Reversible Asynergy

Histopathologic and Electrographic Correlations in Patients with Coronary Artery Disease

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SUMMARY Histopathologic-electrographic studies of ventriculography depicted nitroglycerin responsive and unresponsive asynergic areas were performed in 25 patients. Of 29 areas, 12 improved with nitroglycerin, showing < 10% muscle loss. Seventeen unimproved zones demonstrated significant fibrosis. Epicardial electrograms showed R waves in eight of nine improved zones. Of 11 unimproved zones, eight had Q waves.

VENTRICULOGRAPHY IS CURRENTLY the best method for assessing both the presence and severity of asynergy in living man. However, surprisingly little is known about the underlying characteristics of asynergic zones as defined ventriculographically. In this regard, considerable interest has focused on determining the potential for improvement of abnormally contracting segments of the left ventricle in patients with coronary artery disease. Previous studies from our laboratory and others have shown that nitroglycerin can improve contraction of some asynergic areas, a response which is highly predictive of a corresponding zonal improvement following insertion of a saphenous vein bypass to the artery subserving that segment. Several factors are important determinants of improvement. The presence of pathologic Q waves on the surface electrocardiogram, severe proximal coronary artery disease, and more severe forms of asynergy significantly decrease the incidence of responsiveness to nitroglycerin, while the presence of coronary collaterals enhances the likelihood of improvement.

Visual observations made at the time of surgery have suggested that fibrosis is more common in irreversible asynergic zones. It has also been shown that fibrotic areas are associated with the presence of Q waves in epicardial electrograms. However, no histopathologic or electrographic data are available to compare differing degrees of ventriculographically defined asynergy and the characteristics of potentially reversible and irreversible segments. This study was, therefore, undertaken to more precisely determine the histopathologic and electrographic counterparts of responsive versus unresponsive asynergic segments as defined by nitroglycerin ventriculography.

Histopathologic-electrographic data from five responders showed < 10% muscle loss, of whom four had epicardial R waves. Six unresponsive areas had significant fibrosis, with a QS over four.

Thus, nitroglycerin responsive asynergic areas are generally comprised of histologically intact myocardium and are associated with epicardial R waves.

Methods

Twenty-five patients undergoing open-heart surgery form the basis of this study. Fifteen patients had aortocoronary bypass surgery for angina associated with significant (> 75%) obstruction of at least one major coronary artery; six had bypass surgery in association with aneurysmectomy, while four had aneurysm resections only. None of the patients included in this study had an acute myocardial infarction within four weeks prior to surgery.

Cardiac catheterization was performed in the postabsorptive state after premedication with 50 mg Nembutal, 50 mg Demerol and 0.4 mg Atropine. Right heart catheterization was performed via an antecubital vein cutdown and left heart catheterization either percutaneously through a femoral artery or via a right brachial arteriotomy. Following recordings of left ventricular pressure (using Statham P23Db transducers) and cardiac output (indicator dilution method using indocyanine green), left ventriculography was performed in the 30° right anterior oblique projection using 30–40 cc of meglumine diatrizoate (Renograin-76) injected into the left ventricle. In case was this performed during or immediately after anginal symptoms. When asynergy was observed, nitroglycerin (gr 1/150 sublingual) was administered 15–20 min following the initial ventriculogram. When the characteristic hemodynamic effects of nitroglycerin were observed (fall in systolic and end-diastolic pressure and increase in heart rate), the ventriculogram was repeated in the same degree of obliquity, using the same amount of contrast material and tube-to-table top distance. Selective cine coronary arteriography was then performed by either the Sones’ or Judkins’ technique. Cines were taken on a 10 × 6 inch dual field image intensifier (Siemens) at 64 frames/sec using 35 mm Kodak Shellburst film. Hemodynamics were monitored and recorded on an Electronics for Medicine oscillographic recorder.

