Myocardial viability after primary coronary angioplasty: low-dose dobutamine stress echocardiography versus myocardial contrast echocardiography

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Angioplasty, primary; Myocardial contrast echocardiography; Stress echocardiography.

Background. **Successful reperfusion therapy in patients with acute myocardial infarction (AMI) improves survival. Indeed, after AMI myocardial dysfunction may be reversible (hibernating or stunned myocardium). Low-dose dobutamine stress echocardiography (LDDSE) provides us with the possibility of evaluating viable myocardial segments, while myocardial contrast echocardiography (MCE) allows the study of the microcirculation in the same myocardial areas. The aim of our study was to compare LDDSE and MCE, in the prediction of the recovery of segments in patients with AMI who were submitted to primary coronary angioplasty (PTCA).**

Methods. **We studied 14 patients with AMI. Both LDDSE and MCE with Levovist were performed after primary PTCA. The viability gold standard was a recovery of contractility detected at echocardiography 2 months later.**

Results. **For LDDSE, the sensitivity was 91%, the specificity 71% and the positive and negative predictive values were 93 and 64% respectively. For MCE, the sensitivity was 94%, the specificity 44%, the positive predictive value 89%, and the negative predictive value 59%. Two tests agreed in 81% of the cases. Stress echocardiography and contrast echocardiography agreed in 81% of cases.**

Conclusions. **LDDSE has a very good positive accuracy, it has an acceptable negative predictive value and is relatively cheap. On the other hand, MCE has a good positive accuracy, but a low negative accuracy and carries a high cost. The integration of these two tests, which are too expensive in clinical practice, could improve our comprehension of the post-PTCA pathophysiology.**

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Introduction

The myocardial viability concept is based on two different situations: the stunned myocardium is a post-ischemic, mechanical dysfunction that persists after reperfusion, but it is a reversible condition[1,2]; the second condition, the hibernating myocardium, is a persistently impaired myocardial and ventricular function at rest, due to a chronically reduced coronary blood flow, which may be restored[3] after adequate reperfusion therapy[4-8].

Since the concept of stunned[9,10] and hibernating myocardium[2,11-13] has been introduced, several methods of distinguishing viable from irreversibly injured myocardium have been proposed in the attempt to select patients with coronary artery disease who could benefit from revascularization strategies[8,14,15].

Positron emission tomography, which permits the simultaneous assessment of perfusion and metabolism, is considered the best technique for the detection of viable myocardium, but its high costs limit its application in clinical practice[16-19]. Actually, the most used technique for the evaluation of myocardial viability is low-dose dobutamine stress echocardiography (LDDSE)[20-23]. Dobutamine-induced systolic thickening in asynergic myocardial segments is indicative of viability. The sensitivity of this technique varies from 75 to 80%, while the specificity ranges from 80 to 85%[24,25]. Coronary perfusion may be detected by using a contrast agent injected intravenously. In the past, the necessity of injecting, to obtain myocardial perfusion images, contrast agents directly into the coronary arteries confined the use of this technique to the catheterization laboratory[26].

With the development of intravenous agents[27] and of new ultrasound imaging modalities, such as harmonic imaging[28], it is possible to perform myocardial contrast

echocardiography (MCE) without the need of intracoronary microbubble injection[29,30].

The aim of this study was to compare LDDSE to MCE in the assessment of myocardial viability in patients with acute myocardial infarction (AMI) submitted to primary coronary angioplasty (PTCA).

Methods

Fourteen consecutive patients (12 males, 2 females, mean age 64 years) admitted to our institution with AMI were included in the study. Their clinical data are illustrated in table I.

Eight patients had anterior or anteroseptal AMI, 2 patients had acute anterolateral infarction, and 4 patients had inferior or inferolateral AMI. All the patients were submitted to primary PTCA within 6 hours of symptom onset. In 4 patients with multivessel disease, revascularization was not complete.

After primary PTCA all the patients were submitted to echocardiographic examination using an HP Sonos 5500 machine (Hewlett Packard, Andover, MA, USA) equipped with a multifrequency 2.4-4 MHz probe.

All patients, 4 days after primary PTCA, were submitted to dobutamine stress echo, with an incremental dose of 5, 10, 20 μg/kg/min until a heart rate which did not exceed the resting heart rate by more than 10% was reached. All the patients were off β-blocker agents.

The left ventricular segments were considered viable when an improvement from hypokinesis to normal or from akinesis to hypokinesis was observed.

After washout, the patients underwent MCE with intravenous injection of Levovist in microboli of 0.5 ml alternated to continuous infusion. In 5 min a total dose of 5 ml was injected. The perfusion images were analyzed using power-angio Doppler, while the gain was reduced to below 50 dB to minimize artifacts, and the depth of the ultrasound waves was increased. The end-systolic trigger interval was chosen by positioning the cursor on the apex of the T wave of the ECG or by measuring the systolic interval on the M-mode of the aortic valve.

