43 ± 12%. Coronary revascularization was performed in all 34 patients either by coronary artery bypass surgery (n = 9) or by percutaneous transluminal coronary angioplasty (n = 25). Of the 34 patients submitted to revascularization and entered in the follow-up program, 4 (Patients 31 to 34) were subsequently excluded from follow-up because coronary revascularization was unsuccessful. Of these four patients, two died in the perioperative period, one had early restenosis (within 1 month) and one had a perioperative reinfarction complicated by ventricular fibrillation. A baseline follow-up echocardiogram obtained at least 4 weeks (mean 7 ± 3) after revascularization was available in 30 patients. None of these patients showed clinical, enzymatic, electrocardiographic (ECG) or echocardiographic evidence of a perioperative myocardial infarction, and all were thought to have had successful revascularization, because they were asymptomatic and had fully negative results on functional tests of ischemia, including maximal high dose pharmacologic stress echocardiography.

Baseline echocardiographic examination. Two-dimensional echocardiograms were obtained by using commercially available imaging systems (Hewlett-Packard Sonos 1000, 1500 or 2000 or Diasonics 2.5- and 3.5-MHz transducers). Echocardiographic images were recorded on VHS videotape for subsequent playback and analysis. Regional wall motion was assessed according to the recommendations of the American Society of Echocardiography (24) with a 16-segment model. In all studies, segmental wall motion was semiquantitatively graded as follows: normal = 1; hypokinetic, marked reduction of endocardial motion and thickening = 2; akinetic, virtual absence of inward motion and thickening = 3; and dyskinetic, paradoxic wall motion away from the center of the left ventricle in systole = 4. A wall motion score index was derived by dividing the sum of individual segment scores by the number of interpretable segments. Baseline echocardiography was performed before coronary angioplasty or coronary artery bypass surgery. Inadequately visualized segments were not scored.

Pharmacologic stress echocardiography. All patients underwent, in separate sessions and before coronary revascularization, low dose dobutamine infusion (5 μg/kg per min followed by 10 μg/kg per min, each stage lasting 3 min); infra-low dose dipyridamole (0.28 mg/kg over 4 min); infra-low dose dipyridamole followed by low dose dobutamine echocardiography (Fig. 1). Two-dimensional echocardiograms were continuously obtained and intermittently recorded during drug administration. In the baseline studies as well as during stress, all standard echocardiographic views were obtained when possible. During the procedure, the blood pressure and the ECG were recorded each minute. Off-line assessment of echocardiographic images was performed by two experienced independent investigators unaware of the clinical, angiographic and follow-up data. When there was disagreement between the two readers, which occurred in at least one segment in three patients, a third investigator reviewed the images without knowledge of the previous assessment and a consensus decision was achieved. Interobserver agreement regarding the presence or absence of myocardial viability in a segment by segment assessment was 92%. The low level of interobserver variability between experienced observers in our

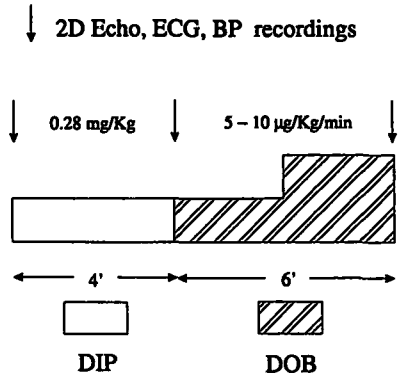
Table 1. Clinical, Echocardiographic and Angiographic Features of the 34 Study Patients

Pt No.	Age (yr)/ Gender	Previous Infarction	Dyssynergic Area	Coronary Angiography (% stenosis)				Wall Motion Score Index						Vessel Revascularized
				LMCA	LAD	LCx	RCA	Baseline	DOB	DIP	Combined DIP-DOB	Ischemia	FU	
1	51/M	Q	Inferobasal	0	75	100	0	1.38	1.38	1.38	1.38	None	1.38	LAD,LCx
2	48/M	Q	Anteroseptal	0	90	0	0	1.38	1.13	1.13	1.06	None	1.13	LAD
3	56/F	Q	Inferobasal	0	0	0	90	1.31	1.31	1.31	1.31	None	1.31	RCA
4	58/M	Q	Anteroseptal	0	100	0	75	1.63	1.5	1.63	1.38	None	1.38	LAD
5	71/M	Q	Posterolateral	0	0	100	90	1.94	1.81	1.94	1.81	None	1.94	RCA
6	62/M	Q	Posterolateral	0	50	90	0	1.44	1.25	1.31	1.19	None	1	LCx
7	47/M	Non-Q	Anteroseptal	0	90	90	0	1.38	1.13	1.18	1	None	1.06	LAD
8	68/M	Q	Posterolateral	75	100	100	100	2	2	2	1.81	None	1.75	LAD,LCx,RCA
9	51/M	Non-Q	Posterior	0	0	0	90	1.25	1	1	1	None	1	RCA
10	61/M	Q	Apical	0	70	0	0	1.81	1.81	1.81	1.81	None	1.81	LAD
11	53/M	Non-Q	Apical	0	90	0	0	1.38	1	1	1	None	1.13	LAD
12	43/M	Q	Posterior	0	0	90	0	1.13	1	1	1	None	1	LCx
13	35/M	Q	Inferior	0	75	0	75	1.38	1.38	1.38	1.25	None	1.25	RCA
14	59/M	Q	Apicoseptal	0	90	0	0	1.63	1.5	1.56	1.5	None	1.38	LAD
15	48/M	Q	Apical	0	90	0	0	1.63	1.63	1.63	1.63	None	1.63	LAD
16	65/M	Q	Anteroseptal	0	90	0	0	1.81	1.63	1.63	1.63	None	1.63	LAD
17	58/M	Q	Posterior	0	0	0	95	1.25	1	1	1	None	1	LAD
18	71/M	Non-Q	Apical	0	90	0	0	1.31	1	1	1	None	1	RCA
19	68/M	Non-Q	Anterolateral	0	100	99	0	1.88	1.88	1.88	1.88	None	1.88	LAD,LCx
20	44/M	Non-Q	Apical	0	90	0	0	1.13	1.06	1	1	None	1	LAD
21	64/M	Non-Q	Apical	0	90	0	0	1.06	1.06	1.06	1	None	1	LAD
22	50/M	Non-Q	Posterior	0	0	0	90	1.13	1	1	1	None	1	RCA
23	45/M	Q	Apicoseptal	0	100	0	100	1.44	1.44	1.44	1.25	None	1.44	LAD,LCx
24	46/M	Q	Anteroseptal	0	100	99	0	1.31	1	1	1	None	1	LAD,RCA
25	64/M	Q	Apicoseptal	0	90	75	90	1.5	1.31	1.38	1.31	None	1.19	LAD,RCA,LCx
26	36/M	Non-Q	Posterior	0	0	75	75	1.38	1.06	1.06	1	None	1	RCA
27	46/M	Q	Apicoseptal	0	0	90	0	1.5	1.31	1.31	1.31	None	1.31	LCx
28	73/M	Q	Anteroseptal	0	90	90	90	1.44	1.44	1.44	1.25	None	1	LAD
29	52/M	Q	Anteroseptal	0	100	90	75	1.88	1.88	1.88	1.88	None	1.88	LAD,RCA,LCx
30	51/M	Non-Q	Apicoseptal	0	100	0	0	1.31	1	1	1	None	1	LAD
31	72/F	Non-Q	Apical	0	100	90	75	1.25	1.06	1.06	1	1.31	No	LAD,RCA,LCx
32	66/F	Q	Posteroinferior	75	90	0	100	1.81	1.63	1.63	1.63	1.88	No	LAD,RCA,LCx
33	65/M	Non-Q	Anteroseptal	0	100	0	0	1.63	1.5	1.63	1.31	None	No	LAD
34	31/F	Q	Anteroseptal	0	100	0	0	1.63	1.19	1.13	1.13	None	No	LAD

DIP = infra-low dose dipyridamole; DOB = low dose dobutamine; F = female; FU = follow-up; LAD = left anterior descending coronary artery; LCx = left circumflex coronary artery; LMCA = left main coronary artery; M = male; Non-Q = Non-Q wave; Pt = patient; Q = Q wave; RCA = right coronary artery.

laboratory has been documented (25) and is probably linked to previous extensive experience in joint reading and development of a priori reading criteria, thus overcoming the otherwise more substantial variability between independent "expert" readers (26). Digital acquisition of images of interest was obtained with a side by side display of rest and peak stress images in a cine-loop mode either on line or off line by an array-processor–based computer for medical image processing (Mipron, Kontron). A wall motion score index was derived for rest and peak stress echocardiograms (0 to 1 min after the end of each infusion) in all patients, as previously described for the baseline echocardiographic examination. A segment was considered to show signs of viability when it improved by ≥1 grade at peak stress (for instance, a hypokinetic segment becoming normal or an akinetic segment becoming hypokinetic).