Epicardial electrograms were obtained prior to or immediately after the institution of cardiopulmonary bypass and prior to elective ventricular fibrillation. Unipolar electrograms were obtained using three silver electrodes mounted in acrylic plastic in the shape of a triangle and recorded between 0.1 to 100 Hz on a Grass model 7B polygraph at 25, 50, and 100 mm/sec paper speed. A flat
probe on a flexible handle was utilized to facilitate recordings from the posterior surface of the left ventricle. With the patient on cardiopulmonary bypass for less than five minutes and prior to elective ventricular fibrillation, a full thickness punch biopsy was obtained using a punch sucker technique.11, 12 A 14-gauge needle with a square, keenly sharpened tip was connected to an aspiration suction line with a Likens tube interposed and a sponge covering the outflow arm of the collecting tube. This technique avoided undue compression, trauma, or distortion. The biopsy specimen was processed routinely, serially sectioned longitudinally and stained by both hematoxylin and eosin and by a connective tissue stain for semi-quantitative estimate of the amount of fibrosis.

To facilitate the correlation of ventriculographically determined asynergic sites with the corresponding anatomic location at the time of surgery, the antero-apical and the inferior zone were specifically examined. These areas were chosen for their ease of demarcation by right anterior oblique ventriculography. In addition, their low vascularity rendered biopsy a safe procedure. During surgery, epicardial electrograms were recorded from multiple sites beginning over the right ventricle and then sequentially from the region next to the septum, antero-apical area, lateral wall and the inferior aspect of the left ventricle. The antero-apical area was taken as the zone between the anterior interventricular groove and a line 4–5 cm parallel and lateral to it extending toward the apex. The inferior area was taken as the epicardial surface bounded by the atrioventricular groove, the posterior interventricular groove and a line 3–4 cm parallel and lateral to it. An average of six sites was recorded from each area. All recordings were obtained during sinus rhythm.

The electrogram pattern from the proposed biopsy site, antero-apical and/or inferior, was then specifically noted. Following institution of cardiopulmonary bypass, a biopsy was taken from this site permitting accurate correlation of electrogram and biopsy.

Severity of asynergy during ventriculography was evaluated both qualitatively and quantitatively.2, 7, 8 A quantitative analysis was performed by superimposing tracings of end-diastolic and end-systolic frames using the apex and mid-aortic valve as fixed points. Hemiaxes were drawn which bisected the long axis at right angles to it. Each hemiaxis was recorded as a percentage change from end-diastole. Severity of asynergy was thus classified as hypokinesis (decreased contraction; <25% hemiaxis shortening), akinesis (absence of contraction; 0–5% hemiaxis shortening) and dyskinesis (paradoxical systolic expansion; hemiaxis lengthening). Improvement following administration of nitroglycerin was considered present if hemiaxis shortening increased by greater than 10%.2, 7, 8

Epicardial electrograms were analyzed for the presence and duration of Q waves. Previous studies have indicated that Q waves are normally absent over the left ventricle immediately lateral to the septum with Q waves of <0.01 sec in duration occasionally seen over the anterior free wall and initial Q waves of ≤0.03 sec. inferiorly.13-19 For purposes of analysis anterior Q waves ≥0.03 sec and inferior Q waves ≥0.04 sec were considered abnormal. In addition, electrogram sites over each area were analyzed for the relative frequency of initial R and Q waves, thereby providing an index of homogeneity of a specified zone.

Each biopsy was examined independently and blindly by at least two observers and classified according to the percent muscle loss present in the biopsy. This included both fibrosis and evidence of myocardial necrosis (healing infarct) which may not have progressed to complete fibrosis; namely, leukocytic infiltration, removal of muscle fibers, macrophages and fibroblasts or early signs of collagen formation.16 The percentage muscle loss and fibrosis was assessed, graded as 0–9%, 10–49%, 50–74% and 75–100% of the biopsy by volume and then correlated with the severity of asynergy. Statistical analysis was performed using the Student's t-test and all values are given as mean ± standard error of the mean (SEM).

**Results**

There were 25 patients (19 male, 6 female) with an average age of 56.9 ± 1.7 years, ranging from 36 to 79.

**Severity of Asynergy, Nitroglycerin Response, and Histopathology**

Of the 25 patients, histopathologic studies were obtained from 29 areas. Nineteen were biopsies, and ten were aneurysm resections.

Eleven hypokinetic and one dyskinetic zone demonstrated improvement after nitroglycerin (table 1). All had less than 10% muscle loss (fig. 1). In contrast, of six akinetic and 11 dyskinetic zones (table 1) which failed to improve after nitroglycerin, 11 showed more than 75% muscle loss (fig. 2) and two more than 50%. Four areas (three akinetic and one dyskinetic) which failed to improve had 30–35% muscle loss (fig. 3).

