Enoximone Echocardiography for Predicting Recovery of Left Ventricular Dysfunction After Revascularization

A Novel Test for Detecting Myocardial Viability

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Background—The possibility that enoximone, a nonglycoside, noncatechol, positive inotropic agent, in combination with 2-dimensional echocardiography may predict recovery of myocardial dysfunction after revascularization has not been yet evaluated.

Methods and Results—Forty-five patients with chronic coronary artery disease and left ventricular dysfunction underwent dobutamine (DE, 5 to 10 μg · kg⁻¹ · min⁻¹) and enoximone (EE, 1.5 mg/kg, over 10 minutes) echocardiography. Myocardial wall motion was scored from 1 (normal) to 4 (dyskinesia): an asynergic segment was considered to have contractile enhancement when the score decreased by ≥1 grade. Of 478 asynergic segments, 216 (45%) exhibited functional recovery after revascularization. Dobutamine- and enoximone-induced contractile enhancement was observed in 41% and 46% of segments, respectively. Compared with DE, EE had higher sensitivity (88% versus 79%, P<0.01) and negative predictive value (90% versus 84%, P<0.05) in predicting functional recovery. The specificity (89% versus 90%) and positive predictive value (87% for both EE and DE) were similar. Concordant interpretation of EE and DE findings was found in 85% (406 of 478) of affected segments. Prerevascularization coronary angiography showed that stenosis severity of vessels supplying areas which only improved with enoximone was significantly greater (89.9%) than that of vessels (77.7%) supplying areas that responded to both agents (P<0.02). Both dobutamine and enoximone increased heart rate (16% and 10%, respectively), whereas enoximone did not cause changes in systolic blood pressure that increased by 14% with dobutamine.

Conclusions—Enoximone echocardiography provides a novel and reliable approach for the prediction of functional recovery after revascularization. Compared with dobutamine echocardiography, the test yields higher sensitivity and induces lesser hemodynamic alterations. (Circulation. 2000;101:1255-1260.)

Key Words: echocardiography • dobutamine • enoximone • myocardial viability

The potential reversibility of chronic ischemic myocardial dysfunction is now well established, but the question remains about which tools available to most clinical centers are both reliable and cost effective.¹² Positron emission tomography imaging of myocardial glucose utilization is a sensitive and accurate modality for identifying myocardial viability,³,⁴ but the technique is time-consuming, expensive, and only available to a few clinical centers. Thallium-201 single-photon emission computed tomography yields the highest sensitivity for detecting viability and is cost-effective and widely available for clinical use.¹³ However, this technique may lack specificity and overestimate the probability of functional recovery.⁶⁻⁸ More recently, the presence of contractile reserve as shown by improved function during dobutamine infusion has been proposed as a more suitable alternative.⁹⁻¹¹ However, the inotropic response to adrenergic stimulation is attenuated in patients receiving β-adrenoceptor blockers. Furthermore, in the presence of critical coronary stenosis, dobutamine, even at low doses, can sometimes induce ischemia that might mask a hibernating state by preventing the improvement of wall motion.¹²⁻¹⁴

Enoximone, a nonglycoside, noncatechol, positive inotropic agent that acts via selective inhibition of the cyclic adenosine monophosphate-specific phosphodiesterase, is widely used for the treatment of heart failure. This agent has also been shown not to increase myocardial oxygen demand¹⁵⁻¹⁸ and could represent a valid alternative for the detection of viable myocardium by means of 2-dimensional echocardiography.

The aim of the present study was to evaluate the sensitivity, specificity, tolerability, and safety of enoximone echocardiography (EE) for predicting functional recovery after revas-
cularization. The optimal infusion modalities were also investigated and the results compared with those obtained with dobutamine echocardiography (DE).

Methods

Study Population
We selected patients with chronic coronary artery disease and left ventricular dysfunction elected to percutaneous or surgical myocardial revascularization. Inclusion criteria were an ejection fraction of \( \leq 45\% \) on contrast ventriculography, the presence of 2 or more akinetic or hypokinetic segments on resting echocardiography, the absence of recent episodes of unstable angina, and the absence of hemodynamically significant valvular disease.