Figure 1. Protocol of the combined infra-low dose dipyridamole (DIP)–low dose dobutamine (DOB) test. BP = blood pressure; ECG = electrocardiogram; 2D Echo = two-dimensional echocardiography.



Echocardiographic follow-up. Postoperative rest wall motion score was determined by two experienced echocardiographers who had no knowledge of stress echocardiographic results. Digital acquisition of images was obtained with a side by side display of echocardiograms obtained at baseline (before revascularization) and at follow-up (after revascularization). Improved segmental wall motion at follow-up was defined as endocardial excursion and wall thickening (score 1 or 2) in areas of akinesia or dyskinesia (score 3 or 4) at baseline, or normalization (score 1) of reduced endocardial excursion and wall thickening (score 2) at baseline.

Statistical analysis. Values are expressed as mean value ± SD. Differences in hemodynamic values before and after the infusions and in wall motion score index under different conditions were tested for significance by analysis of variance and subgroup analysis by the Newman-Keuls test. Calculations of sensitivity, specificity and accuracy were performed according to standard definitions and are reported with the corresponding 95% confidence interval (CI). Differences in the sensitivity, specificity and accuracy of the different tests were evaluated with the chi-square test. A p value < 0.05 was considered statistically significant.

Results

The main clinical, echocardiographic and angiographic features of the 34 study patients are reported in Table 1.

Baseline echocardiographic findings. By inclusion criteria, all patients had a regional dyssynergy in the rest echocardiogram. There were 168 segments with baseline dyssynergy: dyskinesia in 6, akinesia in 83 and marked hypokinesia in 79.

Clinical and hemodynamic findings during pharmacologic stress. None of the 34 patients had significant side effects or showed echocardiographic or ECG signs of ischemia after either dipyridamole or dobutamine infusion. However, in two patients a biphasic pattern (improvement of function followed by subsequent deterioration) and ECG changes were observed after the combined infra-low dose dipyridamole and low dose dobutamine stress. These two patients (Patients 32 and 33) were not included in the final analysis because they were among the four who had no follow-up echocardiographic study as a result of unsuccessful revascularization. The systemic hemodynamic findings—blood pressure, heart rate—in baseline conditions and during the pharmacologic stress tests are shown in Table 2. In comparison with the baseline value, systolic blood pressure increased slightly after dobutamine (p = NS) but did not change significantly after dipyridamole or dipyridamole-dobutamine. No test affected significantly diastolic blood pressure. Heart rate was also unchanged after dobutamine or dipyridamole alone, whereas a mild increase was observed after the combined dipyridamole-dobutamine stress.

Echocardiographic findings. Twenty-seven patients showed improved segmental wall motion during pharmacologic stress testing, whereas in seven patients no contractile reserve could be identified. Improvement in wall motion occurred in the distribution of the vessel that was bypassed or dilated. Wall motion score index was 1.48 ± 0.25 at rest and it improved significantly after dobutamine (1.33 ± 0.32, $p < 0.05$ vs. rest), after dipyridamole (1.34 ± 0.32, $p < 0.05$ vs. rest, p = NS vs. dobutamine) and after combined infra-low dose dipyridamole and low dose dobutamine stress (1.29 ± 0.3, $p < 0.05$ vs. rest, p = NS vs. dobutamine and vs. dipyridamole).

Table 2. Hemodynamic Changes During Stress Echocardiographic Testing

	Baseline	DOB	DIP	Combined DIP-DOB
Systolic blood pressure (mm Hg)	134 ± 19	140 ± 22	134 ± 17	135 ± 20*
Diastolic blood pressure (mm Hg)	77 ± 13	78 ± 17	76 ± 14	74 ± 16†
Heart rate (beats/min)	70 ± 11	73 ± 13	72 ± 12	78 ± 15†

*p = NS, †p < 0.01 versus baseline, dobutamine and dipyridamole.

Follow-up rest echocardiography. Follow-up echocardiographic examination after successful coronary revascularization was available in 30 patients (Table 1). At baseline echocardiography at study entry, these 30 patients showed a total of 145 dyssynergic segments. Regional wall motion improved in time by ≥1 grade in 82 segments ("viable"), whereas in the remaining 63 ("necrotic") no improvement could be observed. Of the 82 viable segments, dobutamine and dipyridamole correctly identified 59 and 55 segments, respectively, whereas combined infra-low dose dipyridamole and low dose dobutamine stress test identified 77. Of the 63 necrotic segments, dobutamine, dipyridamole and combined dipyridamole-dobutamine correctly identified 58, 60, and 56 segments, respectively. The sensitivity of dobutamine and dipyridamole was 72% (CI 60.9% to 81.3%) and 67% (CI 55.8% to 77%, respectively, p = NS). However, with the introduction of the combined method the sensitivity markedly improved to 94% (CI 86.3% to 97.9%, $p < 0.01$ vs. dobutamine and vs. dipyridamole). The specificity of dipyridamole and dobutamine was 95% (CI 86.7% to 99%) and 92% (82.4% to 97.3%), respectively and decreased to 89% (CI 78.4% to 95.4%) for combined dipyridamole-dobutamine stress (p = NS). The accuracy of the dobutamine, dipyridamole and combined dipyridamole-dobutamine stress test in predicting the behavior of the basally dyssynergic myocardial segment after revascularization was 80%, 79% and 92%, respectively (combined dipyridamole-dobutamine = $p < 0.05$ vs. dobutamine and $p < 0.01$ vs. dipyridamole) (Fig. 2). After revascularization 22 patients had improved segmental wall motion, and in 4 of these it was correctly predicted only by the combined dipyridamole-dobutamine stress test.

Discussion

Our results are in agreement with data from previous clinical studies (8–14) showing that ventricular dysfunction of viable tissue can be improved by an inotropic stimulus with an

accuracy of ~80% in predicting functional recovery after revascularization. In addition, the present study demonstrates the feasibility, tolerability and accuracy of a combined infra-low dose dipyridamole and low dose dobutamine regimen for selective assessment of myocardial viability, as well as its superior accuracy versus that either stress separately performed for predicting functional recovery. This finding has potential pathophysiologic and clinical relevance.

Mechanism of viability recognition by dipyridamole and dobutamine. The rationale of applying combined infra-low dose dipyridamole and low dose dobutamine as an effective stimulus for myocardial viability recognition stems from two assumptions: 1) infra-low dose dipyridamole is capable of recruiting contractile reserve in an asynergic but viable segment; 2) infra-low dose dipyridamole has an at least partially independent and additive effect to low dose dobutamine in recruiting inotropic reserve in a basally dyssynergic region.

Infra-low dose dipyridamole as a test for viability. In a dog model of stunned myocardium, Jeremy et al. (27) showed that a significant improvement in percent systolic thickening in the stunned area was achieved with very low adenosine doses, and the same improvement was obtained with adenosine doses up to 100 times higher. Their observation might explain why the inotropic reserve can be recruited with a similar efficacy by low and high doses of dipyridamole (17,18) whereas the ischemic effect increases sharply with increasing doses (21).

