Natural History of Contractile Abnormalities After Acute Myocardial Infarction in Man: Severity and Response to Nitroglycerin as a Function of Time

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SUMMARY The natural history of contraction abnormalities and their response after acute myocardial infarction in man were studied using radionuclide angiography. Sixteen patients were studied before and after sublingual nitroglycerin within 24 hours, 5-7 days and 4-6 weeks after the onset of chest pain. Within 24 hours, central chord shortening in the zone of infarction was reduced to 13.1 ± 9.8%, but improved to 27.2 ± 18.4% (p < 0.001) after nitroglycerin. After 5-7 days, central chord shortening improved similarly, but less markedly, from 12.9 ± 9.2% to 24.4 ± 13.2% (p < 0.001). After nitroglycerin 4-6 weeks after the acute myocardial infarction, the central chord showed no response to nitroglycerin; it was 13.9 ± 10.9% before and 13.4 ± 2.5% after nitroglycerin. Changes in the lateral chords paralleled changes in the central chords in the three studies. Nonischemic zone showed improvement after nitroglycerin in all three studies. Global ejection fraction improved and end-diastolic and end-systolic volumes decreased in all three studies after nitroglycerin.

These data indicate that after acute myocardial infarction, there is a significant reduction in hemiaxis shortening in the central and lateral chords that remains essentially unchanged over 4-6 weeks. However, the asynergic ischemic area improves considerably after nitroglycerin within 24 hours and 5-7 days, but fails to improve after 6 weeks.

EXPERIMENTAL STUDIES have characterized the nature, severity, progression and potential reversibility of regional myocardial contractile abnormalities after both complete and partial coronary obstruction. However, the natural history of contraction abnormalities that occur after acute myocardial infarction in man has not been systematically studied. This is of increasing importance in view of attempts to decrease the extent of ischemic injury after acute myocardial infarction.

Studies from our laboratory and others have shown a good correlation between radionuclide angiography and contrast ventriculography in determining the presence, severity and residual contractile reserve of regional contraction abnormalities. This noninvasive method permits serial evaluation of such abnormalities and the effect of interventions.

Using this technique, we demonstrated increase in hemiaxis shortening in the zone of infarction after the sublingual administration of nitroglycerin in the first 24 hours after onset of chest pain. In the present study, therefore, we undertook to determine both the natural history of contraction abnormalities after acute myocardial infarction in man and their response to nitroglycerin as a function of time using radionuclide angiography.

Methods

Patients

The study group included 16 patients with acute myocardial infarction admitted to the coronary care unit. Six of the 16 were included in an earlier study. Only patients who had significant ST-segment elevation (> 2 mm) and who subsequently developed new
pathologic Q waves (> 2 mm deep and 0.04 second wide) with elevations of MB-CK isoenzyme were included in the study. The initial radionuclide angiogram was done within 24 hours of onset of chest pain (mean 13.0 ± 7.1 hours). All 16 patients were re-studied approximately 1 week after the initial study (mean 6 ± 2.1 days) and again as an outpatient at approximately 6 weeks (38.4 ± 10.4 days) from the time of admission.

Radionuclide Angiograms

Radionuclide angiograms were obtained using a computerized multicrystal scintillation camera (Baird Atomic System Seventy-Seven) and a high-sensitivity, parallel-hole collimator. An 18-gauge percutaneous i.v. catheter was placed in an antecubital vein. After administration of 200 mg of potassium perchlorate, the patient was positioned in the right anterior oblique view and a 12–15-mCi dose of technetium-99m pertechnetate in a volume less than 0.8 ml was rapidly administered and flushed with 10–15 ml of 5% dextrose in water to obtain a bolus injection. Counts were recorded at a framing interval of 40–50 msec during the first pass of the isotope. Data were recorded on computer disc for processing and magnetic tape for long-term storage.

After the first radionuclide angiogram, the patient was given 0.4 mg of nitroglycerin sublingually to reduce the systolic pressure. If no effect was seen after 5 minutes, a second 0.4 mg was given. After systolic pressure decreased, a background frame was counted and a second radionuclide angiogram obtained.