The images were analyzed every 3, 4 or 5 cycles depending on the heart rate of the individual patient. Patients maintained the same position and they were invited to avoid deep breathing. All the apical images were recorded in order to analyze the perfusion in all segments. The perfusion images were stored on optical disk. The segments which were adequately opacified by the contrast medium were considered well perfused; poor perfusion was defined as inhomogeneous, delayed or absent opacification (Figs. 1 and 2).

All the patients were revaluated 2 months later at transthoracic echocardiography. A 1 grade improvement of the wall motion in single segments was considered as a sign of viability (akinesis → hypokinesis or hypokinesis → normokinesis).

The sensitivity, specificity and positive and negative predictive values of both stress echo and contrast echo were calculated on the basis of the improvement in the wall motion detected 2 months after AMI (taken as the gold standard for viability).

Results

A total of 224 ventricular segments were evaluated with LDDSE, while 218 segments could be examined with MCE. For 6 segments of the lateral wall, the poor quality of the images did not allow adequate evaluation of the perfusion.

Table I. Demographic and clinical data of the study population.

Patient	Sex	Age (years)	Diagnosis	Coronarography	PTCA	Stent	Untreated coronary artery
MO	M	77	Anterior AMI	LAD II, 1 cAD, RCA II	*	*	
RL	M	56	Anterior AMI	LAD II	*	*	
LC	M	57	Inferior AMI	LAD II, RCA II	*	*	
AP	M	55	Anteroseptal AMI	LAD II	*	*	
RR	M	53	Anterior AMI	LAD II	*	*	1 cCx 70%
UP	M	68	Inferior AMI	Cx I	*		RCA II 100%, OM II 75%, LAD I 75%
BL	M	57	Inferolateral AMI	RCA I	*	*	
PN	F	70	Anterolateral AMI	LAD II	*	*	
BM	M	58	Anterior AMI	LAD II, Cx II	*	*	
CE	M	63	Anterior AMI	LAD I, II, 1 cLAD	*	*	
RG	M	67	Anterior AMI	LAD II	*	*	
BB	M	76	Inferior AMI	RCA I	Failed		LAD I 90%
ML	F	63	Anterolateral AMI	LAD III, 2 cLAD, RCA II	*	*	
AS	M	72	Anterior AMI	LAD II	*	*	RCA II 75%

AMI = acute myocardial infarction; cLAD = diagonal collateral of LAD; Cx = circumflex coronary artery; cCx = diagonal collateral of Cx; LAD = left anterior descending coronary artery; OM = obtuse marginal; PTCA = coronary angioplasty; RCA = right coronary artery. * operative procedure. I = proximal tract; II = mean tract; III = distal tract.

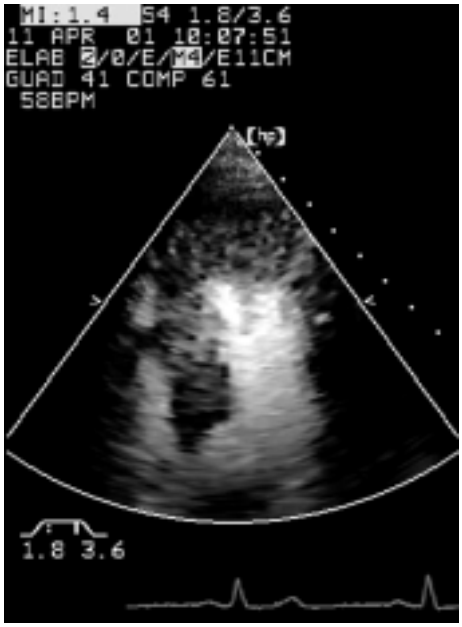

Figure 1. *Myocardial contrast echo in a normally perfused left ventricle.*

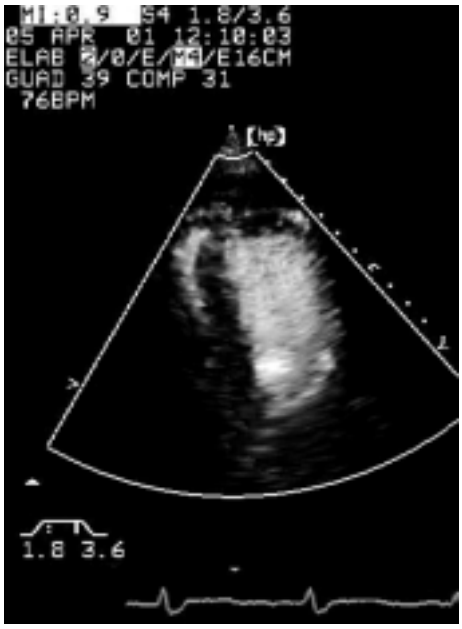

Figure 2. *Myocardial contrast echo showing poor perfusion in the left ventricular apical segments.*

Of 224 segments examined at LDDSE after PTCA, 165 improved during dobutamine infusion and 17 did not; altogether, 182 segments showed recovery at follow-up. Of 42 segments which did not improve after 2 months, 12 had shown recovery of motion during dobutamine infusion and 30 did not. The sensitivity was 91% while the specificity was 71%. The positive predictive value was 93%, the negative predictive value 64% (Table II).

