Dipyridamole Echocardiography Test
A New Tool for Detecting Jeopardized Myocardium
After Thrombolytic Therapy
Leonardo Bolognese, MD; Gianni Sarasso, MD; Angelo S. Bongo, MD; Lidia Rossi, MD;
Donatella Aralda, MD; Cristina Piccinino, MD; and Paolo Rossi, MD

Background. We wished to assess whether dipyridamole echocardiography test (DET) can
detect jeopardized myocardium after thrombolytic therapy.

Methods and Results. Seventy-six consecutive patients with a first acute myocardial infarction
(AMI) were treated with 2 million IU urokinase i.v. within 4 hours of the onset of AMI and
underwent high-dose (as much as 0.84 mg/kg over 10 minutes) DET 8–10 days after AMI. The
results were correlated to the anatomy of the infarct-related vessel (IRV). In patients with
positive DET, we evaluated the wall motion score index (WMSI; a semiquantitative integrated
estimation of extent and severity of the stress-induced dyssynergy). WMSI was derived by
summation of individual segment scores divided by the number of interpreted segments. In a
13-segment model, each segment was assigned a score ranging from 1 (normal) to 4
dyskinetic). Fifty-three patients had positive results on DET. Of these, 42 had dipyridamole-
induced new wall motion abnormalities (WMAs) confined to the infarct zone or adjacent
segments. In these patients, mean WMSI increased from 1.46±0.26 (at resting conditions) to
1.73±0.35 (at peak dipyridamole) (p<0.01), whereas no significant change was detected in
negative patients (1.6±0.34 versus 1.57±0.34, p=NS). Coronary angiography showed a patent
IRV (TIMI grade 2 or 3) in 53 patients and no or minimal reperfusion (TIMI grade 0 or 1) in
23 patients. A patent IRV with critical residual stenosis was found in 35 of 42 patients with
dipyridamole-induced WMAs in the infarct zone and in 18 of 34 patients without WMAs
(p<0.05). Among the 23 patients with occluded IRVs, nine had collateral flow to the distal
vessel; six of these had a positive DET. Thus, the sensitivity and specificity for identifying a
critically stenotic but patent IRV or the presence of a collateral-dependent zone were 66% and
93%, respectively. In a subset of nine patients with a positive DET in the infarct zone or
adjacent segments, DET and a control coronary angiography were repeated 1–3 months after
an angiographically successful (residual stenosis, 50% or less) coronary angioplasty in the IRV.
The repeat DET was negative in eight patients (all with patent IRV at control angiography) and
again positive in one patient, who showed restenosis at angiography. The WMSI at resting
conditions was similar before and after angioplasty, whereas it differed significantly at peak
dipyridamole (1.7±0.2 versus 1.4±0.2, p<0.01).

Conclusions. DET can identify the anatomy of the IRV, and dipyridamole-induced WMAs
within the infarct zone detect regions with jeopardized myocardium that may benefit from
intervention. (Circulation 1991;84:1100–1106)

Thrombolysis is accepted as standard therapy
for acute myocardial infarction. Several rand-
omized studies have shown that throm-
bolysis may reestablish flow in the infarct-
related artery,1–8 preserve myocardial function,9–11
and reduce mortality.4,5,7–9,12 After thrombolysis,
early coronary angiography is valuable because it

---

From Ospedale Maggiore Della Carita' Novara, Divisione di
Cardiologia, Novara, Italy.
Address for correspondence: Leonardo Bolognese, MD, Divi-
sione di Cardiologia, Corso Mazzini 18, 28100 Novara, Italy.
Received April 24, 1990; revision accepted April 30, 1991.