Infra-low dose dipyridamole can recruit an inotropic reserve through two possible mechanisms: hemodynamic (linked to increased coronary flow) or metabolic (due to accumulation of endogenous adenosine). Dipyridamole may increase postischemic function by increasing flow through the Gregg phenomenon (28): Changes in vascular distension affect sarcomere length and thereby influence contractile function (29). This interpretation is consistent with experimental (30,31) and clinical (32) studies demonstrating that a residual flow reserve can be elicited in the presence of a severe coronary stenosis and depressed baseline function. In addition, studies using myocardial contrast echocardiography (33) and positron emission tomography (34) have recently shown that the presence of a residual coronary reserve after dipyridamole infusion identifies segmental viability in patients with wall motion abnormalities at rest. The second, probably more likely, mechanism does not need the increase in coronary flow as the requisite of functional improvement. In an experimental study in a dog model of stunned myocardium, Zughaib et al. (35) showed that the augmentation of endogenous adenosine attenuates myocardial stunning independently of coronary flow or hemodynamic effects. This conclusion is corroborated by the study of Ely et al. (36), who reported beneficial effects of adenosine on ischemia-reperfusion injury in isolated hearts at constant coronary flow. Several flow-independent beneficial effects of endogenous adenosine have been hypothesized (37), including blocking of slow calcium channels (with reduction of cytosolic accumulation of calcium), glycolysis stimulation and inhibition of generation of free radicals.

Additive effect of dipyridamole and dobutamine. No direct experimental data support the additive inotropic action of dipyridamole and dobutamine in viable segments. However, in theory, dipyridamole and dobutamine might have potentially synergic actions because they act on different cellular and molecular targets: $beta_1$-adrenoreceptor of the myocyte for dobutamine, adenosine A_2 receptor of the coronary arteriolar smooth muscle cell for dipyridamole. In addition, administration of high dose dipyridamole does not block the hemodynamic response and potentiates the ischemic strength of high dose dobutamine (23). Furthermore, in a swine model of chronic reduction in perfusion pressure and flow, Mills et al. (38) showed that at baseline, regional myocardial blood flow distal to the stenosis was reduced in both endocardial and epicardial layers in comparison with levels in the normal zone. Transmural flow increased a mean of 280% from baseline in response to adenosine plus phenylephrine but only ~50% in response to adenosine alone. Because the increase in flow is accompanied by an increase in function in both stunned and hibernating myocardium (6), the experimental data of Mills et al. may provide indirect support for our empirical finding that dipyridamole and dobutamine have at least partially additive effects in eliciting a contractile response in viable myocardium.

Study limitations. One limitation of our study is the use of echocardiographically documented improvement of wall motion at follow-up as the criterion for judging the accuracy of stress-induced functional improvement. We did not use an independent standard such as fluorodeoxyglucose or thallium uptake. In addition, an angiographic control study was not performed at the time of follow-up examination. Some segments that did not recover might have been perfused by

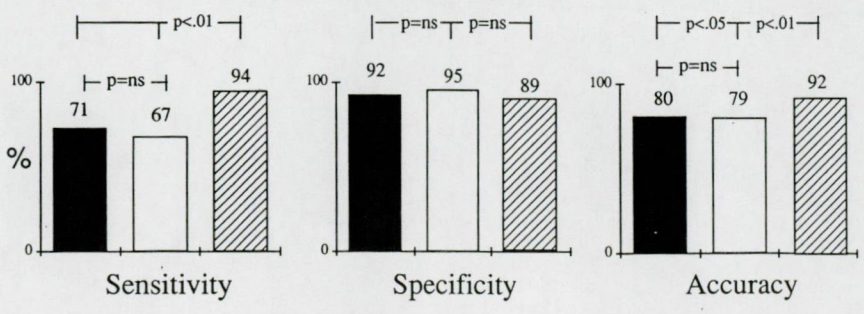


Figure 2. Bar graphs showing sensitivity, specificity and accuracy of dobutamine, dipyridamole and combined infra-low dose dipyridamole and low dose dobutamine test for myocardial viability assessment (gold standard: functional recovery). The combined dipyridamole-dobutamine test results in a significant increase in sensitivity and accuracy without a decrease in specificity compared with the results achieved with separate administration of either dipyridamole or dobutamine. **Solid bars** = dobutamine; **open bars** = dipyridamole; **hatched bars** = dipyridamole + dobutamine.

coronary arteries that had reoccluded, thereby leading to an underestimation of the test's specificity for predicting viability. Nevertheless, the specificity was excellent for dobutamine, dipyridamole and combined infra-low dose dipyridamole and low dose dobutamine, suggesting that this potential problem did not play an important role in the study patients. In addition, all patients were asymptomatic at follow-up and had negative results on functional tests of ischemia (maximal high dose pharmacologic stress echocardiography), suggesting persisting vessel patency in these patients.

The ideal pharmacologic stress for selective myocardial viability assessment should be hemodynamically neutral, with no effect on heart rate or systolic blood pressure, because manipulation of hemodynamic variables can induce variations in wall motion and thickening independently of the local inotropic effect. In addition, the test should not induce ischemia, as this may obscure the assessment of functional recovery. The combined infra-low dose dipyridamole and low dose dobutamine stress slightly deviates from this ideal profile, because it induced a significant, although mild, increase in blood pressure and induced ischemia in two patients who had tolerated well separately administered infusions of dipyridamole and dobutamine.

The study group included a substantial number of patients with only mild left ventricular impairment (average ejection fraction 43 ± 12%). With completion of the present initial feasibility study, the combined infra-low dose dipyridamole and low dose dobutamine test should be assessed in patients with severe left ventricular dysfunction, in whom the clinical question regarding the extent of viable tissue is more important. This validation is currently ongoing, on a multicenter basis, with the VIDA (Viability Identification with Dipyridamole-Dobutamine Administration) project.

Clinical implications. It is generally agreed that either stress-redistribution-reinjection or rest-redistribution thallium protocols may provide cost-effective information regarding myocardial viability in the majority of patients with chronic ischemic left ventricular dysfunction (4). More recently, pharmacologic stress echocardiography has gained increasing acceptance, because of its low cost, widespread availability and use of nonionizing energy, in spite of the recognized limitations of ultrasound technology of depending on patient's acoustic window and observer expertise (39). A more substantial limitation of stress echocardiography is the less than ideal sensitivity in predicting functional recovery after revascularization. The present study shows that combined infra-low dose dipyridamole-low dose dobutamine increases the diagnostic accuracy of low dose dobutamine stress echocardiography, providing a critical stepup in sensitivity, without loss in specificity, with potential to make pharmacologic stress echocardiography even more attractive for detection of myocardial viability.

As a potential limitation of the test, one should consider that direct drug costs, preparation time and imaging time are obviously greater with combined infra-low dose dipyridamole and low dose dobutamine than with either drug separately used. However, when compared with dobutamine alone, the imaging time is increased by only 4 min (up to a total imaging time of 10 min). The preparation time in only trivially increased because the same intravenous line is used for serial administration of dipyridamole and dobutamine. The incremental cost of adding the infra-low dose dipyridamole varies substantially in the various countries. In Italy, the drug cost of 20 mg of dipyridamole (the average low dose in a 70-kg person) is <$1 US. Altogether, the combined test seems to be a user-friendly, non-time-consuming and cost-effective option toward an efficient diagnosis of myocardial viability with pharmacologic stress echocardiography.

