Regional Myocardial Wall Thickening Response to Nitroglycerin

A Predictor of Myocardial Response to Aortocoronary Bypass Surgery

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SUMMARY The peak rate of systolic wall thickening (β± dTwall/ dt) in regions of the left ventricle (LV) was determined preoperatively by biplane roentgen videometry in 18 patients before and after sublingual administration of nitroglycerin (NTG) and 3-23 months (median 12) after aortocoronary bypass surgery. The regional LV response to NTG was a reliable predictor for postoperative improvement in regional wall dynamics after successful aortocoronary bypass grafting. The ejection fraction response to NTG or surgery will not predict the regional myocardial response to NTG or surgery, nor will the regional response predict the global response. Subendocardial myocardial infarction is another cause of unimproved regional myocardial function after NTG and aortocoronary bypass surgery.

AORTOCORONARY BYPASS GRAFT SURGERY relieves angina pectoris in the majority of patients and improves regional myocardial function in the region of a patent graft, provided postoperative graft flow is adequate and there has been no myocardial infarction in the region. Improvement in noninfarcted but hypokinetic myocardial segments is difficult to predict on the basis of a single measurement of regional wall dynamics. Previous studies with sublingual nitroglycerin (NTG) have demonstrated the restoration of normal indices of regional function in areas of the left ventricle presumed to be ischemic.

The present study was performed to assess whether the response of the preoperative peak rate of systolic wall thickening to sublingual NTG could predict the response of the rate of wall thickening to aortocoronary bypass graft surgery in patients with and without transmural or subendocardial myocardial infarction. Graft flow flows to the regions under study were determined postoperatively by videodensitometry.

Material and Methods

Eighteen patients (age 34 to 67 years) who underwent cardiac catheterization and aortocoronary bypass graft surgery for disabling angina pectoris between March 1973 and May 1975 were selected for study (table 1). All patients with technically satisfactory analysis of the preoperative left ventriculograms were recalled without regard to symptoms. Criteria for inclusion in the study were: (1) prior informed consent; (2) absence of cardiomegaly, heart failure, and other heart disease; (3) preoperative control, preoperative postnitroglycerin, and postoperative left ventriculograms technically suitable for regional videometric analysis in a region supplied by a patent aortocoronary bypass graft; (4) no cardiac surgery other than aortocoronary artery bypass grafting (patients with resection of any part of the LV were excluded); (5) no medication known to influence LV function; and (6) minimum of three months elapsed since surgery. This was not a consecutive group of patients and may have been weighted by patients who consented more rapidly to restudy because of postoperative symptoms or positive treadmill electrocardiograms.

References


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The patients were restudied three to 23 months (median 12 months) after aortocoronary artery bypass surgery. Transmural myocardial infarction by definite electrocardiographic and vectorcardiographic criteria14 was present in six patients before surgery; three additional patients were classified as having a subendocardial infarction preoperatively (chest pain of > 15 minutes, myocardial enzyme elevation, and persistent [> 48 hours] new T-wave inversion and/or ST-segment depression without pathologic Q waves or loss of R-wave forces).

All patients were in a postabsorptive state and had been premedicated intramuscularly with 100 mg of pentobarbital before cardiac catheterization. No patient received nitrates within the eight hours before the study. The catheterization study sequence was as follows: (1) aortic and LV pressure determinations; (2) biplane left ventriculography; (3) 7-minute pause, LV pressure record, 0.6 mg of NTG administered sublingually, 3-minute pause, repeat LV pressure record, and repeat biplane left ventriculography; (4) sublingual isosorbide dinitrate (Isordil), 5 mg; (5) selective coronary (and graft for postoperative study) cineangiography. At the postoperative study, the following sequence was substituted for step 3: 5 to 10-minute pause, graft transit times, and spot films for graft dimensions.

Simultaneous biplane LV videangiograms were recorded, 60 video fields/sec, in the right anterior oblique and left anterior oblique orthogonal projections as previously described.1 Meglumine diatrizoate (Renografin 76%, 0.7 ml/kg) was injected over 3 to 4 seconds during deep inspiration. The preoperative videangiograms were always reviewed before the postoperative study in order to place the patient in exactly the same position for both studies. Ventriculography was never performed during or immediately after an episode of angina.

