Long-term function in the remote region after myocardial infarction: importance of significant coronary stenoses in the non-infarct-related artery

Cicero Piva de Albuquerque, Roberto Kalil-Filho, Gary Gerstenblith, Odila Nakano, Vania Barbosa, Giovanni Bellotti, Fulvio Pileggi, Bernardino Tranchesi

Abstract

Background—Left ventricular (LV) function is the most important determinant of outcome after a myocardial infarction. Global LV function after a myocardial infarction is affected not only by wall motion in the infarct zone but also by regional function in the contralateral territory. It was hypothesised that the presence of significant stenoses in coronary arteries supplying the contralateral territory might influence the ability of this region to compensate for damaged myocardium after a myocardial infarction.

Methods and results—79 patients treated with thrombolysis for acute myocardial infarction had coronary and ventricular angiograms within 24 h and at a mean follow-up of 12 months after myocardial infarction. Wall motion in the contralateral territory was analysed and scored by the centre line method and the change over time was correlated with the presence or absence of significant (>70%) diameter stenoses in the non-infarct-related artery. Mean (SD) contralateral territory motion worsened, from 0·74 (1·78) to −1·55 (2·06) SD chord (p < 0·001) in 40 patients with stenoses, whereas contralateral territory motion improved from −0·02 (2·4) to 0·63 (2·21) SD chord (p < 0·05) in the 39 patients without coronary stenoses. The same pattern was present whether or not the infarct artery was patent. The global left ventricular ejection fraction at 12 months was also related to contralateral territory motion (r = 0·71, p < 0·001) and to the presence of coronary stenoses (54 (15%) in those with coronary stenoses and 62 (16%) in those without, p < 0·05).

Conclusion—The results demonstrate that significant stenoses in arteries supplying the non-infarct territory adversely affect global and regional left ventricular function after a transmural infarction. Non-infarct artery anatomy should be considered in intervention strategies to improve left ventricular function after acute myocardial infarction.

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During the past decade patency of the infarct-related artery has become the major goal of treatment strategies in patients with acute transmural myocardial infarction.1 This was predicated on the hypothesis, now confirmed, that early reperfusion salvages myocardium and consequently preserves overall left ventricular function, which is the most important determinant of outcome after an infarction.2–4

Global function after infarction, however, is affected not only by changes in the wall motion of the infarct zone but also by regional function in the contralateral, non-infarct territory.5–6 After acute infarction hyperkinesis in the non-infarct area can normalise overall global ventricular function7 and such hyperkinesis is significantly related to improved in-hospital survival both in patients who have undergone successful thrombolysis and in those who have not.8–9 Less is known, however, about the importance of non-infarct regional function during the long-term follow up of post-infarction patients and about the factors which influence that performance.

It is conceivable that increased demand is placed on the non-infarct zone after a transmural infarction. After a coronary artery is occluded flow to the contralateral myocardium increases to match the increased oxygen requirements in that area caused by a higher regional workload.9 Several investigators have reported that outcome was poorer in post-infarction patients with multivessel disease whether or not they had received thrombolytic therapy.10–11 Coronary stenosis significant enough to result in post-infarction ischaemia originating from this area ("ischemia at a distance") identifies a subset of patients that are at a particularly high risk of death and recurrent infarction.12 The long-term influence of such stenoses on regional and global function, however, has not been reported.

We postulated that the presence of significant stenoses in coronary arteries supplying the non-infarct area, while not severe enough to result in clinical ischaemia, may adversely affect the long-term ability of this region to compensate for damaged myocardium and may influence overall global function. To examine this hypothesis, initial and late (mean follow up of 12 months) regional and global ventricular function were examined in relation to the presence or absence of a significant stenosis in the coronary artery supplying the non-infarct territory in 79 post-infarction patients.
Clinical and angiographic characteristics of patients with and without a coronary stenosis (CS) in the artery supplying the contralateral territory after a myocardial infarction

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>CS present</th>
<th>CS absent</th>
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<tbody>
<tr>
<td>Number of patients</td>
<td>40</td>
<td>39</td>
</tr>
<tr>
<td>Mean age (yr)</td>
<td>54</td>
<td>51</td>
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<tr>
<td>Sex</td>
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<td>8</td>
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<tr>
<td>Infarct related artery:</td>
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<tr>
<td>LAD</td>
<td>21</td>
<td>20</td>
</tr>
<tr>
<td>RCA</td>
<td>18</td>
<td>17</td>
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<tr>
<td>CFX</td>
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<td>2</td>
</tr>
<tr>
<td>Recanalisation rate (%)</td>
<td>65</td>
<td>69</td>
</tr>
<tr>
<td>Follow up (month)</td>
<td>12-7</td>
<td>12-1</td>
</tr>
</tbody>
</table>

CPX, circumflex artery; LAD, left anterior descending artery; RCA, right coronary artery.