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Comparison of Combina ion of *Dipyridamole* and *Dobutamine* During Echocardiography With Thallium Scintigraphy to Improve Viability Detection

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The aim of this study was to investigate the relation between radioisotopic and echocardiographic markers of myocardial viability and their correlation with functional recovery after coronary revascularization. Myocardial viability can be detected by techniques exploring various aspects of cell physiology: thallium-201 scintigraphy and dobutamine and dipyridamole echocardiography focus on cell membrane integrity, β-1 and adrenoceptor, and A2-adenosine receptor-mediated inotropic response, respectively. Fifty-seven patients (mean age 60 ± 8 years) with previous myocardial infarction (>3 months), angiographically assessed coronary artery disease, and resting regional dysfunction underwent rest-redistribution 201-thallium scintigraphy and low-dose pharmacologic stress echo with dobutamine (up to 10 μg/kg/min), very low dose regimen of dipyridamole (0.28 mg/kg over 4 minutes), and combined dipyridamole-dobutamine. Criteria for viability in a 13-segment model for both techniques were percent peak activity in redistribution images >55% for thallium-201 and a decrease in wall motion score >1 grade (1 [normal] to 4 [dyskinetic]) for stress echo. Thirty patients underwent coronary revascularization (bypass surgery in 8, angioplasty in 22) and were followed up at 4 weeks from intervention with a resting echocardiogram. The rate of agreement between thallium-201 and stress echo was 63% for dipyridamole, 66% for dobutamine, and 74% for combined dipyridamole-dobutamine (p <0.05 vs dipyridamole and dobutamine). In the 30 patients who underwent revascularization, a regional resting dyssynergy was observed in 225 segments, assuming that postrevascularization functional recovery (which occurred in 126 segments) was the gold standard; combined dipyridamole-dobutamine showed a higher sensitivity (90% confidence interval [CI] 85% to 95%) than thallium-201, dobutamine, or dipyridamole (87%, CI 81% to 92%; 82%, CI 76% to 89%; and 82%, CI 76% to 89%, respectively). Specificity was lower for viability recognition with thallium-201 (61%, CI 51% to 71%) than with dobutamine (93%, CI 88% to 98%), dipyridamole (95%, CI 91% to 99%), and combined dipyridamole-dobutamine (92%; CI 87% to 97%). Combined adrenergic and adenosinergic stimulation recruits an inotropic reserve in a significant proportion of segments with preserved thallium uptake that were nonresponders after either dipyridamole or dobutamine. When functional recovery after successful revascularization is considered as the postoperative gold standard, thallium has a higher sensitivity than dipyridamole or dobutamine; this sensitivity gap is filled with combined dipyridamole-dobutamine. The specificity of all forms of pharmacologic stress echo is better than thallium-201.

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he identification of viable myocardium has been recognized as an increasingly important goal in clinical cardiology.[1] Myocardial viability can be detected by techniques exploring various aspects of cell physiology: thallium-201 scintigraphy, dobutamine echo, and dipyridamole echo focus on cell membrane integrity, β-1 adrenoceptor, and A2-adenosine receptor-mediated inotropic response, respectively.[2–4] Recently, it has been shown that infra–low-dose dipyridamole added to low-dose dobutamine recruits an inotropic reserve in asynergic segments that were nonresponders after either dobutamine or dipyridamole alone and destined to recover after revascularization.[5] The relation between the combined low-dose adenosinergic-adrenergic stress echo test, thallium uptake, and functional recovery after revascularization in patients with chronic coronary artery disease and left ventricular dysfunction remains unknown. To compare the results of various forms of low-dose pharmacologic stress echo with an independent marker of myocardial viability, we separately administered low-dose dobutamine, infra–low-dose dipyridamole, combined low-dose dipyridamole-dobutamine, and rest-redistribution thallium to 57 consecutive patients referred to the nuclear medicine laboratory for assessment of myocardial viability. In addition, the subset of 30 patients who underwent a successful revascularization procedure were reevaluated by follow-up resting echo to assess the accuracy of various imaging techniques in predicting functional recovery after revascularization.

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METHODS

Study group: The study group was chosen from consecutive patients scheduled for a thallium rest redistribution scintigraphy for the clinical assessment of myocardial viability at the CNR, Institute of Clinical Physiology in Pisa, Italy, and at the Charité Hospital, Berlin, Germany. The inclusion criteria were: (1) history of previous (>3 months) myocardial infarction; (2) angiographically assessed coronary artery disease; (3) technically satisfactory acoustic window; and (4) resting regional wall motion abnormalities of the left ventricle. The patient group comprised 57 consecutive patients (50 men and 7 women, age 60 ± 8 years); 38 patients had Q-wave and 13 non–Q-wave myocardial infarction. The site of the Q-wave infarction was anterior in 35 and inferior in 22 patients. Coronary angiography demonstrated significant stenosis (>50% diameter reduction by quantitative coronary angiography) of 1 vessel in 6 patients, of 2 vessels in 17, and of 3 vessels in 24. Average left ventricular ejection fraction calculated from the apical 4-chamber view by 2-dimensional echocardiography (single plane area-length method) was 31 ± 11%. Coronary revascularization was performed in 30 patients either with coronary artery bypass grafting (n = 8) or with percutaneous transluminal coronary angioplasty (n = 22). Follow-up echocardiogram obtained at least 4 weeks (mean 7 ± 3) after revascularization was available in all 30 revascularized patients. None of these patients had clinical, enzymatic, electrocardiographic, or echocardiographic evidence of perioperative myocardial infarction, and all were thought to have had successful revascularization, because they were asymptomatic and with full negativity of functional tests of ischemia, including maximal high-dose pharmacologic stress echo. The left ventricle was divided into 13 segments for both echocardiographic and scintigraphic data according to a model previously described in detail allowing the clinician to match information obtained with the 2 techniques.[4,6]

Baseline echocardiographic examination: Two-dimensional echocardiograms were obtained by using commercially available imaging systems with digital acquisition capabilities. Echocardiographic images were recorded on magneto-optical disk and VHS videotape for subsequent playback and analysis. In all studies, segmental wall motion was semiquantitatively graded as follows: normal = 1; hypokinetic, marked reduction of endocardial motion and thickening = 2; akinetic, virtual absence of inward motion and thickening = 3; and dyskinetic, paradoxic wall motion away from the center of the left ventricle in systole = 4. Wall motion score index was derived by dividing the sum of individual segment scores by the number of total segments (16-segment model).[7]

Pharmacologic stress echocardiography: On separate sessions and before coronary revascularization, all patients underwent low-dose dobutamine infusion (5 μg/kg/min followed by 10 μg/kg/min, each step lasting 3 minutes); infra–low-dose dipyridamole (0.28 mg/kg over 4 minutes); and infra–low-dose dipyridamole followed by low-dose dobutamine echocardiography. The detailed method has been described elsewhere.[15] A wall motion index score was derived for rest and peak stress echocardiograms in all patients, as previously described for baseline echocardiographic examination. A segment was considered to show signs of viability when it improved ≥1 grade at peak stress (e.g., a hypokinetic segment becoming normal, or an akinetic segment becoming hypokinetic). A change from dyskinetic to akinetic was not considered a criterion of myocardial viability.

Scintigraphic-echocardiographic correlation: The left ventricle was divided into 13 segments for both echocardiographic and scintigraphic analysis, according to a model previously described in detail, allowing the clinician to match information obtained with the 2 techniques.[4,6] Briefly, this model is based on an upper and lower septum for echocardiography and on a single apex for both techniques. A bull's eye plot on the 13-segment model with thallium-201 uptake was assessed in each segment using a cut-off value of 55% of the peak to define viable and necrotic segments, respectively. Assignment of the apex to a specific coronary territory was variable and based on the coronary angiogram as well as on the presence of adjacent defects. The assignment of defects to different diseased vessels has been validated elsewhere[4,6]; however, this scheme was used to represent a simple, anatomic model in which different imaging techniques may converge for transverse and longitudinal studies. To correlate thallium uptake and echocardiographic outcome in the 30 patients who underwent coronary revascularization, a viability index was derived according to the following score: segments demonstrating normal thallium uptake (>75% of peak uptake) were classified as showing "normal viability" and assigned a score of 1. Segments with a mild defect (≥55 to 75% of peak uptake) were classified as showing "mildly reduced viability" and assigned a score of 2. Segments with severe defects (<55% of peak uptake) were classified as showing "severely reduced viability" and assigned a score of 3. The viability scores were summed and divided by the total number of segments analyzed (13-segment model of the left ventricle) to yield a viability index.

Statistical analysis: Values are expressed as mean ± SD. Differences in wall motion score index under different conditions were tested for significance by analysis of variance and subgroup analysis by the Newmann-Keuls test. A p value <0.05 was considered statistically significant. Calculations of sensitivity, specificity, and accuracy were performed according to standard definitions. K statistics was used to determine agreement between techniques used. The 95% confidence intervals (CIs) were calculated for each technique, and the individual intervals were compared. Differences between techniques were considered significant at the 0.05 level when the 95% CI did not overlap.