Forty-five patients (41 males) constituted the final study population: their mean age was 59±10 years (range 35 to 75 years) and mean angiographic left ventricular ejection fraction was 36\% (range 18\% to 45\%). One-vessel disease, defined as diameter stenosis of at least 50\%, was present in 12 patients; 13 patients had 2-vessel disease; and 20 had 3-vessel disease. Twenty-nine patients had a previous myocardial infarction (9.7±8.6 months before the study). In 19 patients, all medications were discontinued \( \geq 48 \) hours before the echocardiographic study; the other 26 patients were examined while still receiving antiischemic therapy, but \( \beta \)-adrenergic blocking agents were withdrawn at least \( 48 \) hours before the study. Percutaneous transluminal coronary angioplasty was performed in 21 patients and 24 underwent coronary artery bypass grafting.

Echocardiographic Protocol
Each patient underwent DE or EE within 1 week before revascularization. The test sequence varied, but normally DE was performed before EE in a separate session (\( >4 \) hours). All patients gave written informed consent.

DE was performed using a low-dose protocol. Echocardiographic imaging was performed at baseline and during intravenous infusion of dobutamine (5 to 10 \( \mu \)g \( \cdot \) kg\(^{-1} \) \( \cdot \) min\(^{-1} \)). Each step lasted 5 minutes. EE was performed using a dose of 1.5 mg/kg. Enoximone, diluted with saline to a concentration of 2.5 mg/ml, was infused over 10 minutes. The maximum infusion rate did not exceed 12.5 mg/min in order to avoid venous burning sensation. Echo images were recorded soon after the infusion.

During both DE and EE study, echo images were obtained from the standard parasternal long-axis and short-axis views as well as from the apical 4- and 2-chamber views; 12-lead ECG was monitored continuously and recorded on paper every 2 minutes. Blood pressure was measured with a cuff sphygmomanometer at 5-minute intervals.

In order to choose the optimal dose of enoximone, echo images, ECG, and blood pressure were also recorded at the end of 0.5-mg and 1.0-mg injections for the initial 12 patients.

All studies were performed with a Hewlett-Packard Sonos 2500 ultrasound system equipped with a 2.5/2.0 MHz transducer. Images were digitized from 4 views, using a commercially available stress program (Hewlett-Packard Sonos 2500 ultrasound system). The generated cine loops were stored on a HP Rewritable Optical Disk for later review.

Echocardiographic Image Processing and Analysis
The images were interpreted by 2 investigators. In case of disagreement, a third experienced cardiologist was consulted and a majority decision was taken. The left ventricle was divided into 16 segments according to the recommendations of the American Society of Echocardiography. For each segment, systolic wall motion and thickening was visually graded with a semiquantitative 4-grade scoring system (normal or hyperkinetic, 1; hypokinesia, 2; akinesis, 3; and dyskinesia, 4). Because both normal and hyperkinetic segments are given a score of 1, dobutamine or enoximone-induced hyperkinesis in normal segments cannot improve the wall motion score. Conversely, in hypo- or akinetic segment, a decreased score \( \geq 1 \) grade reflects improved regional left ventricular function (eg, a hypokinetic segment becoming normal or an akinetic segment becoming hypokinetic). Deterioration in regional wall motion was considered to be due to myocardial ischemia when the wall motion score increased by one grade or more; however, akinesis becoming dyskinesia was not considered a sufficient criterion for the occurrence of ischemia, as this alteration can be due to passive stretching.\(^{19} \) In our center, intra- and interobserver variabilities in the interpretation of regional function are 7.1\% and 4.2\%, respectively.\(^{20} \)

Echocardiographic Follow-Up
After revascularization (mean 3.2±0.4 months), regional wall motion was assessed by 2 experienced echocardiographers who had no knowledge of the results of the stress echocardiography. Segmental wall motion was considered to have improved after revascularization when endocardial excursion and wall thickening (score 1 or 2) were observed in areas that were akinetic or dyskinetic (score 3 or 4) at baseline, or when contractility normalized (score 1) in areas of reduced endocardial excursion and wall thickening (score 2).

Assignment of Myocardial Regions in Relation to Revascularized Vessels
Coronary angiograms and bypass surgery reports were reviewed for coronary anatomy and location of revascularization. Basal and midanteroseptal, basal and midanterial free wall, and 2 anteroapical segments were considered as the distribution territory of the left anterior descending coronary artery and its side branches; basal, midlateral, and midposterior segments were designated as the distribution territory of the left circumflex artery; finally, the basal and midinferior wall and basal and midposterior septum were assigned to the right coronary artery perfusion bed. Three additional segments were assigned to overlapping regions: left anterior descending/circumflex for the apicalateral region, left anterior descending/right coronary for the interoapical region, and right coronary/circumflex for the posterobasal region. The overlapping perfusion territories varied depending on the type of coronary distribution.