Methods

PATIENT POPULATION

We studied 79 patients enrolled in thrombotic protocols of a cohort of 162 consecutive patients with an acute myocardial infarction. Coronary angiography was performed within 24 hours of myocardial infarction in every patient. All living patients with at least six months of follow up (n = 146) were contacted, and encouraged to undergo repeat angiography. Patients were not included in the analysis if they had undergone angioplasty or bypass surgery (n = 37) or if a follow up catheterisation was not available (n = 30).

Patients were divided into two groups according to the presence (group 1) or absence (group 2) of significant coronary stenoses (>70% diameter stenosis) in the non-infarct-related artery.

Group 1 consisted of 40 patients (36 men and four women) (mean (SD) age of 54 (8) years). The infarct-related artery was the left anterior descending artery in 21 patients, the right coronary artery in 18, and the circumflex artery in one (table). Thrombolytic therapy resulted in acute recanalisation of the infarct-related artery in 26 patients, seven of these patients had reoccluded arteries at the one year follow up angiogram. Fourteen patients had occluded arteries at initial catheterisation and six of these had patent infarct-related arteries at follow up. Eleven patients had significant three vessel disease (>70% diameter stenosis in all three main coronary arteries).

Group 2 consisted of 39 patients (31 men and 8 women) (mean age 51 (10) years) with <70% diameter stenosis in the non-infarct-related artery. In this group, 27 patients had patent infarct-related arteries initially, and three patients had reoccluded arteries at the follow up angiogram. Six of the 12 patients with occluded arteries at first angiography had patent infarct-related arteries at 12 months.

Medications during the study period were decided by the patient's physician. At the time of the infarction five (6%) patients were on beta blockers and eight (10%) were on calcium channel blockers. At the time of the repeat angiogram patients were being treated with aspirin (47 (59%), beta blockers (17 (21%), calcium channel blockers, (14 (18%)) and nitrates (12(15%)).

ANGIOGRAPHIC STUDY

Cardiac catheterisation was routinely performed via the brachial artery. Films were assessed by two independent observers blinded to patient status and ventricular analysis. "Flow" in the infarct-related artery was classified according to the criteria of the TIMI (thrombolysis myocardial infarction) study group, and the presence of grade 2 or 3 flow at 90 minutes after the infusion of the fibrinolytic agent was regarded as a therapeutic success. Collateral flow to the infarct-related artery was graded from 0 to 3 and grades 2 or 3 were regarded as significant. All suspect lesions were seen in at least two orthogonal projections. Coronary stenosis in the non-infarct artery was defined as an intraluminal coronary narrowing of greater than 70%. The internal contour of the suspect vessel was drawn on paper and compared with

Figure 1  (A) 100 chords drawn perpendicular to the centreline, delineating the end systolic and end diastolic contours of the left ventricle from a patient with an anterior wall myocardial infarction. (B) Plot of normalised motion and (C) standard deviations per chord in the same patient. The broken lines indicate the mean motion of the corresponding chord in normal ventriculograms.
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Figure 1

A)

Initial Follow up

B)

Initial Follow up

Figure 2 Mean motion in the contralateral wall initially and at 12 month follow up. (A) in patients with coronary stenoses and (B) in patients without stenoses.

obtained from an individual patient was compared with the mean motion of the corresponding chord in normal ventriculograms and expressed in units of standard deviations from the normal mean. Positive values reflect hyperkinesis whereas negative values express hypokinesis (fig 1C). Normal regional motion for the above analysis was obtained from 104 patients with chest pain who underwent diagnostic cardiac catheterisation in our laboratory and were found to have no coronary stenoses, normal cardiac anatomy, and normal global left ventricular function. Infarct wall motion was measured along chords 26–40 in patients with occlusion of the left anterior descending coronary artery and in chords 61–75 in those with occlusion of the right coronary artery and circumflex artery. Right coronary artery and circumflex artery territories were considered contralateral areas for left anterior descending infarcts and vice versa. All infarcts in the circumflex artery territory in this subset of patients caused primarily inferior wall motion abnormalities in the right anterior oblique projection.

STATISTICAL ANALYSIS
Values are mean (SD) unless stated otherwise. We used the SAS statistical package (Statistical Analysis System Institute, Cary, NC) for statistical analysis. We used the $\chi^2$ test to analyse categorical variables, analysis of variance and Student's $t$-test for continuous variables, and profile analysis for differences within a given sample. Linear regression was used to correlate two continuous variables. Values of $p < 0.05$ were regarded as significant.