RESULTS

Baseline echo findings: By inclusion criteria, all patients had a regional dyssynergy in the resting echo-

	+ DIP -		+ DOB -		+ DIP DOB -	
+ Thallium	195	167	212	151	260	105
-	17	118	19	115	24	108

FIGURE 1. 2 × 2 tables showing concordance between thallium rest redistribution results and pharmacologic stress echo results with dipyridamole (DIP, *left panel*), dobutamine (DOB, *middle panel*), and dipyridamole-dobutamine (DIP-DOB, *right panel*).

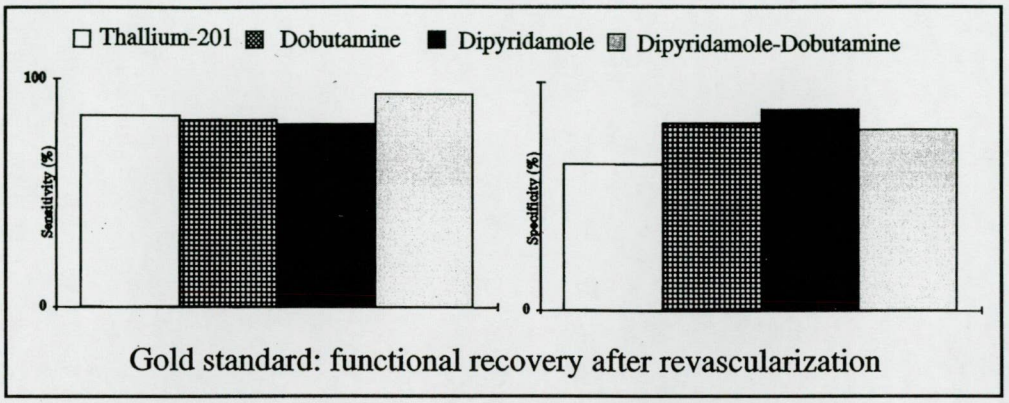

FIGURE 2. Bar graph showing sensitivity and specificity of dobutamine, dipyridamole, combined dipyridamole-dobutamine, and thallium rest redistribution test for myocardial viability assessment (gold standard: functional recovery).

cardiogram. There were 497 segments with baseline dyssynergy. Global resting wall motion score index was 1.84 ± 0.4.

Correlation between stress echocardiographic and thallium-201 scintigraphic data: In the study group evaluated preoperatively by both techniques using the 13-segment model of the left ventricle, 497 segments had resting wall motion abnormalities; of these, 363 were viable with thallium (73%), 231 with dobutamine (46%, $p < 0.001$ vs thallium), 212 with dipyridamole (43%; $p < 0.001$ vs thallium), and 284 with combined dipyridamole-dobutamine (57%, $p < 0.001$ vs thallium). The rate of agreement between thallium-201 uptake and a positive response to stress echo was 63% ($k = 0.30$; 0.21 to 0.40) for dipyridamole, 66% ($k = 0.33$; 0.23 to 0.43) for dobutamine, and 74% ($k = 0.44$; 0.33 to 0.55) for combined dipyridamole-dobutamine (Figure 1).

Follow-up study: per-segment analysis: Follow-up echocardiographic examination after successful coronary revascularization was available in 30 patients. In the 30 patients who underwent revascularization, a regional resting dyssynergy was observed in 225 segments; of these, 149 (66%) were viable with thallium, 110 (48%) with dobutamine, 108 (48%) with dipyridamole, and 122 (54%) with combined dipyridamole-dobutamine. Assuming postrevascularization functional recovery (which occurred in 126 segments) as the gold standard, combined dipyridamole-dobutamine showed a higher sensitivity (90%, CI 85% to 95%) in identifying viability than thallium-201, dobutamine, or dipyridamole (87%, CI 81% to 92%; 82%, CI 76% to 89%; 82%, CI 76% to 89%). Specificity was lower for viability recognition with thallium (61%, CI 51% to 71%) compared with dobutamine (93%, CI 88% to 98%), dipyridamole (95%, CI 91% to 99%), and combined dipyridamole-dobutamine (92%, CI 87% to 97%) (Figure 2).

Follow-up study: per-patient analysis: In the per-patient analysis, the correlation between wall motion score index at follow-up and low-dose stress echocardiography was good for both dobutamine and dipyridamole ($r = 0.83$, $p < 0.0001$ and $r = 0.81$, $p < 0.0001$, respectively), but better for combined dipyridamole-dobutamine ($r = 0.88$, $p < 0.0001$). The correlation between wall motion score index at follow-up and viability index with thallium was good ($r = 0.71$, $p < 0.0001$), but worse when compared with either dobutamine or dipyridamole alone or with combined dipyridamole and dobutamine.

DISCUSSION

In patients with chronic coronary artery disease and reduced left ventricular function, a significant proportion of segments with preserved thallium-201 uptake exhibit an inotropic response only to combined dipyridamole-dobutamine, with no contractile improvement in single infusion of dipyridamole or dobutamine. When functional recovery after successful revascularization is considered as the diagnostic gold standard thallium has a higher sensitivity than dipyridamole or dobutamine; this sensitivity gap is filled with combined stress dipyridamole-dobutamine. The

specificity of all forms of pharmacologic stress echo is significantly better than thallium.

Pathophysiologic basis of myocardial viability recognition: the "viability cascade": Thallium and low-dose pharmacologic stress echo are all capable in identifying viable myocardium, but the underlying mechanisms of this recognition are different. Thallium demonstrates the ability of the myocardium to take up a cation by an active process that takes place at the level of the cell membrane.[8] Stress echo assesses the ability of the cardiac muscle to increase its contraction in response to an inotropic stimulus, acting either directly on the myocardium through a β-1 adrenergic stimulation with dobutamine,[9] or primarily on the coronary arterioles through A2-adenosine receptor stimulation with dipyridamole.[10] These different cellular functions are not all simultaneously and equally present in viable myocardium, but are hierarchically ranked according to a sequence outlining a "viability cascade," which can be considered conceptually germane to the well-known "ischemic cascade"—by which regional flow heterogeneity consistently precedes the regional wall dysfunction during transient ischemia.[11] It is an educated guess that a preserved inotropic response to either dobutamine or dipyridamole expresses a mild degree of damage, which will allow prompt restoration of function after revascularization. In more advanced levels of damage, intracellular glycogen accumulation and myofibrillar units drop out, offering a morphologic substrate to the reduced or absent inotropic response to low-dose dobutamine infusion. Increasing levels of damage are associated with loss of response also to combined dipyridamole-dobutamine. For presumably severe levels of damage, a segment can be unresponsive to combined dipyridamole-dobutamine and still be capable to uptake a significant amount of thallium. This is likely to correspond to a more advanced form of cellular damage, by which only cellular functions strictly essential to cell survival—such as membrane integrity—are preserved.[12]

Comparison with previous studies: After the pioneering study of Pierard et al[3] in patients evaluated early after an acute myocardial infarction, several studies have documented the usefulness of dobutamine echocardiography for the recognition of viable myocardium in patients with left ventricular dysfunction and chronic coronary artery disease.[6,13–24] These studies have assessed the accuracy of this technique in predicting improvement in systolic wall thickening after revascularization, showing a good accuracy, comparable to the 83% that we found in the present study. The functional response to dipyridamole has been evaluated in few studies.[5,4,25] In particular, 2 recent studies showed an accuracy similar to dobutamine in predicting spontaneous[25,26] or revascularization-induced[5] functional recovery. The relative value of thallium uptake and contractile response to dobutamine in predicting functional recovery after revascularization has been assessed in a few studies,[13,15–24] and has been the object of a recent meta-analysis by Bax et al.[27] In this meta-analysis, thallium showed a high sensitivity (90%, comparable to the 87% that we observed in the present study) and a limited specificity (47%, comparable to the 61% that we observed in the present study). A limitation of the present results may be due to the time lag (4 weeks) between revascularization and echocardiographic follow-up: a recovery is potentially detectable also after a longer period. This may have changed the results of the diagnostic accuracy reported.