provides anatomic and prognostic information re-
garding multivessel involvement and minimal resid-
ual lesion of the infarct vessel. However, cardiac
 catheterization carried out soon after thrombolytic
therapy does not appear to be necessary or even
desirable in most patients.13 The role of functional
tests after thrombolysis in identifying selected pa-
tients who will need further intervention remains to
be validated.14 Dipyridamole echocardiography has
been shown to be an accurate and inexpensive non-
exercise-dependent stress test for evaluating patients
with suspected or proven coronary artery disease.15
We have previously shown that it is feasible, safe, and useful for predicting multivessel coronary artery disease soon after acute myocardial infarction. The only echocardiographic criterion considered in identifying multivessel coronary artery disease was the presence of a transient asynergy developing after dipyridamole in a territory remote from the infarct zone. However, we also described another pattern of echocardiographic positivity: a new wall motion abnormality confined to the infarct zone or adjacent segments. The angiographic correlates of this echocardiographic sign remain to be established. We hypothesized that this sign might represent a marker of jeopardized myocardium subtended by either a patent infarct-related vessel with a critical residual stenosis or an occluded infarct vessel with collateral flow. To investigate this hypothesis, we performed dipyridamole echocardiography 8–10 days and coronary angiography 10–14 days after acute myocardial infarction in 76 consecutive patients treated with intravenous thrombolysis within 4 hours of the onset of chest pain. Furthermore, in a subgroup of nine patients with dipyridamole-induced wall motion abnormalities in the infarct zone, we repeated dipyridamole echocardiography and coronary angiography after an angiographically successful coronary angioplasty in the infarct-related vessel.

Methods

Patient Population

The initial study group comprised 79 patients with a first acute myocardial infarction. Inclusion criteria were chest pain of at least 30 minutes’ duration, electrocardiographic ST segment elevation of 0.1 mV or more in at least two leads, and initiation of intravenous thrombolytic therapy within 4 hours of the onset of chest pain.

Three patients were excluded because of a technically inadequate two-dimensional echocardiogram at rest. Thus, 76 consecutive patients (65 men and 11 women; age range, 34–69 years; mean±SD age, 55.4±9.3 years) were admitted into the study.

In all patients, acute myocardial infarction was documented by serial creatine kinase determination.

All patients received a bolus administration of 1 million IU urokinase i.v. that was repeated 60 minutes after termination of the first dose. After initial urokinase therapy, all patients were promptly anticoagulated with an intravenous infusion of heparin that was titrated to maintain partial thromboplastin time at twofold to threefold that of baseline values.

All patients received dipyridamole echocardiography 8–10 days and coronary angiography 10–14 days after acute myocardial infarction. Nine patients with dipyridamole-induced wall motion abnormalities in the infarct zone repeated the test and a control coronary angiography 1–3 months after an angiographically successful (residual stenosis, 50% or less) coronary angioplasty in the infarct-related vessel.

Informed consent was obtained from all patients.

Dipyridamole Echocardiography

Two-dimensional echocardiographic and 12-lead electrocardiographic monitorings were performed in combination with dipyridamole infusion: 0.56 mg/kg over 4 minutes, no dose for 4 minutes, and then 0.28 mg/kg over 2 minutes. The cumulative dose was 0.84 mg/kg over 10 minutes. Aminophylline (70–240 mg over 1–3 minutes) was always given, either at the end (15 minutes) of a negative test or in the presence of an obvious new dyssynergy.

Two-dimensional echocardiograms were continuously recorded during and for as long as 10 minutes after dipyridamole administration. Commercially available, wide-angle, phased-array imaging systems (model 77020 AC, Hewlett-Packard 3.5-MHz transducer; SSH-160 A, Toshiba Sonolayer Alfa 2.5- and 3.75-MHz transducers) were used.

A wall motion score index was derived for rest and peak dipyridamole echocardiograms in each patient. The left ventricle was divided into 13 segments. Segmental wall motion was graded as normal, normal motion at rest with normal or increased wall motion (hyperkinesia) after dipyridamole (score, 1); hypokinetic, marked reduction of endocardial motion (score, 2); akinetic, virtual absence of inward motion (score, 3); or dyskinetic, paradoxic wall motion away from the center of the left ventricle in systole (score, 4). The wall motion score index was derived by summation of individual segment scores divided by the number of interpreted segments. Inadequately visualized segments were not scored.

