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Clinical Investigations

Changes in the Response of Hibernated Myocardium to Inotropic Stimulation after Angioplasty: A Doppler Myocardial Imaging Study

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Summary

Background: Angioplasty of an infarct related artery (IRA) performed several weeks or months after myocardial infarction (MI) may improve myocardial function.

Hypothesis: We hypothesized that, as Doppler myocardial imaging (DMI) allows for the quantitative assessment of the systolic movement of myocardial segments, it may be a sensitive method for assessing changes in regional myocardial contraction and contractile reserve pre and post angioplasty of the IRA.

Methods: In all, 39 patients (30 men, mean age 53.4 ± 8.3 years), 1 to 6 months after MI, who qualified for IRA angioplasty on the basis of myocardial viability in the infarcted zone as demonstrated by dobutamine stress echocardiography, were included in the study. Peak regional myocardial systolic velocities (S wave) of the infarcted segments were measured at rest and during low-dose dobutamine infusion (15 μg/kg/min) 1 day before angioplasty (Exam 1), 2 to 5 days (Exam 2), and 30 days (Exam 3) after successful angioplasty. The long-axis movement of the mitral annulus and of the basal and medial segments of the posterior (20 patients), anterior (17 patients), and lateral walls (2 patients) was evaluated.

Results: At rest, S-wave velocity of the infarcted segments increased between Exams 1 and 2, without further improvement between Exams 2 and 3 (4.9 ± 1.2 vs. 5.6 ± 1.3 cm/s, $p < 0.05$ and 5.6 ± 1.3 vs. 5.5 ± 1.3 cm/s, NS, respectively). However, S-wave velocities measured during low-dose dobutamine infusion differed significantly both between Exams 1 and 2, and 2 and 3 (7.0 ± 1.5 vs. 7.8 ± 1.8 cm/s; $p < 0.01$; 7.8 ± 1.8 vs. 8.5 ± 1.6 cm/s; $p < 0.05$).

Conclusions: Resting contractility at an infarct zone demonstrated rapid initial improvement after angioplasty of the IRA with no further change, whereas contractile reserve improved not only immediately after angioplasty but also during the next month.

Key words: Doppler myocardial imaging, contractile reserve, angioplasty, myocardial infarction

Introduction

Contractile reserve, demonstrated by dobutamine stress echocardiography (DSE), is commonly used for the evaluation of myocardial viability to predict improvement of segmental contractility after revascularization.[1, 2] Several papers reported the smaller than expected improvement of regional left ventricular (LV) contractility at rest following revascularization.[3, 4] This can be caused by histopathologic changes in the hibernated myocardium, whereby the proliferation of the fibrous tissue precludes improvement of resting systolic function. Earlier studies evaluated the efficacy of revascularization procedures based on improvement of LV contractility at rest.[5–9] However, although hibernated myocardium is capable of responding to inotropic stimulation, there have been few reports dedicated to the influence of revascularization on contractile reserve.[3, 4, 10–12]

Prior attempts to perform echocardiographic evaluation of wall motion abnormalities were either based on semiquantitative visual assessment, or on the application of image processing techniques based on the centerline method.[13, 14] With the introduction of Doppler myocardial imaging (DMI), quantifying of regional myocardial contraction and relaxation velocities became possible.[15, 16] Regional systolic velocities have been shown to correlate well with other measures of contractility.[17, 18] The purpose of the present study was (1) to evaluate the effects of angioplasty on the segmental contractility at rest and during low-dose dobutamine stress echocardiography (LDDSE); (2) to investigate whether and to what

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extent contractility at rest and contractile reserve of asynergic but viable myocardium change shortly after and 1 month following successful angioplasty; and (3) to compare DMI velocity measurements with the conventional regional wall motion score index (WMSI).