Statistical Analysis
Sensitivity, specificity, and positive and negative predictive value were calculated in the usual fashion. Differences between the results of DE and EE were evaluated using the \( \chi^2 \) test; a Fisher’s exact test was used when appropriate. Continuous variables were expressed as mean±SD and compared by a paired \( t \) test. We used the segment as the unit of analysis for assessing concordance between DE and EE because Sawada et al\(^{21} \) showed that a segment by segment analysis was appropriate in the absence of any consistent intrapatient correlation of the segment data. \( P \leq 0.05 \) was considered statistically significant.

Results

Preintervention Echocardiographic Findings
From a total of 720 left ventricular segments, 230 were classified as akinetic (8 segments were dyskinetic) and 286 as hypokinetic. Seventeen akinetic segments were excluded from the postintervention evaluation because of aneurysmectomy (\( n=10 \)) or because they were not grafted or the vessel responsible for their perfusion had not been dilated (\( n=7 \)). Of the 286 hypokinetic segments, 21 were excluded from the postintervention evaluation because of aneurysmectomy (\( n=6 \)) or because revascularization had not been successful (\( n=15 \)).

Dobutamine Versus Enoximone: Hemodynamic Responses and Side Effects
The hemodynamic response to dobutamine and enoximone is shown in Figure 1. With dobutamine, there was a significant increase in systolic blood pressure (14\%) and heart rate
(16%), whereas with enoximone, systolic blood pressure showed no change and heart rate increased to a lesser extent (10%).

No significant adverse effects nor chest pain or ECG and echocardiographic ischemic changes occurred during or after administration of enoximone. By contrast, dobutamine caused transient ischemia in 4 patients (chest pain, 2 of them associated with diagnostic ST-segment depression). Ventricular premature beats (Lown class 1 to 2) were observed in 8 patients with dobutamine and in 4 patients during enoximone. Five patients had vein pain during enoximone infusion and in 2 of them, enoximone had to be temporally washed out by physiological saline.

**Dobutamine Versus Enoximone: Contractile Responses**

The contractile response to dobutamine and enoximone, along with functional recovery after revascularization are summarized in Figure 2. Of 213 akinetic segments that could be successfully revascularized, 65 and 71 (41 patients) segments showed improved wall motion during DE and EE, respectively (31% versus 33%, *P*=NS). Wall motion improved during the infusion of dobutamine and enoximone in 131 and 148, respectively, of the 265 successfully revascularized hypokinetic segments (42 patients; 49% and 56%, *P*=NS). Thus, viability was detected more frequently in hypokinetic than in akinetic segments (*P*<0.01) with both DE and EE. The wall motion score index was 2.07±0.32 at rest and improved significantly with dobutamine (1.78±0.34, *P*<0.01 vs baseline).

**Follow-Up Clinical Data and Rest Echocardiography**

Three months after revascularization, no patients had angina and 9 still complained of dyspnea on effort (NYHA, class II). Follow-up coronary angiography was performed in 29 patients (20 had percutaneous angioplasty and 9 had bypass surgery), of whom 4 had restenosis and were excluded from the study. Of 20 patients not undergoing follow-up coronary angiography, 11 had a negative exercise ECG test, 3 had negative results both on rest/stress myocardial scintigraphy and on exercise ECG test, and 6 had a negative stress echocardiogram.

Resting echocardiograms 3 months after revascularization revealed improved wall motion in 216 (45%) of the 478 dyssynergic segments (Figure 2). The improvement was found in 75 (35%) of the 213 akinetic segments and in 141 (53%) of the 265 hypokinetic segments (*P*=0.01).

**DE Versus EE: Prediction of Functional Recovery**

The Table shows the sensitivity, specificity, accuracy, and positive and negative predictive value of DE and EE for predicting functional recovery after revascularization.

Postrevascularization improvement occurred in 170 of 196 (87%) and 190 of 219 (87%) segments that responded during DE and EE, respectively. Of 282 and 259 segments that had no response to dobutamine and enoximone, respectively, only 46 (16%) and 26 (10%) segments showed functional recovery at follow-up. Thus, the positive predictive value was the same (87%) for EE and DE. However, EE had a significant greater negative predictive value than DE (90% versus 84%, *P*<0.05). Similarly, there were no significant differences in specificity between the 2 methods (89% versus 90%). However, the sensitivity of EE (88%) was significantly higher than that of DE (79%, *P*<0.01).

**Effects of Enoximone Dose (in 12 Patients)**

The effects of enoximone on heart rate increased in a dose-related fashion. Neither systolic nor diastolic pressure were affected by increasing the enoximone dose (Figure 3).