Of 191 segments which showed signs of reperfusion after PTCA, 20 did not show recovery of wall motion at follow-up, while of 27 segments with poor or absent perfusion in the acute phase, 11 improved and 16 did not show any change 2 months later. The sensitivity of the perfusion study was 94%, while the specificity was 44%. The positive predictive value was 89%, while the negative predictive value was 59% (Table III).

In 177 segments (81%) of 218 segments studied with both methods, the viabilities as assessed by stress echo and perfusion were concordant in predicting recovery of wall motion.

As reported in table IV, the two tests were not concordant for 41 (19%) segments.

Table II. The diagnostic accuracy of low-dose dobutamine echocardiography.

	Stress echo+	Stress echo-	Total
Follow-up+	165	17	182
Follow-up-	12	30	42
Total	177	47	224

Sensitivity 91%; specificity 71%; positive predictive value 93%; negative predictive value 64%.

Table III. The diagnostic accuracy of myocardial contrast echocardiography.

	Perfusion+	Perfusion-	Total
Follow-up+	171	11	182
Follow-up-	20	16	36
Total	191	27	218

Sensitivity 94%; specificity 44%; positive predictive value 89%; negative predictive value 59%.

The results of MCE were compared with those of coronary angiography after PTCA (Table V). Twenty-two perfused segments at MCE depended on coronary arteries with critical stenosis which were not treated at the time of primary PTCA. Twenty-nine segments did not show perfusion although the related coronary arteries were open. Of these, 25 segments were supplied by coronary arteries successfully opened at PTCA, and 4 by normal coronary arteries. The perfusion study had a sensitivity of 84% and a specificity of 31% in predicting coronary artery patency. The positive predictive value was 88% and the negative predictive value 26%.

Discussion

With the observation that hypokinetic or akinetic myocardium could recover its contractility after revascularization, Braunwald and Rutherford[11] and Pierard et al.[25] introduced the concept of stunned and hibernating myocardium. They demonstrated that myocardium

Table IV. Comparison of stress echocardiography and contrast echocardiography: non-concordant segments and diagnostic hypothesis.

Group	No. segments	Basal echo	Stress echo	Contrast echo	Follow-up	Hypothesis
A	8 (3.7%)	Akinetic	Not viable	Perfused	Recovery	Stunned myocardium
B	9 (4.1%)	Akinetic	Not viable	Not perfused	Recovery	Microcirculation recovery
C	9 (4.1%)	Akinetic	Viable	Perfused	Akinetic	Stunned myocardium
D	2 (0.9%)	Normal	Viable	Not perfused	Akinetic	Hibernated myocardium
E	1 (0.46%)	Normal	Viable	Perfused	Akinetic	Later microcirculatory damage
F	2 (0.9%)	Normal	Viable	Not perfused	Recovery	Real false negative of contrast
G	10 (4.6%)	Akinetic	Viable	Perfused	Akinetic	Mismatch perfusion/viability

Table V. Comparison of the results of contrast echocardiography and angiography.

	Perfusion+	Perfusion-	Total
Patent coronary artery	157	29	186
Stenotic coronary artery	22	10	32
Total	179	39	218

Sensitivity 84%; specificity 31%; positive predictive value 88%; negative predictive value 26%.

which had lost its contractile function is not always necrotic and may recover its function after adequate reperfusion.

The concept of viable myocardium had an important impact in clinical practice, promoting research on methods able to identify myocardial segments which could benefit from reperfusion. The observation that viable myocardium can show a transitional contractile recovery after inotropic drug administration, led to the introduction of LDDSE in the evaluation of myocardial viability[25]. LDDSE is a low-cost, non-invasive, simple method, easy to perform in every hospital with a coronary care unit; therefore it constitutes the first choice test for the assessment of myocardial damage due to AMI. The sensitivity of this method in exploring viable myocardium is usually tested by evaluating the long-term recovery of the myocardium[20].

The technologic advancements of echocardiographic equipment and the introduction of contrast agents able to pass through the pulmonary circulation and to opacify the myocardium through the coronary circulation after injection in a peripheral vein, has initiated the era of contrast echocardiography[27,28,31]. A myocardial segment which shows perfusion after the injection of a contrast agent following AMI treated with primary PTCA, should be viable[32,33].