Relation of wall motion abnormalities to coronary artery perfusion was assessed according to the method of Feigenbaum. Positivity of the test was linked to detection of marked worsening of wall motion (change of one level or more) in the same area showing asynergy at rest in at least one view. The increase in asynergy from baseline was considered in terms of either severity (e.g., hypokinesia to dyskinesia) or extension (e.g., new wall motion abnormalities of directly adjacent segments). We have previously described the very high interobserver agreement with diagnosis achieved in our laboratory. A single experienced observer reviewed all echocardiographic examinations without knowledge of patient data.

Coronary Arteriography

Selective coronary arteriography was performed with the Judkins or Sones technique. Multiple views of each coronary artery were obtained, including cranio-caudal views. All angiograms were interpreted by two experienced angiographers without knowledge of the dipyridamole echocardiographic results. Differences in interpretation were resolved by consensus. Location and severity of coronary artery lesions were recorded according to Coronary Artery Surgery Study (CASS) criteria. Significant coronary stenosis was defined as 70% or greater reduction in the luminal diameter of the left main coronary artery, left anterior descending coronary artery, left circum-
flex coronary artery, or right coronary artery or its branches. Stenosis severity was estimated in the projection in which it was most severe. The infarct-related artery was identified by consideration of the electrocardiogram and the location of wall motion abnormalities on ventriculography. Anterograde flow in the infarct-related artery was graded in accordance with the criteria described by the Thrombolysis in Myocardial Infarction (TIMI) investigators. Angiographic reperfusion of the infarct-related artery in the present study was defined as TIMI grade 2 or 3. Collateral vessels were determined to be present if any segment of the infarct-related artery filled in by any manner other than continuous anterograde.

Statistical Analysis

Continuous data are expressed as mean±SD values. Differences between paired data were analyzed by two-tailed paired t test, and differences between groups were analyzed by unpaired t test. Nonparametric differences were examined using a χ² test. Sensitivity and specificity were evaluated according to standard definitions. A probability value of less than 0.05 was considered to be statistically significant.

Results

Patient Characteristics

The electrocardiographic localization of acute myocardial infarction was anterior in 30, inferior in 43, and lateral in three patients. Ten patients had a non-Q wave infarction (five anterior and five inferior). Thirty-two patients had one-vessel, 24 had two-vessel, 10 had three-vessel, and five had nonsignificant coronary artery disease.

Dipyridamole Echocardiographic Findings

All patients had asynergy at the basal echocardiographic study. There was no complication during
dipyridamole infusion; no patient had significant arrhythmias or severe hypotension (decrease of more than 30 mm Hg). Fifty-three patients had positive results on dipyridamole echocardiography. Of these, 42 presented dipyridamole-induced new wall motion abnormalities confined to the infarct zone or the adjacent segments (Figure 1).

In patients with positive dipyridamole echocardiography, wall motion score index increased from $1.44 \pm 0.3$ at resting conditions to $1.77 \pm 0.33$ at peak dipyridamole ($p<0.01$), whereas no significant change was detected in negative patients. In the subset of 42 patients with dipyridamole-induced wall motion abnormalities in the infarct zone or adjacent segments, wall motion score index increased from $1.46 \pm 0.26$ at resting conditions to $1.73 \pm 0.35$ at peak dipyridamole ($p<0.01$).

**Coronary Angiographic Findings**

Fifty-three patients had partial or complete anterograde flow in the infarct-related vessel (TIMI grade 2 or 3), and 23 had no or minimal anterograde flow (TIMI grade 0 or 1). Collaterals to the infarct-related artery were seen in 25% of the patients (19 of 76).