**Severity of Asynergy, Nitroglycerin Response, and Epicardial Electrograms**

Twenty asynergic areas in 15 patients were examined with epicardial electrograms (table 2). Of 11 areas which demonstrated initial R waves, seven were hypokinetic, three akinetic, and one dyskinetic. In contrast, of nine areas with initial Q waves, one was hypokinetic, one akinetic, and seven dyskinetic (P < 0.01).

| Table 1. Correlation of Asynergy, Response to Nitroglycerin, and Histopathology |
|-------------------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|
| NITROGLYCERIN RESPONSE | NO. OF AREAS | SEVERITY OF ASYNERGY | % HEMIAXIS SHORTENING CONTROL | % HEMIAXIS SHORTENING NITROGLYCERIN | MUSCLE LOSS (% BY VOLUME) 0-9 | MUSCLE LOSS (% BY VOLUME) 10-49 | MUSCLE LOSS (% BY VOLUME) 50-74 | MUSCLE LOSS (% BY VOLUME) 75-100 |
|--------------------------|--------------|-----------------------|-------------------|------------------|----------------|----------------|----------------|----------------|----------------|
| IMPROVED                  | 11           | Hypokinetic           | 15.5 ± 1.2        | 33.9 ± 3.2*      | 11             | —              | —              | —              |
|                           | 1            | Dyskinetic            | —3.0              | 20.0             | 1              | —              | —              | —              |
| UNIMPROVED                | 6            | Akinetic              | 2.8 ± 0.6         | 4.7 ± 2.1        | —              | 3              | 2              | 1              |
|                           | 11           | Dyskinetic            | —4.5 ± 0.6        | —5.5 ± 0.7       | —              | 1              | —              | 10             |

*P < 0.001.
Epicardial electrograms consistently showed initial R waves over all sites in eight of nine areas which improved with nitroglycerin (fig. 4). In contrast, of the 11 segments unresponsive to nitroglycerin, eight demonstrated initial Q waves in all electrogram recordings (table 2 and fig. 5). One hypokinetic area which improved had local Q waves while three akinetic areas which did not respond to nitroglycerin showed an initial R wave in the epicardial electrogram (table 2).

Severity of Asynergy, Nitroglycerin Responsiveness, Histopathologic, and Electrographic Features

In nine patients, both histopathologic and electrographic data were available from the same site in 11 areas. Of four hypokinetic zones which improved after nitroglycerin, from $15.3 \pm 1.9$ to $40.7 \pm 5.1\%$ (P < 0.01), and one dyskinetic zone which improved, from $-3.0$ to $20.0\%$, all had less than 10% muscle loss. Four of these five also had initial R waves in the corresponding epicardial recordings. One hypokinetic area demonstrated an initial Q wave.

In contrast, there were six areas unimproved by nitroglycerin. Of three akinetic zones one had greater than 50% fibrosis and a QS complex, while two had 10-49% muscle loss with associated initial epicardial R waves. The three dyskinetic segments demonstrated over 75% muscle loss with associated epicardial Q waves.

Discussion

The demonstration of an increase in inward systolic motion of asynergic segments of the left ventricle following nitroglycerin2 or post-extrasystolic potentiation5 has given impetus to the concept that these “responsive” asynergic zones consist of viable, chronically ischemic myocardium possessing residual contractile ability. Conversely, asynergic zones which are “unresponsive” to these interventions have been considered to be comprised primarily of scar tissue.2 However, the possibility also exists that the “improvement” is more apparent than real. Thus, the increase in inward systolic motion may represent improvement of an asynergic area occurring as a passive accompaniment of enhanced contraction of its surrounding normal myocardium.

Experimental data from our laboratory has tended to support the prior concept since direct measurements of asynergic zonal contraction indicated that improvement in contractile ability can occur in a partially ischemic area of myocardium following administration of nitroglycerin.17 In addition, post-extrasystolic potentiation has also been shown to result in segmental improvement in contraction of ischemic myocardium.18 However, it is difficult to directly extrapolate this experimental data to the clinical setting.