Analysis of Angiographic Data

Radionuclide angiograms were processed as previously described from our laboratory. After applying a computer correction for crystal bias and for the second injection background, a region of interest comprising the left ventricle was selected and a time-activity curve generated. This resulted in a series of four to eight peaks (diastole) and valleys (systole) that were used to derive a computer-generated representative cycle. This cycle could be played in cine mode to qualitatively analyze the contraction pattern of the left ventricle. In addition, computer-derived and superimposed images of end-diastole and end-systole were used to provide a quantitative index of wall motion using a hemiaxis method.

The ischemic zone (clinically defined by the new pathologic Q waves) for the purpose of this study was the hemiaxis chord that most closely bisected the asynergic zone. A longitudinal chord was drawn from the midpoint of the aortic valve plane to the apex. For example, a chord was drawn to bisect the inferior wall (fig. 1). Lateral chords were drawn parallel to the aortic valve plane and placed equidistant on either side of the central chord and averaged. Each hemiaxis was measured and recorded as percent change from end-diastole to ascertain the amount of regional contraction. Hemiaxis shortening for the nonischemic zone was similarly calculated as percent shortening.

Ejection fraction was determined using the difference-in-counts method after appropriate background correction of 35% according to the formula \( \frac{ED_c - ES_c}{ED_c - BA} \), where \( ED_c \) = end-diastolic counts, \( ES_c = \) end-systolic counts and \( BA = \) background activity.

Volumetric analysis was performed using the method described by Rerych et al. End-diastolic volume was obtained using the area-length formula of Dodge and associates using the formula 0.85A², where A = area of the end-diastolic image obtained from the radioisotope angiogram by planimetry and L = length from aortic root to apex by direct measurement. The percent change in end-diastolic and end-systolic volume was then determined from the control to the nitroglycerin study in each patient.

Statistical analysis was performed using two-way analysis of variance. A p value < 0.05 was considered significant. All values are given as mean ± sd.

Results

Clinical Features

Of the 16 patients, 13 were male and three were female (table 1). Patients were 22–89 years old (mean

**FIGURE 1.** Computer-derived and superimposed radionuclide angiographic end-diastolic and end-systolic perimeters in the right anterior oblique view. The central chord is drawn to the center of the asynergic area and the dotted lines represent lateral chords. (left) Control study. (right) After sublingual nitroglycerin (TNG). Both central and lateral chords demonstrate improved hemiaxis shortening.
56 ± 16.3 years). Except for one patient who presented with acute left ventricular failure and had received diuretics and digitalis, none showed clinical evidence of cardiac failure (S3 gallop or basilar rales) at the time of the initial study. At the 1-week study, four patients were receiving diuretic therapy for clinical or radiologic manifestations of cardiac failure and two patients were on both digitalis and diuretics (table 1). At the time of the 6-week study, four patients were on digitalis and diuretics. None showed clinical evidence of cardiac failure.

**ECG and Enzymes**

Six patients had anterior and 10 inferior myocardial infarction. Of the six with anterior myocardial infarctions, three were anteroseptal (new Q waves V1-V4), one anterolateral (new Q waves Vc-V4) and two patients had Q waves in all six precordial leads. All six patients with anterior and eight of 10 with inferior myocardial infarctions demonstrated a contraction abnormality on the first study corresponding to the electrocardiographic location of infarct. There was no relationship between the degree of CK elevation and the extent of contraction abnormalities. Individual peak CK and MB-CK values are shown in table 1. Mean total CK was 917 ± 400 ml and mean MB-CK was 113 ± 46 ml.

**Hemiasis Shortening**

Figure 2 shows progressive changes in radionuclide angiograms before and after nitroglycerin in the three studies in a patient with an anterior myocardial infarction.