Methods

Study Population

The study profile is presented in Figure 1. In all, 96 consecutive patients, 1 to 6 months after myocardial infarction (MI), with single-vessel disease, qualifying for angioplasty of an infarct-related artery (IRA), underwent viability study with full-dose dobutamine stress echocardiography (FDDSE) in accordance with the generally accepted methodology.[1] Echocardiographic images were acquired during the infusion of dobutamine, starting at a dose of 5 μg/kg/min and increased every 3 min to 40 μg/kg/min. Of 96 consecutive patients after MI, 50 were qualified for angioplasty of the IRA based on positive FDDSE. Angioplasty of the IRA was unsuccessful in 11 patients.

The presented data apply to the remaining 39 patients after successful IRA angioplasty. Patients met the following inclusion criteria: first MI, significant residual stenosis (> 70%), and reduced flow in the IRA (Thrombolysis In Myocardial Infarction [TIMI] scale flow < 2 grade), LV dysfunction of the infarct zone at standard echocardiographic examination, and myocardial viability in the infarct zone demonstrated during FDDSE. Another inclusion criterion was the reduction of IRA stenosis by > 50% during angioplasty with an increase of TIMI flow to > 2. Patients with multivessel coronary heart disease, unstable angina, and significant valvular diseases were excluded. All patients gave written informed consent. The Ethical Committee of our Institution approved the study protocol.

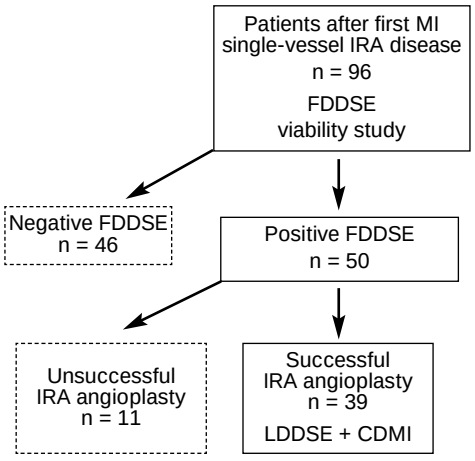

FIG. 1 Study profile. Full-dose (up to 40 mcg/kg/min) dobutamine stress echocardiography (FDDSE) was performed in 96 consecutive patients with single-vessel, infarct-related artery (IRA) disease. Based on a positive FDDSE viability study, 50 patients qualified for IRA angioplasty. Infarct-related artery angioplasty was unsuccessful in 11 patients. Low-dose (up to 15 mcg/kg/min) dobutamine stress echocardiography (LDDSE) and color Doppler myocardial imaging (CDMI) studies were performed in the remaining 39 patients after successful IRA angioplasty. MI = myocardial infarction.

Echocardiographic Examination

Patients qualifying for angioplasty underwent both conventional cardiac ultrasound examination, including regional and global assessment of LV function, and DMI study 1 day prior to the revascularization procedure (Exam 1), 2 to 5 days after the procedure (Exam 2), and 1 month (Exam 3) after successful angioplasty of IRA. Examinations were conducted at rest and during LDDSE, to assess contractile reserve. In LDDSE, the initial dose of 5 μg/kg/min was increased every 3 min by 5 μg/kg/min until the maximal dose of 15 μg/kg/min was reached. All echocardiographic examinations were performed using the GE-Vingmed System Five scanner (Vingmed Sound, Horten, Norway). Two-dimensional (2-D) echocardiographic examinations were carried out using the second harmonic imaging mode, with a transmit frequency of 1.7 MHz. Ejection fraction was calculated using the bi-plane Simpson method. The mean values of the three different cardiac cycles were obtained. Wall motion scores of the 16 segments were assessed according to the five-point scale (0- not visible, 1-normokinetic, 2-hypokinetic, 3-akinetic, 4-dyskinetic) and WMSI was calculated by the standard equation. All 2-D studies were reviewed independently by two experienced echocardiographers blinded to the clinical and angiographic data.