The present study indicates that an area of the left ventricle which responds to nitroglycerin is characterized by the presence of histologically normal myocardium. In contrast, unresponsive areas are comprised of significant amounts of fibrotic and necrotizing myocardium. This correlation strongly suggests that it is the involved segment itself which...
is the primary determinant of asynergic zone responsiveness, thus being similar to the experimental finding. In addition, presence of normal appearing myocardium in a responsive area would better explain the correlation between asynergic responsiveness to nitroglycerin and following saphenous vein bypass surgery.2

In a previous study, a major determinant of potential responsiveness of an asynergic zone to nitroglycerin was the severity of asynergy.2 As table 1 clearly shows, the general trend is for more severe forms of asynergy to be associated with greater degrees of muscle loss, thereby explaining this relationship. However, notable exceptions do occur (fig. 1). Thus, the severity of asynergy alone, as depicted ventriculographically is not always adequate in defining the characteristics of the underlying asynergic zone.

In studies of experimental coronary occlusion, Wilson originally demonstrated that epicardial Q waves are related to myocardial infarction.19 Kaiser et al. showed that epicardial electrograms could differentiate areas of myocardial fibrosis from functioning myocardium during open heart surgery.9, 19 The present study confirms this finding but, in addition, indicates that initial R waves can be recorded over areas in which considerable although nontransmural fibrosis is present. This finding is consistent with previous experimental work.9, 20 Thus, it appears that although a local Q wave indicates significant replacement of myocardium by fibrotic tissue, an R wave does not necessarily indicate normal underlying myocardium and may be consistent with localized areas of fibrotic replacement (table 2). In addition, the finding of R waves over areas which failed to improve is consistent with the known dissociation between the amount of electrical and mechanical dysfunction that occurs in the experimental setting of acute ischemia.21

Although methodological problems are associated with the use of a biopsy technique to determine the histo-

<table>
<thead>
<tr>
<th>TNG response</th>
<th># of areas</th>
<th>Severity of asynergy</th>
<th>% Hemiaxis shortening</th>
<th>Epicardial electrogram</th>
<th>Initial R wave</th>
<th>Initial Q wave</th>
</tr>
</thead>
<tbody>
<tr>
<td>Improved</td>
<td>8</td>
<td>Hypokinetic</td>
<td>14.4 ± 1.3</td>
<td>31.5 ± 3.1*</td>
<td>7</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>Dyskinetic</td>
<td>-3.0</td>
<td>20.0</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>Unimproved</td>
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<td>Akinetic</td>
<td>2.6 ± 0.4</td>
<td>5.5 ± 1.0</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>7</td>
<td>Dyskinetic</td>
<td>-3.0 ± 0.7</td>
<td>-5.0 ± 0.9</td>
<td>-</td>
<td>7</td>
</tr>
</tbody>
</table>

*P < 0.001,
†P < 0.01. (Improved vs. Unimproved)

FIGURE 4. Epicardial recordings from a dyskinetic area which improved after nitroglycerin (hemiaxis shortening from -3.0 to 20.0%). Note initial R waves from all electrode sites (A.B.C). In each panel, upper is epicardial and lower is standard ECG lead II.

FIGURE 5. Unipolar electrogram recording from an unimproved area (hemiaxis shortening unchanged from 4.0 to 7.0 with nitroglycerin). A wide initial Q (.06 sec) was recorded. Recording speed 50 mm/sec.
pathology of responsive and unresponsive myocardium, the difficulty of sampling error was minimized by utilizing discrete, easily demarcated zones of the left ventricle. Moreover, biopsy material was obtained from a previously recorded site permitting accurate comparison of histology with the corresponding electrogram. This should minimize to the extent possible the potential for sampling error and thus allow these correlations to be made with relative accuracy in living patients.

If coronary bypass surgery is to be of value in preserving and improving asynergic areas of the left ventricle, it is clear that this will depend on the degree to which the presence of potentially viable myocardium can be predicted preoperatively. The present study indicates that an abnormally contracting segment which improves with nitroglycerin is comprised of histologically intact myocardium and is usually associated with epicardial R waves. Thus, the further clarification of the characteristics of an asynergic segment using nitroglycerin or post-extrasystolic potentiation ventriculography provides a means of preoperatively determining which segments may benefit from coronary bypass grafting.

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References

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