**Ischemic Zone**

**Central chord.** All six patients with anterior infarction and eight of 10 with inferior infarction had a reduction in hemiasis shortening in the infarct zone (fig. 3). Two patients, both with inferior myocardial infarctions, did not show asynergy in the first study. Mean hemiasis shortening in the central chord was 13.1 ± 9.8% before and 27.2 ± 18.4% (p < 0.001) after nitroglycerin in the initial study (fig. 3). Central chords in three anterior and one inferior myocardial infarction did not respond.

In the second study, mean hemiasis shortening was 12.9 ± 9.2% before and 24.4 ± 13.2% (p < 0.001) after nitroglycerin. Six patients did not improve significantly in the second study.

In the third study, 15 of 16 patients did not improve after nitroglycerin. The patient who improved after nitroglycerin was one of the two patients with inferior myocardial infarction who did not show significant asynergy in the initial study. Mean hemiasis shorten-

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Mean age of subjects at time of study: 56 ± 16.3 years.
Time of study 1: 13.0 ± 7.1 hours after infarction; peak total CK: 917.0 ± 400.2 IU/ml; peak MB-CK: 115.5 ± 46.5 IU/ml.
Abbreviations: MI = myocardial infarction; Inf = inferior; Ant = anterior.
ing was 13.9 ± 10.9% before and 13.4 ± 12.5% after nitroglycerin.

Lateral chord. Changes in the lateral chords were similar to those in the central chord in all three studies (fig. 4). Two patients with inferior myocardial infarction and one with anterior myocardial infarction did not show significant asynergy in the initial study. Two patients with inferior and one with anterior myocardial infarction did not improve significantly after nitroglycerin.

Mean lateral chord hemiaxis shortening was 18.6 ± 10.5% before and 28.4 ± 15.8% (p < 0.001) after nitroglycerin in the initial study (fig. 4). In the second study, hemiaxis shortening improved similarly, from 18.2 ± 9.8% to 25.6 ± 10.4% (p < 0.001). In contrast, in the third study, there was no significant improvement. Hemiaxis shortening was 22.1 ± 13.9% at control and 18.1 ± 12.9% after nitroglycerin.

Nonischemic Zone

Changes in the nonischemic zone in the individual patients before and after nitroglycerin in the three studies are shown in figure 5. Mean hemiaxis shortening in the nonischemic zone in the first study was 37.2 ± 13.5% before and 45.7 ± 15.2% (p < 0.001) after nitroglycerin. Similarly, in the second study, hemiaxis shortening improved from 35.5 ± 12.5% to 44.5 ± 14.2% (p < 0.001), and in the third study contraction improved from 38.5 ± 14.0% to 44.0 ± 15.6% (p < 0.05).

Ejection Fraction and Left Ventricular Volumes

Individual changes in ejection fractions are shown in figure 6. Eight of 16 patients in the initial study showed improvement in ejection fraction after nitroglycerin, with a mean ejection fraction of 35.4 ±
11.3% before and 41.4 ± 11.7% after nitroglycerin ($p < 0.002$). In the second study, mean ejection fraction was 38.4 ± 10.9% before and 42.1 ± 11.6% after nitroglycerin ($p < 0.08$). In the third study, ejection fraction increased from 40.2 ± 8.8% to 45.3 ± 14.5% ($p < 0.026$) after nitroglycerin.

In the first study, end-diastolic volume decreased by 22.9 ± 13.0% and end-systolic volume decreased by 30.5 ± 16.9% after administration of nitroglycerin. In the second study, end-diastolic volume decreased by 13.0 ± 8.0% and end-systolic volume decreased by 16.5 ± 11.9%. In the third study, the decrease in end-diastolic volume was 24.7 ± 16.3% and in end-systolic volume the decrease was 34.5 ± 15.9%.

Heart Rate and Blood Pressure

Heart rate and blood pressure changes are summarized for all three studies in figure 7. Systolic and diastolic pressure decreased significantly ($p < 0.005$). Heart rate increased slightly but significantly for...
Figure 5. Nonischemic zone hemiaxis shortening in the three studies before (C) and after nitroglycerin (TNG). Values are mean ± SD.

studies 1 and 2 (both $p < 0.005$) and insignificantly for study 3 ($p = 0.053$). One patient in study 1, two patients in study 2 and two patients in study 3 had diastolic pressures greater than 90 mm Hg.