Contractile responses during enoximone were strongly dose-dependent. The lowest dose of 0.5 mg/kg induced wall motion improvement in only 25% of dyssynergic segments, whereas 1.0 mg/kg and 1.5 mg/kg of enoximone resulted in contractile enhancement in 43% (*P*<0.01, versus 0.5 mg/kg) and 54% (*P*<0.01, versus both 0.5 and 1.0 mg/kg) of the 282 segments that were affected by increasing the enoximone dose (Figure 3). The effects of enoximone on heart rate increased in a dose-related fashion. Neither systolic nor diastolic pressure were affected by increasing the enoximone dose (Figure 3).

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dyssynergic segments, respectively. Sensitivity increased in a dose-dependent fashion: 45% for 0.5 mg/kg, 70% for 1.0 mg/kg, and 87% for 1.5 mg/kg, respectively (P<0.001 for all interdose differences). Accordingly, specificity was highest with 0.5 mg/kg (98%) and progressively decreased with 1.0 mg/kg (92%) and 1.5 mg/kg (88%) (Figure 4).

Concordant Interpretation of DE and EE
Of a total of 478 involved segments, 167 (35%) showed improvement and 239 (50%) were unchanged during both DE and EE. Thus, the global interpretation of echo imaging for predicting functional recovery by DE and EE was concordant in 406 (85%) of affected segments (Figure 5). Among the 72 (15%) segments with discordant assessment by the 2 techniques, 22 improved with DE and remained unchanged with EE; conversely, 50 segments were considered viable by EE and necrotic by DE (21 segments in anterior, 19 in lateral, 5 in posterior, and 5 in inferior wall). These 50 segments were present in 15 patients, with a mean 3.3 segments per patient (2 patients had 2 segments, 8 patients had 3, 3 patients had 4, and 2 patients had 5 segments). Fourteen of these 15 patients had multiple vessel disease (4 had 2- and 10 had 3- vessel disease). Stenosis severity of vessels supplying areas which only improved with enoximone was significantly greater (89.9±7.7%) than that of vessels (77.7±17.5%) supplying areas that responded to both agents (P<0.02). The overall concordance of the 2 methods was also high, both in functionally recovered (88%) and in unchanged segments (83%).

Discussion
The present study demonstrates the feasibility, tolerability, and accuracy of enoximone as a stressor for the echocardiographic assessment of myocardial viability, as well as its superior sensitivity to dobutamine for predicting functional recovery. Our findings have potential pathophysiological and clinical relevance.

Mechanism of Viability: Recognition by Enoximone
The effects of enoximone are mediated by inhibition of phosphodiesterase III, which continuously degrades intracellular cAMP. Intracellular increase in cAMP enhances the entry of calcium into cells by activating membrane-bound calcium channels, therefore augmenting inotropic state. In patients with congestive heart failure, including those with coronary artery disease, enoximone has been shown to be extremely safe over a wide range of doses (0.25 to 3.0 mg/kg). Experimental and clinical studies have shown that enoximone exerts a positive inotropic effect, not accompanied by a significant increase in myocardial oxygen consumption. Additionally, the action of enoximone is not influenced by α- or β-adrenergic blockade or by catecholamine depletion that may occur in severe heart failure and can attenuate the response to dobutamine. Therefore, enoximone in combination with 2-dimensional echocardiography appears particularly suitable for the identification of viable myocardium.

EE Versus DE
Besides similar specificity and positive predictive value, EE showed better sensitivity and negative predictive value than dobutamine. This may be due to the different cardiovascular properties of the 2 agents. When viable myocardium is supplied by critically stenotic coronary arteries, some asynergic but viable segments may show no improvement even at low-dose dobutamine infusion. In our study, dobutamine infusion caused heart rate and systolic blood pressure to increase significantly and induced severe ischemia in 4 patients. This confirms that dobutamine, even in relatively low doses, can sometimes precipitate transient myocardial ischemia in patients with severe coronary disease. Our results agree with those of Afridi et al, who showed that most segments deteriorate during dobutamine infusion at doses ≥20 μg · kg⁻¹ · min⁻¹, but worsening of wall motion can also be observed in some patients with doses as low as 7.5 μg · kg⁻¹ · min⁻¹. Therefore, the possibility that DE may underestimate myocardial viability has to be considered.