In general, it has been found that if a segment has no thallium uptake, it usually has no inotropic response, whereas the presence of thallium uptake may be associated with contractile response. When functional recovery is considered the gold standard, thallium has a superior sensitivity than dipyridamole or dobutamine alone, but a lower specificity than low-dose pharmacologic stress echo. The results of our study are fully consistent with these previous reports, although some features are unique to the present study design: (1) different forms of low-dose pharmacologic stress were used; (2) combined dipyridamole-dobutamine stress was also compared in a direct fashion with thallium; and (3) 2 separate analyses were performed, with a "horizontal" gold standard of viability represented by thallium uptake and a "longitudinal" gold standard represented by functional recovery after revascularization for all techniques.

Clinical implications: Different stresses have slightly different features, dipyridamole being the most specific and dipyridamole-dobutamine the most sensitive. Thallium is the least specific in predicting functional recovery. Although there is clearly "more myocardial viability than meets the eye,"[28] it is equally true that functional recovery is a physiologically important end point with demonstrated prognostic impact. When the prediction of functional recovery is the diagnostic end point, combined dipyridamole-dobutamine is more efficient than thallium in patients with a moderate left ventricular dysfunction.

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The prognostic value of myocardial viability recognized by low dose dipyridamole echocardiography in patients with chronic ischaemic left ventricular dysfunction

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Aims The aim of this study was to assess the prognostic value of myocardial viability recognized as a contractile response to vasodilator stimulation in patients with left ventricular dysfunction in a large scale, prospective, multicentre, observational study.

Methods and Results Three hundred and seven patients (mean age 60 ± 10 years) with angiographically proven coronary artery disease, previous (>3 months) myocardial infarction and severe left ventricular dysfunction (ejection fraction <35%; mean ejection fraction: 28 ± 7%) were enrolled in the study. Each patient underwent low dose dipyridamole echo (0·28 mg . kg^{-1} in 4 min). Myocardial viability was identified as an improvement of ≥0·20 in the wall motion score index. By selection, all patients were followed up for a median of 36 months. One-hundred and twenty-four were revascularized either by coronary artery bypass grafting (n=83) or coronary angioplasty (n=41). The only end-point analysed was cardiac death. In the revascularized group, cardiac death occurred in one of the 41 patients with and in 16 of the 83 patients without a viable myocardium (2·4% vs 19·3%, $P<0·01$). Outcome, as estimated by Kaplan–Meier survival, was better for patients with, compared to patients without, a viable myocardium, who underwent coronary revascularization (97·6 vs 77·4%, $P=0·01$). Using a Cox proportional hazards model, the presence of myocardial viability was shown to exert a protective effect on survival (chi-square 4·6, hazard ratio 0·1, 95% CI 0·01–0·8, $P<0·03$). The survival rate in medically treated patients was lower than in revascularized patients irrespective of the presence of a viable myocardium (79·7% vs 86·2, P=ns).

Conclusion In severe left ventricular ischaemic dysfunction, myocardial viability, as assessed by low dose dipyridamole echo, is associated with improved survival in revascularized patients.
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Key Words: Dipyridamole stress echocardiography, myocardial viability, prognosis, revascularization.

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Introduction

The echocardiographic hallmark of myocardial viability by pharmacological stress echocardiography is

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Table 1 Patient characteristics

	Medically treated group (n=183)	Revascularized group (n=124)	P
Sex (male/female)	154/29	100/24	ns
Age (years)	60 ± 9	60 ± 2	ns
Hypercholesterolaemia (%)	35	42	ns
Diabetes (%)	23	25	ns
Hypertension (%)	42	41	ns
Smoking habit (%)	51	62	ns
History of angina (%)	38	39	ns
History of congestive heart failure (%)	36	35	ns
Ejection fraction (%)	27 ± 7	29 ± 6	ns
WMSI at rest	2·31 ± 0·4	2·17 ± 0·34	ns
WMSI at peak dipyridamole	2·2 ± 0·4	2·01 ± 0·34	ns
Delta WMSI>0·20 (%)	21	33	
Coronary anatomy			
one-vessel disease (%)	35	23	ns
two-vessel disease (%)	37	35	ns
three-vessel disease (%)	27	43	0·05

WMSI=wall motion score index.

represented by a transient recovery in contractile function, which is present in viable, but not in necrotic tissue. Several studies have documented the ability of pharmacological stress echocardiography, either by an inotropic or by a vasodilator stimulus, to predict functional recovery in patients with left ventricular dysfunction and chronic coronary artery disease after a revascularization procedure[1–12]. Low dose dipyridamole stress echocardiography has been shown to be an effective tool in the detection of myocardial viability[13,14]. In fact, it has been demonstrated that viable segments have a recruitable coronary reserve which, in its turn, is mirrored by inotropic reserve[15]. The diagnostic accuracy of low dose dipyridamole in the detection of myocardial viability is comparable to that elicited by low dose dobutamine stress echocardiography[16,17].

Although it is clinical practice for myocardial viability to be identified by low dose pharmacological stress echo its prognostic meaning remains unclear to date. With the increasing prevalence of ischaemic heart failure, a potentially large population might benefit from intervention based on the results of testing for myocardial viability. At present, however, we are not always sure how to look for it, when to look for it, and its meaning, in terms of prognostic stratification and impact on patient management. The aim of this study was to assess the prognostic value of low dose dipyridamole echo in patients with chronic ischaemic heart disease and global severe left ventricular dysfunction in a prospective, large scale, observational, multicentre, study design. The VIDA (Viability Identification with Dipyridamole Administration) study enrolled 307 patients from 11 centres, all with established experience in stress echo and quality-controlled in stress echo reading.

Methods

Patients selection

The study population consisted of 307 consecutive patients enrolled from 1 January 1995 to 30 June 1997 in each of the participating centres and selected on the basis of the following criteria: (1) angiographically-proven coronary artery disease (>75% reduction of at least one major coronary vessel visually assessed at coronary angiography performed any time prior to study enrolment): (2) chronic ischaemic disease (no acute myocardial infarction in the preceding 3 months, in order to avoid a significant component of stunned myocardium): (3) a global severe left ventricular dysfunction (ejection fraction <35% by the single plane area–length method with 2D echocardiography); and (4) a transthoracic echocardiogram of adequate quality to assess resting regional wall motion (the echocardiogram was considered adequate if >13 out of the maximum total of 16 segments could be visualized). Follow-up information was available in all patients. Demographic characteristics of the study patients are presented in Table 1.

Of the total population of 307 patients, 124 were revascularized and 183 were medically treated. The decision to revascularize was made by the referring physician during the usual work-up of the patients, taking into consideration several variables, including clinical presentation, coronary anatomy, left ventricular function, evidence of ischaemia and documentation of viability by independent techniques such as rest–redistribution Thallium or PET. Stress echo data were collected and analysed by stress echocardiographists who were not involved in patient treatment, either

surgically or medically. Since the project was investigative and used a novel protocol for the detection of myocardial viability, the data were not considered for clinical decision making.

Resting and stress echo

After an electrocardiogram had been recorded at rest and intravenous access was secured, all patients underwent, in the same session at study entry, resting echo and stress echo during a low dose dipyridamole infusion (0·28 mg . kg^{-1} over 4 min).

Regional wall motion was assessed according to the recommendations of the American Society of Echocardiography, using a 16-segment model of the left ventricle[18]. In all studies, segmental wall motion was semiquantitatively graded as follows: normal=1; markedly hypokinetic, marked reduction of endocardial motion and thickening=2; akinetic, virtual absence of inward motion and thickening=3; and dyskinetic, paradoxical wall motion away from the centre of the left ventricle in systole=4. It was agreed a priori to ignore 'mild' or 'questionable' hypokinesia, which was graded as normal. A wall motion score index was derived by dividing the sum of individual segment scores by the number of interpretable segments[18].

A wall motion score index was derived for the rest and peak stress echocardiograms in all patients, as previously described for the baseline echocardiographic examination. A segment was considered to be viable when it improved by one grade or more at peak stress (for instance, a hypokinetic segment becoming normal, or an akinetic segment becoming hypokinetic). In order to quantify the amount of myocardium showing a contractile reserve elicited by low dose dipyridamole, myocardial viability was assessed also according to a continuous parameter defined as the delta wall motion score index expressing the difference between the rest wall motion score index and the low dose wall motion score index. This parameter provides information, not only on the presence but also on the extent of contractile reserve of the dysfunctioning myocardium[20]. Patients with a worsening regional function during dipyridamole infusion were identified as ischaemic and viable.