Videodensitometric measurements of the mean transit times in the vein grafts of the blood-contrast mixture were obtained after injection of 1 to 3 ml of Renografin at the orifice of each graft as previously described.3, 11, 12 The volume of the graft was determined from biplane orthogonal roentgenograms.11, 12 Graft blood flow is equal to graft volume divided by mean transit time of the bolus along the graft.11, 12

End-diastolic and end-systolic LV volumes and the ejection fraction (EF) were determined from biplane roentgen videometry interfaced with a CDC 3500 computer as previously described.3 Only regular beats were analyzed.

The same videometric system was used to determine wall thickness throughout several cardiac cycles at 60 video fields/sec and to calculate and display the peak rate of systolic wall thickening as previously described.10 Up to three segments in each of the anterior and posterolateral walls and one inferior wall segment are capable of analysis, depending on the magnification and orientation of the cardiac silhouette and the definition of the epicardium. Regional LV function was analyzed in as many segments supplied by a patent graft as was technically possible.

The accuracy and reproducibility of the videometric techniques,10 computer analysis of wall thickness determination,1, 8, 10 and EF3 have been reported.

Similarly, the reproducibility and accuracy of the videodensitometric method of determining graft flows have been documented in prior human and animal studies.1, 11, 12

Segments were classified quantitatively as "normal" when the peak rate of systolic wall thickening (pdtw/dt) was greater than or equal to 5.0 cm/sec, "hypokinetic" when the pdtw/dt was less than 5.0 cm/sec, "akinetic" when the pdtw/dt was equal to 0, and "dyskinetic" when the pdtw/dt was less than 0 because of systolic wall thinning.10

Heart rate was measured from the electrocardiogram recorded simultaneously with the ventriculogram on videotape. Aortic diameters were measured at end systole on all ventriculograms with the same videometric system to verify that appropriate magnification factors had been used for studies both before and after operation.

Coronary cinearteriograms before and after operation were compared in multiple views by at least two observers to determine whether there were any changes in the native coronary circulation. The reported stenosis of a coronary artery is the visually estimated maximum narrowing in arterial diameters.

The operative techniques utilized in all patients were mild to marked hypothermia (15° to 33°C); venting via the left atrium or pulmonary veins (12 patients) or left ventricular apex (six patients); and blood flows on cardiopulmonary bypass of 2.0 to 2.4 L/min/m². Ventricular fibrillation was not established deliberately. The aorta was clamped for 10 to 20 minutes per graft. A reversed segment of autogenous saphenous vein was used for all grafts. In the entire study population, three patients had single grafts, 10 had double grafts, and five had triple grafts.

Results

Clinical

In these 18 patients (table 1) the left anterior descending coronary artery was bypassed in 16 (five grafts subsequently occluded); the left circumflex artery was bypassed in 13 (four grafts subsequently occluded). The right coronary artery was bypassed in nine (one graft subsequently occluded).

All grafts were patent in nine patients (50%), one graft was occluded in eight patients, and two grafts were occluded in one patient.

In the nine patients with all grafts patent, only four patients were completely revascularized; that is, they had no other coronary arteries with ≥ 50% stenosis that were not grafted. Eight patients had one vessel left ungrafted (see table 1) and six patients had two vessels left ungrafted.

At the time of postoperative study, 13 patients were free of angina, three had class II (NYHA) angina, and two had class III angina. One patient had a postoperative transmural myocardial infarction in the region of an occluded graft.

Total Ventricular Functional Status

After NTG (table 1), mean changes included a decrease of 5 mm Hg in the LV end-diastolic pressure (P < 0.01) and the systemic mean blood pressure (P < 0.05), a decrease of 9 ml/m² in end-diastolic volume index (P < 0.01) and 3 ml/m² in the stroke volume index (P < 0.05), and increases of 4% (EF units) in the EF (P < 0.05) and 6 beats/min in heart rate (P < 0.05).

There was no statistically significant change in the LV end-diastolic pressure and volume, stroke volume, EF, and mean systemic blood pressure between the preoperative pre-NTG and the postoperative determinations. The heart rate
TABLE 1. Clinical Data and Ventricular Functional Status

<table>
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<tr>
<th>Case no.</th>
<th>Age (yr), sex</th>
<th>Location of myocardial infarction preop</th>
<th>Degree of stenosis, graft status*</th>
<th>No. of vessels left ungrafted§</th>
<th>LVEDP (mm Hg)</th>
<th>SBP (mm Hg)</th>
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Mean change from Pre to NTG

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<tr>
<th>Range</th>
<th>Median change</th>
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<tr>
<td>-5*</td>
<td>-5</td>
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<td>(+5 to -16)</td>
<td>(-5)</td>
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</table>