The DMI study was performed using a real-time color Doppler myocardial imaging system (CDMI). At frame rates of > 60 frames/s, this system has a high temporal resolution of < 20 ms. The general principles of CDMI modalities have been described previously.[15, 16, 19] The single observer experienced in the interpretation of DMI studies performed the examinations. Images were registered during expiration from the apical views (long-axis, four-, and two-chamber views). The color-coded Doppler myocardial velocity images were superimposed on the standard gray scale 2-D images. All 2-D and CDMI studies were digitally stored and the measurements were made off-line. Mean myocardial velocities of the infarcted segments were derived from CDMI data with dedicated software (Echopac Version 6.1, Vingmed Sound) (Fig. 2). The sample volume was placed at the center of the basal and mid segments. Apical segments were excluded from analysis due to a less defined velocity profile. The S-wave velocity for each segment was measured from three different cardiac cycles and averaged. Mean S-wave velocity in the infarct zone was calculated as an average of S-wave velocities of basal and mid segments.

Statistical Analysis

All continuous data are expressed as mean ± standard deviation (SD). Analyses of variance were performed to estimate interexamination differences using the Newman-Keuls test.

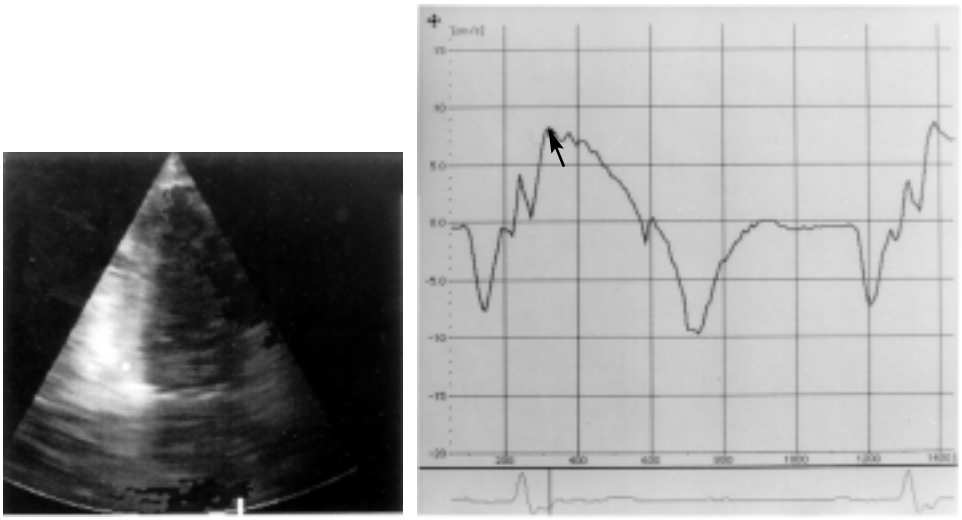

FIG. 2 Tissue velocity map superimposed on a two-dimensional apical two-chamber view. Myocardial velocity profiles sampled from basal posterior wall. Arrow indicates peak systolic contraction velocity of the posterior wall (S wave).

A p value of < 0.05 was considered statistically significant. Interobserver agreement in the interpretation of 2-D studies was calculated both for rest and low dose of dobutamine examinations. To assess intraobserver reproducibility, a single observer reanalyzed all studies twice, at least 1 month apart. The levels of intra- and interobserver reproducibilities for DMI studies were assessed in 10 randomly selected patients. The inter- and intraobserver variabilities of regional wall motion pattern were assessed as percent agreement. Variability of DMI measurements was expressed as the mean percent error, derived as the difference between the two sets of measurements divided by the mean of the observations.