Discussion

The present study demonstrates that contraction abnormalities that occur within 24 hours of an acute Q-wave infarct persist relatively unchanged after 1

Figure 6. Ejection fraction response to nitroglycerin (TNG) in each patient in each study. Values are mean ± SD. C = control.
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Figure 7. Effect of nitroglycerin (TNG) on heart rate and systolic and diastolic blood pressure. Values are mean ± sd. C = control.

and 6 weeks (figs. 3 and 4). Similarly, there was no demonstrable change in either nonischemic zone contraction or ejection fraction over this period (figs. 5 and 6). Others have also found little change in ejection fraction in serial studies.21, 22, 26-28 Rigo et al. found an increase in ejection fraction, from 0.38 to 0.45, in 14 patients.20 Similarly, Schelbert et al. found a variable and insignificant overall change in global ejection fraction early with only a slight overall increase, from 0.42 to 0.49 when a subgroup was restudied 2-39 months later.21 Reduto et al. also found no significant changes in serial ejection fraction. Moreover, no qualitative changes in contraction of the zone of infarction were seen in serial studies.18

Patients with acute anterior infarcts showed greater persistent reductions in hemiaxis shortening than those with an inferior infarct (figs. 3 and 4). This is similar to the findings of Bertrand et al.22 in their angiographic study, as was our observation that two patients with inferior infarction had no demonstrably significant asynergy. Reduto et al.18 have had a similar experience in two of the patients with acute inferior myocardial infarction. We previously found that an increase in hemiaxis shortening occurred after administration of nitroglycerin in the acutely injured zone in the first 24 hours after the onset of chest pain.18 The present study reaffirmed this finding. However, an additional striking observation was the initial respon-

siveness of the acutely injured zone to nitroglycerin, which diminished as a function of time. Thus, in the first 24 hours, central zone hemiaxis shortening improved significantly, decreased slightly in 1 week and was not demonstrable in 6 weeks (fig. 3). The same time course was seen in the lateral portions of the infarct (fig. 4). The 24-hour observations are consistent with preliminary data from Shah et al., using nitroprusside.24 However, the time period over which this zonal response could be demonstrated was totally unexpected.

Several explanations are possible for these findings. In view of the multifactorial clinical determinants of the rate of evolution of a myocardial infarction, the time course over which irreversible injury occurs after an acute myocardial infarction in man is variable, resulting in the potential for intervention.

An alternate explanation, however, is that these observations represent passive inward motion of a nonviable zone of left ventricle. The major argument against this representing a passive response to afterload reduction is the diminution of this response over time. However, a change in compliance over the 6-week healing period of the infarct remains a plausible explanation for these findings; progressive compliance changes do occur in the early weeks after an acute infarction.1, 23, 26-28

The limitations of radionuclide angiography must
be considered. The overall accuracy of radionuclide angiography compared with contrast ventriculography has been well-documented in our laboratory\textsuperscript{11, 17} and by others.\textsuperscript{18} However, significant technological limitations do preclude an evaluation of transmural events. In addition, the accuracy of edge detection to enhance depiction of more subtle wall motion changes would be further enhanced by higher count and frame rates. Nonetheless, the sequential changes observed and previous correlative studies make it unlikely that the observations of the present study can be explained solely by the limitations of radionuclide angiography.

If there is a relatively long time course before irreversible injury occurs after the onset of an acute myocardial infarction, the clinical implications would be considerable. This would suggest that the time constraints of interventions designed to reduce the ultimate size of an infarct are not nearly as stringent as experimental studies have suggested.\textsuperscript{19, 20} However, further studies are required to clarify the mechanism of the increase in hemiasis shortening and the degree to which this favorable change in wall motion can be prolonged.\textsuperscript{6}

References

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