*P < 0.01; †P < 0.05.
LAD = left anterior descending coronary artery; LCx = left circumflex coronary artery; RCA = right coronary artery; — = normal or < 50% stenosis; ≥50% < 100% stenosis; = total occlusion; P = patent graft; O = occluded graft; d = large diagonal branch >50% stenosed, left ungrafted; A = anomalous distribution supplies large area of posterolateral wall.
§Refers only to a coronary artery with ≥50% stenosis left ungrafted for anatomic and technical reasons or a vein graft supplying ≥50% stenosed artery which was ungrafted.
¶Value determined from study eight days after surgery.
**-1 = dyskinesia; 0 = akinetic.

Abbreviations: LVEDP = left ventricular end-diastolic pressure; SBP = mean systemic blood pressure; EDV1 = end-diastolic volume index; EF = ejection fraction; dP/dT = peak rate of systolic wall thickening; NTG = nitroglycerin; Ant = anterior; Lat = lateral; Inf = inferior; SEI = subendoventricular infarction; PL = posterolateral.

Increased slightly (9 beats/min average) after surgery (P < 0.05).

Predictability of EF

The change in EF preoperatively before and after NTG gave a positive correlation with the change in EF before NTG and surgery and after surgery (r = 0.64, bYX = 0.8). This relationship is not strong enough for predictive purposes in individual patients, particularly those with an EF change of less than 10% after NTG.

Regional Ventricular Functional Status

Thirty LV segments (18 patients) (table 1) analyzed on the preoperative control, post-NTG, and postoperative left ventriculograms were supplied by a patent graft. Four of these segments were supplied by graft flows of < 40 ml/min (and three of these four were associated with a > 50% stenosed, ungrafted diagonal branch as well) and were excluded from the data in figure 1 because a graft flow of < 40 ml/min would appear to preclude improvement to normal and could cause postoperative deterioration in regional wall thickening; these four segments did deteriorate by an average of 2.1 cm/sec postoperatively. Of the remaining 26 segments (fig. 1), 15 were supplied by grafts with blood flows of > 60 ml/min and two by grafts with blood flows of > 40 ml/min but < 60 ml/min; in nine graft flow measurements were not technically satisfactory.

All eight preoperatively hypokinetic segments (dP/dT = 0 < 5 cm/sec; fig. 1, eight of the ten segments in the left panel) that improved to normal after preoperative NTG improved to normal after surgery. All six preoperatively hypokinetic segments that improved at least 1.2 cm/sec after NTG (fig. 1, middle panel) improved after surgery (five of these six to normal).
### MYOCARDIAL THICKENING AFTER NITROGLYCERIN/Chesebro et al.

<table>
<thead>
<tr>
<th>EDVI (ml/m²)</th>
<th>EF (%)</th>
<th>Regional function</th>
<th>Graft flow (ml/min)</th>
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**Figure 1.** Peak rate of systolic wall thickening ($\phi dT_w/dt$) in segments supplied by patent grafts. Determinations are preoperatively before (control) and after nitroglycerin (NTG) and a median of 12 months after surgery. Note that ordinate starts at $-1$ (dyssynergic) and that there are two akinetic and one dyskinetic segments that did not improve after NTG or surgery. O = segments associated with no decrease in regional function elsewhere in LV; * = segments associated with decreased regional function elsewhere in LV (graft occlusion or decreased postoperative regional wall dynamics); x = preoperative subendocardial infarction; * = preoperative transmural infarction.
The seven hypokinetic segments that improved \(< 1.2\) cm/sec after NTG (fig. 1, right panel) did not improve \(\leq .6\) cm/sec after surgery. There was documented subendocardial infarction in the region of four and transmural infarction in three of these seven segments. Graft blood flows to these segments ranged from 49 to 110 ml/min (median 82 ml/min). All three akinetic or dyskinetic segments were in a region of preoperative myocardial infarction (subendocardial in one and transmural in two) and remained unchanged after both NTG and surgery despite a graft blood flow of 67 ml/min supplying two of the three segments for which measurements were technically satisfactory.