Figure 2 shows the relation of dipyridamole echocardiography test results to residual stenosis and anatomy of the infarct-related vessel. Of the 42 patients with dipyridamole-induced ischemia in the infarct zone, 35 had angiographic reperfusion (TIMI grade 2 or 3) of the infarct-related artery with critical residual stenosis. Six patients had a totally obstructed infarct-related artery with collateral flow to the distal vessel, and one had an occluded infarct-related vessel without angiographic evidence of collateral flow. Of the 34 patients with negative dipyridamole echocardiography, 18 had a patent infarct-related artery (five with minimal or no residual stenosis) (18 of 34 versus 35 of 42, $p<0.05$), and 16 had a totally obstructed infarct-related vessel, with collateral flow to the distal vessel in only three cases. Thus, the sensitivity and specificity for identifying a critically stenotic but patent infarct-related vessel or the presence of a collateral-dependent zone were 66% and 93%, respectively. Furthermore, among the 48 patients with significant coronary artery disease, the 13 patients with negative dipyridamole echocardiography had higher wall motion score indexes at resting conditions than the 35 patients with positive dipyridamole echocardiography (1.6±0.3 versus 1.3±0.3, $p<0.01$). In the subset of 42 patients with dipyridamole-induced wall motion abnormalities in the infarct zone or adjacent segments, the 24 patients with more severe stenosis (90% or more) had higher wall motion score indexes (1.7±0.3 versus 1.5±0.2) and lower dipyridamole times (4.7±3 versus 7.2±2 minutes) than the nine patients with less severe stenosis.

**Coronary Angioplasty and Dipyridamole Echocardiography Test Results**

In a subset of nine patients with a positive dipyridamole echocardiography test, both dipyridamole echocardiography and control coronary angiography were repeated 1–3 months after an angiographically successful (residual stenosis, 50% or less) coronary angioplasty of the infarct-related vessel. The repeat dipyridamole echocardiography test was negative in eight patients (all with a patent infarct-related vessel at control angiography) and again positive in one patient, who showed restenosis at control angiography. The wall motion score index in resting conditions was similar before and after angioplasty,
whereas it differed significantly at peak dipyridamole
(1.7±0.2 versus 1.4±0.2, p<0.05) (Figure 3).

**Discussion**

We have previously shown that dipyridamole echocardiography is feasible and safe after uncomplicated acute myocardial infarction. It can reliably and noninvasively identify one of the most important diagnostic concerns regarding these patients—multivessel involvement. The present study shows that dipyridamole echocardiography can also identify the anatomy of the infarct-related vessel, which can be reliably inferred from the mechanical behavior of the infarct zone during stress. In fact, dipyridamole-induced worsening of a resting dyssynergy and the extension of the dyssynergy to the adjacent zone were invariably associated with two angiographic patterns of the infarct-related vessel—patency of the vessel with critical residual stenosis or total occlusion of the vessel with the presence of collateral circulation. These two angiographic patterns might represent the anatomic background for the occurrence of dipyridamole-induced flow maldistribution phenomena. A tight stenosis might provoke vertical steal phenomena with subendocardial underperfusion in the presence of relative subepicardial overperfusion. The occluded vessel with collateral circulation might represent horizontal steal phenomena, diverting blood from the occluded vessel to the normally perfused bed. The final common pathway of these two mechanisms, both triggered by inappropriate coronary artery dilation, is a further reduction of the perfusion to the infarct zone, with a consequent echocardiographic positivity of dipyridamole testing. Similar results were achieved by Picano et al using a low-dose dipyridamole protocol on a symptomatic population in the early postinfarction period.

A patent infarct-related vessel or an occluded vessel with collateral flow was found in 21 patients without dipyridamole-induced ischemia in the infarct zone. A possible reason for these findings is that the extent of salvaged myocardium was low in these patients. In fact, if the occluded vessel is only minimally opened after thrombolytic therapy or it is opened too late, the amount of salvaged myocardium would be limited. It is consistent with this interpretation that wall motion score index in patients with negative dipyridamole echocardiography was higher than in patients with a positive test, indicating a more pronounced mechanical impairment.