Unlike dobutamine, enoximone caused a lesser increase in heart rate, did not induce any change in systolic blood pressure, and was associated with a lesser increase in blood pressure. Thus, enoximone appears to be a better stressor for the identification of viable myocardium.
pressure, and did not precipitate transient acute ischemia. We found that the vessels supplying the segments that showed viability by enoximone alone had significantly more severe stenosis than those supplying segments with a positive response to both stresses (90% versus 78%, \( P < 0.02 \)). This finding confirms that the superior sensitivity of enoximone in detecting viability probably relates to the lesser increase in myocardial oxygen consumption. Therefore, in the setting of restricted blood flow, enoximone may avoid the development of superimposed ischemia, which may sometimes occur with dobutamine\(^{12-14}\) and mask a hibernating state by concealing the improvement of wall motion. Furthermore, these segments considered viable by EE and necrotic by DE were present in 33% of study patients, most of them showing \( \geq 3 \) segments defined as viable by EE only. This figure is also in line with currently used criterion for definition of contractile reserve (presence of improved wall thickening or movement in at least 2 abnormal segments).\(^9,14,32\) Accordingly, on a per-patient as well as on a per-segment basis, EE may substantially have a sensitivity superior to DE.

In agreement with previous findings,\(^6,7,11,32\) the contractile response to inotropic stimulation was related to the degree of baseline dysfunction: more hypokinetic than akinetic segments manifested contractile enhancement during both dobutamine and enoximone stimulation. A previous study\(^33\) showed that viable hypokinetic segments retaining contractile reserve show minimal fibrosis on transmural myocardial biopsies, whereas akinetic segments lacking contractile reserve only contain islets of viable myocytes surrounded by extensive fibrosis.

### Optimal Dose of EE Test

In agreement with previous studies,\(^26,31\) we found that the inotropic response to enoximone is strongly dose-dependent. Only 25% of dyssynergic segments improved contractility at the dose of 0.5 mg/kg but the contractile response increased progressively with increasing doses. Accordingly, the sensitivity for predicting functional recovery was only 45% for 0.5 mg/kg and increased to 70% and 87%, respectively, for 1 and 1.5 mg/kg. Importantly, increasing the dose did not reduce specificity, yielding an acceptable diagnostic accuracy.

Previous studies\(^26,31\) have shown that enoximone improves cardiac performance without significantly affecting blood pressure and heart rate. Indeed, in our study both systolic and diastolic pressure remained unaffected at any of the doses we used. However, the effects of enoximone on heart rate were dose-related, and significant increases occurred with high doses (Figure 4). The discrepancy between our observation and those reported in the literature may depend on different administration schedules: to reach the target dose, we used shorter injection times (10 minutes) than previously reported in clinical studies.\(^26,31\)

### Limitations of the Study

Follow-up angiography was not performed in all patients. Thus reocclusion, or restenosis entailing reduction of resting blood flow and leading to underestimation of the tests’ specificity, cannot be definitively excluded. Nevertheless, the specificity was excellent for both DE and EE, suggesting that this potential problem did not play any relevant role in our patients. In addition, all patients who had no follow-up angiography remained asymptomatic and had negative results on functional stress tests, suggesting persisting vessel patency.

We used only low-dose dobutamine infusion at 5 and 10 \( \mu g \cdot kg^{-1} \cdot min^{-1} \) for detection of contractile reserve. Although this represents the first\(^1\) and the most frequently used protocol,\(^6,7,10,11,32\) other investigators have demonstrated the usefulness of higher doses for optimal evaluation.\(^8,14\)

Therefore, the possibility that the dobutamine protocol we used could have resulted in a somewhat lower diagnostic accuracy cannot be completely ruled out.

### Clinical Implications

Although pharmacological stress echocardiography has gained increased acceptance for the detection of myocardial viability, a substantial limitation of stress echocardiography is its less-than-ideal sensitivity. The present study shows that enoximone in combination with 2-dimensional echocardiography yields a better sensitivity than DE, without loss in specificity. Furthermore, enoximone induces lesser hemodynamic alterations and provides the potential for a new and attractive approach for the detection of myocardial viability. Importantly, the superior sensitivity of enoximone for predicting functional recovery is based on its ability of inotropic stimulation without increasing myocardial oxygen consumption. The latter feature makes enoximone more appealing than dobutamine in patients with critical stenosis and ischemic left ventricular dysfunction, in whom the presence and extent of residual viable tissue is sought. Besides the practical advantage related to its easier administration, EE can also be performed in patients receiving \( \beta \)-adrenoceptor blockers without the need to withdraw the medication, as is the case when dobutamine is used.

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