Results

Angioplasty was successful in 39 patients (78%) (30 men, 9 women, mean age 53.4 ± 8.3 years). At the time of the study patients were on average 13 ± 8 weeks after an acute MI; 31 patients were after Q-wave MI. All individuals were receiving antianginal medication, including beta blockers (n = 28). All patients had single-vessel IRA disease. The mean coronary artery stenosis of 87.0 ± 6.8% before angioplasty was reduced to 21.0 ± 11.4% following the procedure ($p < 0.001$). Stents were implanted in 21 patients. Angioplasty of the left anterior descending artery (LAD) was performed in 17 patients, circumflex artery (LCx) in 2 patients, and the right coronary artery (RCA) in 20 patients. During LDDSE, heart rate increased from 65.1 ± 9.3 beats/min at baseline to 71.2 ± 8.6 beats/min during dobutamine infusion. Compared with the initial values (Exam 1), LV ejection fraction (EF) improved at Exams 2 and 3 (54 ± 8 vs. 62 ± 9 and 61 ± 9%, respectively; both $p<0.01$). Of 624 segments, 574 (92%) were analyzable by standard 2-D echocardiography. Before angioplasty, 195 segments (34%) had impaired contractility: 87 segments were hypokinetic, 102 were akinetic, and 6 were dyskinetic. After angioplasty, contractility improved in 72 of 195 asynergic segments (37%), normalized in 46 of 87 hypokinetic segments (52%), and improved in 26 of 102 akinetic segments (25%). The improvement of 53 of 72 segments (73%) was already noticeable at the first examination after angioplasty. Wall motion score index values at rest and during low-dose dobutamine infusion are summarized in Table I.

In all patients, mean systolic velocity of each analyzed segment was measured by CDMI at rest and during low-dose dobutamine infusion. At rest, systolic velocity in the infracted segments was significantly lower before than shortly after angioplasty (4.9 ± 1.2 vs. 5.6 ± 1.3 cm/s; $p < 0.02$). However, no

TABLE I Wall motion score index (WMSI) before and after angioplasty

WMSI	Exam 1 1 day before angioplasty	Exam 2 2–5 days after angioplasty	p Value	Exam 2 2–5 days after angioplasty	Exam 3 30 days after angioplasty	p Value
Rest	1.53 ± 0.31	1.37 ± 0.27	$p < 0.01$	1.37 ± 0.27	1.30 ± 0.27	NS
Low-dose dobutamine infusion	1.34 ± 0.29	1.31 ± 0.30	NS	1.31 ± 0.30	1.28 ± 0.28	NS

Values are expressed as mean ± standard deviation.

TABLE II Regional mean systolic wave velocities (S wave) in an infarct zone before and after angioplasty

S wave (cm/s)	Exam 1 1 day before angioplasty	Exam 2 2–5 days after angioplasty	p Value	Exam 2 2–5 days after angioplasty	Exam 3 30 days after angioplasty	p Value
Rest	4.9 ± 1.2	5.6 ± 1.3	< 0.02	5.6 ± 1.3	5.5 ± 1.3	NS
Low-dose dobutamine infusion	7.0 ± 1.5	7.8 ± 1.8	< 0.01	7.8 ± 1.8	8.5 ± 1.6	< 0.05

Values are expressed as mean ± standard deviation. S-wave velocity for each segment was measured from three different cardiac cycles and averaged. Mean S-wave velocity in an infarct zone was calculated as an average of S-wave velocities of basal and mid segments.

further improvement at rest was observed in the 1-month study. During infusion of low-dose dobutamine, systolic velocity increased not only between Exams 1 and 2 (7.0 ± 1.5 vs. 7.8 ± 1.8 cm/s, $p < 0.01$), but also between Exams 2 and 3 (7.8 ± 1.8 vs. 8.5 ± 1.6 cm/s, $p < 0.05$). These results are summarized in Table II.

Reproducibility

The inter- and intraobserver concordances of resting wall motion analyses were 88 and 92%, respectively. The inter- and intraobserver concordances of the assessments of the response of wall motion during low-dose dobutamine infusion were excellent: 92 and 94%, respectively. For final assessment, discrepancies in wall motion score between the two observers were settled by consensus, and in no case was the disagreement greater than 1 grade.

Intraobserver errors for rest and low-dose dobutamine S-wave velocities were 3.3 and 2.1%, respectively. For interobserver variability the numbers were 6.1 and 3.8%, respectively.