The aim of our study was to compare echo-dobutamine versus echocontrastography for the assessment of myocardial viability in patients admitted to hospital for AMI, who underwent primary PTCA. The results were compared to the recovery of the myocardium as assessed 2 months later at basal transthoracic echocardiography.

As observed in previous studies[20], our results confirm that echo-dobutamine has a high sensitivity. We found a sensitivity of 91%, which is limited by a specificity of 71%. Echocontrastography had a sensitivity of 94% and a specificity of 44%.

From our results it is clear that echo-dobutamine, having a low cost and a good sensitivity, may be the best test for the evaluation of the viability of stunned myocardium. On the other hand, contrast echocardiography has a high cost and a low specificity that, as far as the viability of the myocardium is concerned, limit its use.

The two tests coincided in viability assessment in 81% of cases. In the remaining 19% of cases (only 41 segments; Table IV) the two tests yielded contrasting data. However, by integrating stress echo, contrast echocardiography and coronarography, we should be able to formulate a pathophysiological profile for each myocardial segment.

As described in table IV, several hypotheses were formulated to explain particular situations. Group A had akinetic and non-viable segments that were well perfused and showed wall motion recovery at follow-up examination and was hence considered as stunned myocardium. Group B had both akinetic, non-viable segments with no perfusion at MCE that improved at follow-up and was considered as microcirculatory recovery. Group C had akinetic segments that were viable and well perfused but remained akinetic at follow-up examination and was hence defined as persistently stunned myocardium. Group D had non-perfused but viable segments that remained akinetic at follow-up and was considered as hibernating myocardium. One patient of group E had normal wall motion and viable and well perfused segments that became akinetic at follow-up. This was attributed to later microcirculatory damage. Group F, with normal, viable but non-perfused segments was considered as false negative. Finally, group G with persistent akinesia in viable and perfused segments was explained as a mismatch between perfusion and viability.

Probably the group A and C segments were both stunned: group A only in the acute phase, but with excellent recovery at a distance, while group C segments remained stunned after 2 months.

For segments of group B, an improvement in microcirculatory function after the tests, as suggested by some studies which indicate that the evaluation of via-

bility after PTCA should be performed later than 8 days, could be supposed.

Segments viable during stress echo but unperfused at echocontrastography did not recover at follow-up (group D): they could be hibernated.

In the group E segment probably irreversible damage of the microcirculation developed later.

At this stage too many limits influence the clinical application of contrast echocardiography technology. Indeed, the perfusion of the left ventricular lateral wall segments is not easily visualized at echocontrastography because of intrinsic problems of the technique. This was the problem with group F segments. On the other hand, 10 segments of group G showed the limits of echocontrastography as a marker of viability. The perfusion may not be synonymous of viability: in fact, a reduced flow could be shown in reperfused but necrotic areas.

A limit of the comparison between echocontrastography and coronarography is that perfusion of the single myocardial segments was correlated with the epicardial coronary arteries in accordance with the "classical" distribution pattern; this pattern, however, presents wide individual variations. Bearing these limits in mind, echocontrastography appeared relatively sensitive (84%) in the identification of coronary patency, but poorly specific (31%). In fact, 29 segments judged as unperfused were actually revascularized by an open epicardial coronary artery. Twenty-five of them (86%) belonged to a revascularized coronary artery and the poor perfusion could be partially attributed to microcirculation damage (no-reflow phenomenon).

Another 4 sectors (14%) are supplied by normal vessels; therefore they should be considered as false negative results.

As above mentioned, the specificity of echocontrastography in identifying coronary patency is very low, about 31%. In 22 segments, there was myocardial perfusion despite critical coronary stenosis. It is probable that those areas were perfused in basal conditions and that they became ischemic only during stress.

In conclusion, only LDDSE should be used in clinical practice for the assessment of myocardial viability. MCE may detect the no-reflow areas in the evaluation of coronary patency[34,35], but has a poor specificity in estimating viability. The integration of tests identifies a pathophysiological profile for each myocardial segment. This may be used to derive diagnostic and prognostic indications.

But which are the costs for this integrated approach? LDDSE requires two doctors, a trained nurse for 45 min, a specialized echocardiograph, an electrocardiograph, a defibrillator, an infusion pump and a low-cost drug (Dobutrex, 12,76). On the other hand, MCE investigation requires one doctor, a trained nurse for half an hour, a new generation echocardiograph, and an expensive drug (Levovist, 206,58).

The combination of the two techniques is too expensive for uncomplicated cases in which PTCA is performed. Perhaps in patients with multivessel disease, after an emergency PTCA, both techniques could help cardiologists in programming subsequent interventions.

MCE is a test in an evolving stage[29,30]. Probably, the development of newer contrast agents and software allowing continuous myocardial perfusion analysis will allow for the application of this technique in other clinical settings.

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