Echocardiographic monitoring was performed throughout the dipyridamole infusion and up to at least 5 min after the end of the infusion. Two-dimensional echocardiographic images were recorded at baseline and at the end of the dipyridamole infusion. All readings were entered into the data bank at the time of initial evaluation.

Quality control of stress echocardiographic readings

Quality control of the diagnostic performance in the different centres was of critical importance to acquire meaningful information for the data bank. In the enrolled centres, the quality control was performed based upon two criteria, each one having to be met to fulfil the quality control requirements[19,20].

For the first criterion, 20 stress echo studies were videotaped in the coordinating centre (Institute of Clinical Physiology in Pisa). In all 20 studies, the reading of two experienced independent observers was concordant as to presence and site of dyssynergy, and the stress results were in full agreement with the presence and site of coronary stenoses during coronary angiography. The unanimous reading of the two observers was arbitrarily assumed to be the 'gold standard' against which the reading of each participating centre was evaluated. The reader from each centre interpreted the videotape in a blinded fashion, with no access either to clinical and angiographic data or to the interpretation given by other observers. It was assumed a priori that the minimum threshold of concordance, to pass this part of the quality control, had to be 90%.

The second criterion consisted of random sampling of 20 consecutive studies from each contributing centre. These 20 studies were examined in a blinded fashion by an experienced cardiologist–echocardiographist from the coordinating centre — whose reading was arbitrarily assumed to be the 'gold standard'. It was assumed a priori that 80% was the minimum threshold of concordance to pass quality control. The lower concordance cut-off, in comparison with the first reading, was because this second set of tapes was not selected on the basis of superior quality but randomly sampled from each centre in a consecutive fashion.

All the 11 enrolled centres met the minimum requirements of quality control.

Follow-up data

Follow-up data were obtained from at least one of four sources: review of the patient's hospital records, personal communication with the patient's physician and review of the patient's chart, a telephone interview with the patient conducted by trained personnel, or patient visits to staff physicians at regular intervals in the outpatient clinic. The only event considered was cardiac-related death. For patients who died in hospital or at home, the cause of death was elucidated from the medical record, the family and the local physician who signed the death certificate. The definition of cardiac-related death required documentation of significant arrhythmias or cardiac arrest, or both, or death attributable to congestive heart failure or myocardial infarction in the absence of any other precipitating factors. In the case of death out of hospital, for which no autopsy was performed, sudden unexpected death was attributed to a cardiac cause. Therefore the outcome events were all causes of cardiac death for survival. Myocardial revascularization was performed either by coronary artery bypass grafting or percutaneous transluminal

angioplasty. Follow-up data were obtained in all patients.

Statistical analysis

Results are expressed as mean value ± SD. The individual effect of certain variables on event-free survival was evaluated with the use of the Cox regression model (SPSS Software, 1997). The analysis was performed according to the unmodified forward selection stepwise procedure. In this case, the variables were entered in the model on the basis of a computed significance probability; accordingly, the variable that has the most significant relationship to dependent outcome is selected first for inclusion in the model, and a solution to the functional form of the equation is computed. At the second and subsequent steps, the set of variables remaining at each point is evaluated, and the most significant is included if it improves the prediction of the outcome (dependent variable), but in this case this probability is conditional on the presence of the variable already selected. The algorithm ceases to select variables when there is no further significant improvement in the prediction of the whole model.

Variables selected for examination were: age, gender, history of angina, history of heart failure, history of myocardial infarction, hypertension, hypercholesterolaemia, diabetes mellitus, smoking habit, ejection fraction, revascularization procedures, wall motion score index at rest, rest–low dose stress wall motion score index variation (delta low dose dipyridamole wall motion score index). Continuous variables were compared by the unpaired two-sample t-test. Proportions were compared by the chi-square statistic; a Fisher's exact test was used when appropriate. Kaplan–Meier life table estimates of spontaneously occurring event-free survival were used to summarize the follow-up experience in these patients and to clarify presentation. Differences of survival curves were tested with the log-rank statistic.

Receiver–operating characteristics analysis was used to determine the 'optimal' cut-off value for the prediction of late events, with respect to the wall motion score index at rest and the number of viable segments. The best cut-off value was defined as the point with the highest sum of sensitivity and specificity.

A P value below 0·05 was considered statistically significant.

Results

Feasibility and tolerability of dipyridamole stress echocardiography

No patient had major complications during the test. The test was completed in all patients. In four patients, low dose dipyridamole was associated with an ischaemic response (worsening of regional wall motion).

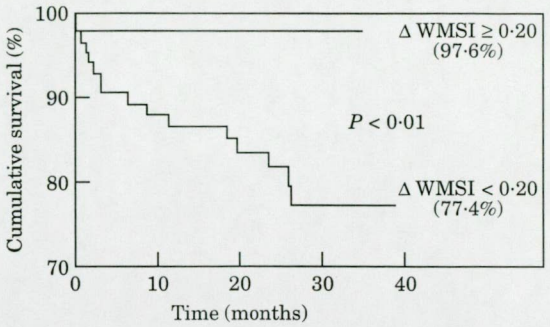

Figure 1 **Kaplan–Meier survival curves (with the endpoint as death, only) in patients undergoing coronary revascularization. Myocardial viability could be distinguished by the number of segments which had improved, using as a cut-off value the difference between the resting wall motion score index and the low dose dipyridamole wall motion score index (delta WMSI) set at 0·20. A small amount of viable myocardium is associated with a greater incidence of cardiac death (P<0·01).**

Rest and low dose findings

The resting wall motion score index was 2·25 ± 0·36. Following dipyridamole, the wall motion score index was 2·12 ± 0·39 (P<0·01 vs rest wall motion score index). Seventy-seven patients (25% of the total population) had a delta low dose wall motion score index higher than or equal to 0·20, with an inotropic response to low dose dipyridamole in at least four segments on resting dysfunction. In the revascularized group (n = 124) viability was present in 41 (33%) patients.

Follow-up data: cardiac-related death

Patients were followed-up for a median of 36 months (range:1–39). During the follow-up, there were 54 cardiac deaths. In the revascularized group, cardiac death occurred in one of the 41 patients with and in 16 of the 83 patients without a viable myocardium (2·4% vs 19·3%, P<0·01). Kaplan–Meier survival estimates showed a better outcome for patients with, compared to patients without, a viable myocardium who underwent coronary revascularization (97·6 vs 77·4%, P=0·01). In Fig. 1, the cumulative survival rates in patients with a high grade of myocardial viability (delta wall motion score index ≥0·20) vs those with a low grade or no viability (delta wall motion score index <0·20) are shown. At the univariate analysis, in the revascularized group, myocardial viability was the only significant variable. In the stepwise analysis, the only independent predictor was the presence of myocardial viability exerting a protective effect on survival (chi-square 4·6, hazard ratio 0·1; 95% CI 0·01–0·8, P<0·03) (Table 2). The sensitivity and specificity of the test for the prediction of death at the cut-off value of 0·20 was 94% and 38%,

Table 2 Stepwise predictors of cardiac death in revascularized patients

	Chi-square	HR	95% CI	*P*
Delta WMSI	4·6	0·1	0·1–0·8	0·03

WMSI=wall motion score index; HR=hazard ratio.