Another possible explanation is that the infarct-related vessel is successfully reperfused with no significant residual impairment in flow reserve of that vessel. In this way, the infarct zone remains viable but jeopardized in physiological terms. In fact, five patients in our series with a negative dipyridamole echocardiography test and a patent infarct-related vessel had a residual stenosis of less than 70% or “normal” coronary arteries.

**Study Limitations**

Some possible limitations of this study should be acknowledged. First, we used a subjective semiquantitative analysis of angiographic findings, which is the one usually adopted in practice as well as in clinical studies. A quantitative computerized analysis would have required more time, apparatus, and expense. Furthermore, it is feasible only in a limited number of high-quality angiograms, and there is no available demonstration that it predicts physiological impairment in flow reserve in patients after myocardial infarction.
Second, we used a semiquantitative analysis of the stress echocardiography results. This approach has both merits and limitations. It is known that the wall motion score index provides an integrated estimation of the extent and severity of left ventricular dysfunction. It does not require computer facilities, and it is simple and easy to obtain. Certainly, the subjective analysis by a single observer has the drawback of being operator dependent; this is a potential limitation of the study. However, the accuracy and reproducibility of stress echocardiography readings have been demonstrated to be very high in experienced hands.23

Last, another possible problem relates to the “tethering” effect (i.e., the possibility that the diprydiamole-induced changes in wall motion might be results of mechanical factors or changes in loading conditions rather than true ischemia). However, this possibility seems unlikely in the model that we studied for several reasons. First, some experimental studies have shown that the mechanical effects of an ischemic region extend only to regions immediately adjacent to an ischemic zone, a zone of mild hypofunction that extends less than 1 cm from the ischemic border.24,25 Second, systemic hemodynamic and, in particular, blood pressure changes are trivial with diprydiamole infusion as extensively documented by large-scale clinical experience and invasive hemodynamic studies.26 Third, after diprydiamole, the normal mechanical behavior in the infarct zone consists of unchanged27 or even increased motion and thickening, probably results of the inotropic effect of increased flow.26,28 Fourth, in the patients undergoing angioplasty, the mechanical correction of the stenosis in the infarct-related vessel induced a complete resolution of the diprydiamole-induced dyssynergy, suggesting that the abnormal response to diprydiamole is related to ischemia.

Clinical Implications

There are few nonangiographic methods with which to predict viability after thrombolysis, and they require expensive and sophisticated technology.14 The present study demonstrates that diprydiamole echocardiography provides a simple method with which to identify the presence of jeopardized but viable myocardium after thrombolysis. This represents crucial information in uncomplicated patients who have had intravenous thrombolytic therapy, because it allows a better selection of patients who might benefit from further intervention. The feasibility, safety, low cost, and availability of diprydiamole echocardiography make this technique a simple and useful tool that may be incorporated in the acute management of patients with myocardial infarction whenever the expertise required for stress echocardiography is available.

Acknowledgment

We are very grateful to Maria Grazia Ferraris for technical assistance.

References

7. ISIS-2 Collaborative Group: Randomized trial of intravenous streptokinase, oral aspirin, both or neither among 17,187 cases of suspected myocardial infarction. Lancet 1988;2:349–360

**Key Words** - echocardiography, dipyridamole - thrombolysis - myocardial infarction
Dipyridamole echocardiography test. A new tool for detecting jeopardized myocardium after thrombolytic therapy.
L Bolognese, G Sarasso, A S Bongo, L Rossi, D Aralda, C Piccinino and P Rossi

Circulation. 1991;84:1100-1106
doi: 10.1161/01.CIR.84.3.1100

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1991 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/84/3/1100