Discussion

In the present study, standard WMSI along with regional systolic velocities (S wave) derived from DMI was used to assess the changes in contractile function. The results demonstrate the beneficial impact of angioplasty of the IRA on the contractility of the jeopardized segments at rest. The degree of improvement was less than expected considering the positive results of inotropic stimulation during FDDSE prior to revascularization. However, in most of the infarcted segments, contractile reserve observed before angioplasty was maintained and even improved during follow-up.

After IRA angioplasty, at rest contractility improved only in 72 of 195 dyssynergic segments (37%), with 53 (73%) improving shortly after angioplasty. This was in agreement with the modest but noticeable increment of LVEF. The difference between WMSI values before and immediately after angioplasty indicated a rapid improvement in contractility of the hibernated myocardium. One month later a slight decrease in WMSI was detected, but it did not reach statistical significance. In the other studies, slight improvement following revascularization was noticed even months after the procedure.[20–22] Similar observations concerning contractility at rest were made based on the analysis of systolic velocity in CDMI studies. A detected mild increase of velocities directly after angioplasty without any further improvement parallels the observed relatively small improvement of global contractility at rest. This might be caused by the pathologic changes occurring in the infarct zone. If the amount of the fibrotic tissue in relation to the viable cardiomyocytes is too high, the myocardial contractility at rest may not improve after angioplasty.[23–25] Other factors, such as lack of microvascular integrity[26, 27] or chronic hibernation[28] may also play a role in the unsatisfactory recovery of basal contractility after revascularization. A varying lag in contractile recovery should also be considered.[4, 20–22]

Asynergic but viable myocardium thickens under inotropic stimulation during DSE. This change in contractility can be expressed as an improvement in WMSI. However, such an assessment is only semiquantitative, based on subjective wall motion analysis, and therefore imprecise. In the case of initially akinetic segments, the change of the score reflects the change of their function. It is difficult, however, to differentiate between various degrees of hypokinesia. In addition, normokinetic segments could demonstrate subtle contraction disturbances that may not be detected by visual examination. This lack of sensitivity and subjectivity, inherent to visual assessment, could explain the absence of significant WMSI changes during low-dose dobutamine infusion in the present study. Although a slight decrease in WMSI was observed between the exams performed just after angioplasty and 1 month later, it did not reach statistical significance. Doppler myocardial imaging, which quantitatively assesses the systolic movement of myocardial segments, offers more detailed and objective possibilities for the assessment of contractile reserve. In the present study, an increase in S-wave velocity during low-dose dobutamine infusion was noted not only shortly after angioplasty, but also 1 month later. The improvement in perfusion[29] and integrity of cellular membranes after revascularization[26, 27] could cause a greater response of the muscle to inotropic stimulation, resulting in an increase in contraction velocity. Doppler myocardial imaging can measure contraction velocity directly and quantitatively. In the earlier studies, an improvement in contractile reserve was attributed to successful revascularization.[3, 4, 10–12] However, to the best of our knowledge there are no reports of the use of DMI for such purpose. This mode of imaging is commercially available in many echocardiographic machines and can be used for quantitative assessment of the contractile reserve. One may expect

that improved contractile reserve in an infarct zone after revascularization, over and above the level of an improvement observed at rest, should contribute to a better overall clinical outcome. Better tolerance of inotropic stimulation during exercise should also improve exercise capacity.

Limitations of the Study

The main limitation of the present study is the lack of myocardial blood flow measurements. Nevertheless, it is widely accepted that there is a close link between flow and function. Although myocardial viability was not verified by an independent method such as scintigraphy, DSE is a generally approved diagnostic method for this purpose. One month follow-up might have been too short to demonstrate the complete functional recovery; however, later assessment might have been hampered by increasing occurrence of restenosis.

Conclusions

Results obtained in the present study suggest that (1) late IRA angioplasty improves the segmental contractility of the myocardium; (2) improved contractility at rest is observed mainly shortly after angioplasty; and (3) contractile reserve, as assessed by DMI, improves gradually over a period of several weeks.

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