Relation of Regional and EF Changes

There was no statistical correlation \((r \leq 0.06)\) between changes in regional LV function \((5dT_w/dt)\) and the EF both before and after NTG (before surgery) and before NTG and surgery and after surgery. This is consistent with our previous observations.\(^1\)

Discussion

This study demonstrates that an intervention (NTG) ventriculogram can predict preoperatively the functional status of the regional myocardium and the response after successful aortocoronary bypass graft surgery. Subendocardial as well as transmural myocardial infarction can preclude improvement after both NTG and surgery even though bypass graft blood flows appear adequate \((> 60\) ml/min). The EF response to NTG or surgery will not predict the regional myocardial response to NTG or surgery, nor will the regional response predict the global response.

The mechanisms of action whereby NTG improves regional LV function in apparently ischemic but viable myocardium are not clear from this study; they are probably multiple, but this remains controversial. The mechanisms suggested include the peripheral arterial and central venous actions in decreasing myocardial oxygen requirements,\(^16, 17\) enhanced regional myocardial blood flow that may be due to increased collateral blood flow\(^18, 19\) which has been demonstrated in man at open heart surgery,\(^20\) possible transmural redistribution of myocardial blood flow,\(^21, 22\) and perhaps a reflex increase in contractility that experimentally could be prevented by beta blockade.\(^23\) The small reflex increases in heart rate in response to sublingual NTG in man suggest that the last-named mechanism plays a minor role. The intervention with NTG appears safe, and thus far a paradoxic depression of LV function has not been observed in man during cardiac catheterization and left ventriculography, although theoretically this could occur in the presence of global myocardial ischemia if arterial pressure is not maintained.\(^24\)

The postoperative change in peak rate of systolic wall thickening related best to the status of the underlying myocardium as predicted by the NTG response; it was not related to the arterial pressure, LV end-diastolic pressure or volume, or EF, none of which changed significantly after surgery. As previously noted,\(^1\) the postoperative changes in peak rate of systolic wall thickening were independent of changes in heart rate. The effect of changed dynamics elsewhere in the LV as a result of infarction, graft occlusion, progression of coronary disease or low graft flow (fig. 1, solid dots) was also considered as in previous studies\(^1\) and did not appear to account for the observed results.

The use of dynamic measurements of wall thickness as an index of regional myocardial viability is supported by the study of Heikikä et al.\(^25\) in open-chest pigs. Systolic myocardial wall thinning (dyskinesis) or the absence of myocardial wall thickening (akinesis) was observed after experimental acute myocardial infarction by coronary arterial occlusion or damage to the myocardium by freezing. They also demonstrated continued akinosis in infarcted segments after administration of isoproterenol, which increased the extent and velocity of LV wall thickening by more than 200% in normal myocardial regions. The lack of improvement in akinetic and dyskinetic segments after NTG and after successful aortocoronary bypass graft surgery in this study and in previous studies from our laboratory\(^1, 9\) is consistent with the results of these experiments.

Others have observed that improvement in regional LV function after NTG as measured by increased hemiaxis shortening was reflected in an increase in the monoplane EF after NTG.\(^26, 28\) In contrast, we have found that the myocardial wall thickening response to NTG will not predict the EF response determined by biplane LV volume measurements using Simpson's rule. Previous studies from our laboratory\(^6\) have also demonstrated the differing regional responses to NTG within the same LV and even within the same anterior or posterolateral myocardial wall. In coronary artery disease, myocardial ischemia may be heterogeneous within the LV, and the independence of regional and global LV function is not surprising. Independence of regional function and EF may also be related to 1) the small size of the regions studied in relation to the size of the LV, 2) measurement of regional myocardial wall thickening, which reflects more specifically the region under study and is less influenced by adjacent myocardial motion than are measurements of endocardial motion only,\(^21, 27\) and 3) the use of biplane EF measurement, which more accurately assesses the EF as compared with monoplane EF measurement.\(^12, 29, 30\) The limitation of angiographic measurement of regional LV function, including wall thickness, was previously discussed.\(^1\) The postoperative EF responses would ideally be evaluated in patients with all diseased \((> 50\%\) stenosis) coronary arteries and their major branches bypassed and with all coronary artery bypass grafts patent; however, this does not invalidate the regional LV function changes observed and their relation to the EF.

This study also documents that clinical subendocardial myocardial infarction (as defined above) must be considered as a cause of abnormal and irreversible regional myocardial dysfunction. This dysfunction is usually hypokinesis (Madigan NP, Rutherford BD, Chesebro JH, Ritman EL: unpublished observations) but in the posterolateral LV may be akinesis (patient 8) or dyskinesis,\(^21\) as documented by the videometric measurement of systolic wall thickening.

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