Results
LEFT VENTRICULAR FUNCTION IN THE CONTRALATERAL AREA
In all patients mean motion in the wall remote from the infarction decreased from 0.37 (2.14) SD/chord initially to $-0.45$ (2.39) SD/chord after a year of follow up ($p < 0.05$). This change was entirely due to a significant worsening in function seen in patients with a stenosis in the coronary artery supplying this area. Contralateral wall motion worsened from 0.74 (1.78) to $-1.55$ (2.06) SD/chord ($p < 0.001$) in patients with stenoses, whereas it improved from $-0.02$ (2.4) to 0.63 (2.21) SD/chord ($p < 0.01$) in those patients without a significant stenosis. Regional motion in the contralateral segment was initially similar in the two groups, but at the follow up there was a significant difference ($-1.55 \neq 0.63$, $p < 0.05$). The same pattern was present whether or not the infarct related artery had been recanalised (fig 2). Contralateral territory function worsened in those patients with two vessel as well as in those with three vessel disease (from 0.83 (1.61) to $-1.22$ (1.56) and from 0.36 (2.56) to $-2.51$ (2.32) SD/chord, respectively, $p < 0.05$ for baseline $v$ follow up and $p = NS$ for two vessel $v$ three vessel disease).
FUNCTION IN THE INFARCT AREA

Overall infarct wall motion improved from $-5.03$ (2.77) SD/chord initially to $-3.60$ (2.54) SD/chord at the time of the repeat catheterisation. Patients with coronary stenoses had similar wall motion in the infarct area at the time of the infarct as patients without stenoses $-5.18$ (2.48) and $-4.89$ (3.05) SD/chord respectively. Motion in the infarct zone was also similar in both groups at the follow up $-3.65$ (2.78) SD/chord vs $-3.56$ (2.31) SD/chord. There was no association between the change in motion in the infarct area and in the contralateral area ($r = 0.17$, $p = 0.14$).

GLOBAL FUNCTION

Mean left ventricular ejection fraction in all patients was 58 (13)% at the initial catheterisation and 58 (10)% at follow up. Soon after infarction and at follow up 12 months later the ejection fraction significantly correlated with motion in the contralateral wall ($r = 0.71$, $p < 0.001$, fig 3). Left ventricular function at this time was relatively well preserved in patients without stenoses (ejection fraction 62 (13)%). Global function was, however, significantly worse in patients with a clinically significant stenosis in the non-infarct artery (ejection fraction 54 (15)%, $p < 0.01$). This difference primarily reflects decreased function in the infarct zone in both groups, which is compensated for by improved contralateral function in the group without stenoses but not in the patients with coronary stenoses. Global ejection fraction significantly improved in patients who did not have coronary stenoses, from an initial 57 (13)% to 62 (16)% at the follow up but remained depressed in patients with stenoses (55 (15)% to 54 (15)%; $p = NS$). Similar trends were present for those patients with double and triple vessel disease (from 54 (14)% to 55 (13)% and from 58% (14) to 51% (15%) respectively). The presence of stenoses in the vessel supplying collaterals to the infarct territory was also significantly related to function in patients with occluded infarct-related arteries. In eight patients with persistently occluded infarct-related arteries significant angiographically visible collateral circulation developed in four with coronary stenosis in the artery supplying the collaterals. Global ejection fraction in these four patients decreased from 53 (17)% to 46 (20)% ($p = 0.05$) whereas it improved from 50 (9)% to 72 (3)% ($p < 0.05$) in those without stenoses in the contralateral artery supplying the collaterals. The left ventricular ejection fraction did not change during the follow up in patients with persistently occluded infarct-related arteries without significant collaterals at angiography.

Discussion

The present study is the longest follow up report of paired ventriculographic assessments of function in patients who did not have revascularisation interventions after thrombolytic therapy.

We found that the presence of a 70% or greater narrowing of the diameter of the coronary artery supplying the non-infarct regions was associated with impaired motion in that region and with a lower global left ventricular ejection fraction at a mean of twelve months after an infarction. This finding was observed whether or not the infarct-related artery itself was patent.

The influence of contralateral stenoses on the function of the non-infarct zone seems to parallel the influence of these stenoses on the development of symptomatic ischaemia "at a distance" and the associated poor prognosis. However, the mechanisms of chronic regional dysfunction in humans are complex and not completely understood. One possible explanation for the reduced wall motion in patients with coronary disease is that recurrent ischaemic episodes related to stenoses in the artery supplying that territory result in reduced left ventricular function over time. Alternatively, it has been noted that more modest flow reductions not associated with ischaemia can nevertheless result in decreased function, this matches the decreased flow so that a balanced though downregulated supply and demand can be maintained ("hibernating myocardium"). Therefore, it is also possible that stenoses in non-infarct coronary arteries that are not severe enough to induce ischaemia may nevertheless limit the ability of this region to compensate for depressed function in the infarct zone.

We found that the presence of significant stenoses in arteries supplying non-infarct territory also influenced global left ventricular function. We also showed that the previously reported short-term association between non-infarct regional wall motion and global ejection fraction was maintained during long-term follow up. Interventions such as bypass surgery and angioplasty, which improve flow to non-infarct regions supplied by stenotic vessels, may result in better preservation of
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Regional and global function at least in the first year after infarction. Because left ventricular function is the most important determinant of survival, lifestyle, and work status in post-infarction patients, future studies to improve outcomes in those patients should consider intervention strategies designed to improve flow in non-infarct arteries.

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