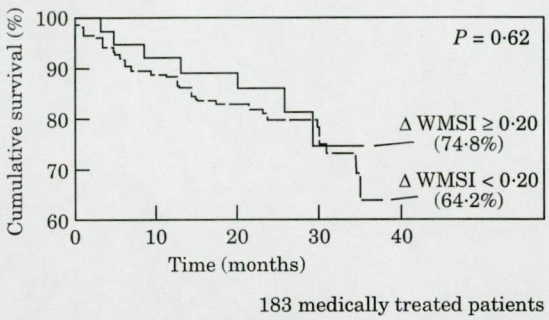

Figure 2 **Kaplan–Meier survival curves (with the endpoint as death, only) in medically treated patients. Myocardial viability could be distinguished by the number of segments which had improved, using as a cut-off value the difference between the resting wall motion score index and the low dose dipyridamole wall motion score index (delta WMSI) set at 0·20. The presence of viable myocardium is not related to better survival (*P*=ns).**

respectively. In the 183 who were medically treated, the incidence of cardiac death was similar in patients with and without a viable myocardium (17% vs 21%, *P*=ns) (Fig. 2). In the medically treated group, the sensitivity and specificity of the test for the prediction of death at the cut-off value of 0·20 was 80% and 20%, respectively. The survival rate in medically treated patients was lower than in revascularized patients irrespective of the presence of a viable myocardium (79·7% vs 86·2, *P*=ns).

Discussion

In patients with severe left ventricular dysfunction undergoing coronary revascularization, the presence and extent of myocardial viability identified by low dose dipyridamole is associated with a higher probability of survival. The extent of myocardial viability is related to better survival when a high number of segments transiently improve their function with low dose stress echocardiography. In the present population, no other clinical variable and/or resting echo parameter was able to predict the outcome. When coronary revascularization was undertaken in the absence, or with a small area of viable myocardium, the procedure was linked to a higher incidence of cardiac death.

Comparison with previous studies

The rapidly growing literature on the prognostic value of myocardial viability suggests that patients with global left ventricular dysfunction and extensive viability treated with revascularization are more likely to survive than medically treated patients[21–28]. A protective effect has been documented when myocardial viability is recognized with either nuclear medicine[21–26] or stress echo techniques[27,28]. The main finding of the present study, i.e. the striking protective effect of myocardial viability on survival of revascularized patients, is in keeping with the available evidence. Some peculiarities of the present study should, however, be considered: (1) the sample size of 307 patients, which is one of the largest populations studied to date; (2) the strict enrolment criteria, allowing only patients with documented coronary artery disease to be included, rather than patients with unknown coronary anatomy or idiopathic cardiomyopathy, as in other series[22]; (3) the inclusion of patients studied >3 months after a myocardial infarction, thus excluding patients with a significant stunning phenomena linked to recent myocardial infarction; (4) the use of an ischaemic stressor alternative to dobutamine, such as dipyridamole, allowing myocardial viability to be studied through a pharmacological tool totally unrelated to beta-adrenoreceptor myocyte density rather than to adenosine accumulation[14]; (5) finally, the study design — prospective multicentre, with peripheral readings from quality control centres — allowed the 'effectiveness' of the prospective value of low dose stress echocardiography to be assessed.

Improved survival in revascularized patients: the pathophysiological rationale

Our patients, with severe resting dysfunction submitted to revascularization, had a clearly better survival when a significant amount of viable myocardium could be detected before revascularization by low dose pharmacological stress echo. In our study, low dose functional recovery translates into a survival benefit for revascularized patients — all of whom had depressed left ventricular function at study entry. The relationship between the risk of cardiac death and the reduction in ventricular function shows a hyperbolic trend[29]: our patient population was located in the steep segment of the curve, where it is possible that an improvement in regional function obtained with a revascularization procedure is likely to translate into a dramatic improvement of prognosis. The high surgical risk in this population is outweighed by a long-term improvement of survival when a large amount of dysfunctional but viable myocardium is present. The absence of viable myocardium downstream of a critical coronary artery stenosis substantially weakens the indication for revascularization and directs clinical decisions towards medical therapy or — when possible — cardiac transplantation.

Study limitations

The patient population underwent coronary revascularization on the basis of standard clinical criteria and

independent of the stress echo result. Patients were not allocated to a treatment in a randomized fashion but according to the clinical judgement of the referring physician; nonetheless there were no significant differences among the study groups relative to global ventricular function, medical treatment and coronary anatomy. The study design was observational, and did not interfere with patient management. The information on myocardial viability recognized by low dose stress echocardiography was not considered in the decision to revascularize, since at the time of data acquisition, physicians ignored the meaning of this parameter in terms of potential benefit at long-term follow-up. There is now an emerging body of literature that suggests that patients who are revascularized have a better prognosis, but the evidence was not as firm and universally accepted at the time of data collection as today.

The decision to revascularize a patient is complex and multifactorial, taking into account many different variables, including clinical presentation, coronary anatomy, left ventricular function, evidence of ischaemia, and documentation of viability by several different independent techniques. In addition, local access to invasive procedures can vary widely. Even when all these variables were kept constant — in the very same centre — there was vast room for opinion, intuition and bias. We used a vasodilator stressor for the detection of myocardial viability, dipyridamole, a less conventional stressor for the detection of myocardial viability than dobutamine, but with some advantages over it: first, the infra-low dose used in the present study is hardly an ischaemic dosage; in fact only four patients out of 307 developed myocardial ischaemia; second, the infra-low dose is not influenced by beta-blocking treatment (23% in our patient population)[30], widely employed today in patients with global ventricular dysfunction and coronary artery disease.

We used a cut-off value for the detection of myocardial viability, translating a continuous variable into a dichotomous one; a 0·20 value corresponds on average to four segments showing viability, which is equivalent to 25% of the ventricle.

Clinical implications

Patients with chronic coronary artery disease and severe left ventricular dysfunction represent a common, and increasingly frequent, problem in modern cardiological practice. The documentation of an extensive inotropic response by low dose dipyridamole stress echo in these patients carries important diagnostic, prognostic and therapeutic indications. From the diagnostic viewpoint, the inotropic response identifies myocardial viability and a high likelihood of recovery upon revascularization. From the prognostic viewpoint, an important inotropic response is associated with a substantially better survival with revascularization therapy, and with a trend to better survival with medical therapy. From the therapeutic viewpoint, the greater the amount of viable myocardium detected, the tighter the indication to revascularize these patients. More viability means lower acute risk and better long-term survival following revascularization. On the basis of the present results and consistent with nuclear medicine findings, the prognostic protection conferred by viability is only detected when it exceeds a critical threshold of at least four segments with resting dysfunction[24,31].

In striking contrast with the beneficial value shown in revascularized patients, a dipyridamole-induced contractile response lacked prognostic prediction in patients who were not revascularized. This result might appear to conflict with the potentially substantial protective effect of myocardial viability, as already demonstrated in patients evaluated early after an acute myocardial infarction[20,21]. Nonetheless the meaning of myocardial viability in medically treated patients with severe chronic left ventricular dysfunction and coronary artery disease is controversial and the large body of evidence present in the literature has not provided sound and consistent results up to now[32]. The real prognostic meaning of myocardial viability in medically treated patients with coronary artery disease remains uncertain to date, with some studies representing a detrimental, others a neutral, and still others a beneficial effect on survival[23,25–26,32–36]. In a preliminary report of the VIDA study — subproject dobutamine stress echo study[37], 204 medically treated patients with chronic ischaemic left ventricular dysfunction, had a better survival in the presence of a large area of viable myocardium (Δ wall motion score index $\geq 0{\cdot}18$) compared to those with a small area or no myocardial viability (Δ wall motion score index $<0{\cdot}18$) (70·8% vs 53·9%, $P<0{\cdot}02$). It is also possible that, due to the non-randomized nature of the study, some form of referral bias was unavoidable leading to the exclusion from revascularization of 'sicker' patients with viable myocardium.

The consequences of these clinical implications are far-reaching. Low dose dipyridamole stress echo should allow removal of some patients (those with severe left ventricular dysfunction and evidence of myocardial viability) from the cardiac transplant list, reorienting some of them towards the more accessible and less expensive coronary revascularization. Therefore, in the clinical framework of ischaemic cardiomyopathy, myocardial viability has to be taken into consideration along with the conventional clinical variables such as coronary anatomy, ejection fraction and inducible ischaemia to orient the treatment of the patients with left ventricular dysfunction. The presence of myocardial viability can guide the clinical cardiologist, but only when a considerable amount of it is detectable. In fact, similar to ischaemia, a viable response can be titrated: it is not a binary, dichotomous answer but a continuous response that should be titrated in different shades of gray.

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