Left Ventricular Function and Adrenergic Hyperactivity before and after Saphenous Vein Bypass

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SUMMARY Forty patients with severe angina pectoris were studied before and two weeks after saphenous vein bypass surgery (SVG) in order to assess the effect of this operation on left ventricular performance as judged by systolic time intervals (STI). The patients were divided into two groups: group I included 29 patients in whom no postoperative infarction occurred and group II was composed of 11 patients with postoperative infarction. For group I the preop PEP/LVET was 0.39 ± 0.01 preop and slightly but significantly increased at 0.42 ± 0.004 (P<0.025) two weeks postop. The mean preop PEP/LVET was 0.33 ± 0.01 for group II and dramatically increased to 0.54 ± 0.02 (P<0.001) after surgery.

Another striking abnormality was a marked shortening of electromechanical systole (QS1), which was uniformly present in the postoperative studies. Follow-up studies in 16 patients and urinary catecholamine determination in five patients suggested excessive adrenergic activity was responsible for the abbreviated QS1. This phenomenon must be considered when interpreting the results of SVG on left ventricular function.

IT IS WELL DOCUMENTED that saphenous vein bypass has a beneficial effect upon angina pectoris but there is no universal agreement concerning its effect upon left ventricular performance. Improvement, lack of improvement, and deterioration in left ventricular performance following saphenous vein bypass surgery all have been reported.1-11

In an effort to help resolve these questions we have studied 40 patients undergoing elective saphenous vein bypass surgery for angina pectoris. The systolic time intervals were used to evaluate left ventricular performance before and after surgery. In the course of the investigation it became apparent that excessive adrenergic activity was influencing our measurements. This was particularly true in the early postoperative period. Thus we have also specifically addressed this aspect of the problem in order to determine what role it might play in producing the conflicting results of prior investigations.

Material and Methods

Forty patients undergoing elective saphenous vein bypass for angina pectoris were studied. All subjects underwent preoperative coronary arteriography and quantitative left ventriculography.12-14 Twenty-two of the patients also underwent postoperative catheterization two weeks after surgery. Six patients were receiving digitalis during the study. The mean age of the patients was 51 years. There were 34 males and six females. Preoperatively all were Functional Class III or IV because of angina. Fifteen had had one or
more myocardial infarctions. The preoperative ejection fraction was normal (>55%) in 29 and abnormal in 11, the lowest being 28%. The indication for surgery in all instances was severe angina pectoris refractory to medical therapy. In 12 (30%), the operation was performed for stable angina, in 23 (58%) for progressive angina, and in three (8%) for variant angina.

The surgery employed standard techniques. The operative procedure was performed with the aid of cardiopulmonary bypass, hemodilution perfusion, and moderate total body hypothermia (28–32°C). Aortic cross-clamping and cold cardioplegia with topical lactate slush were used to protect the myocardium for all posterior left ventricular grafts and for small or difficult anastomoses elsewhere where extended ischemia times were anticipated. Electrically-induced ventricular fibrillation was commonly employed as a measure of myocardial ischemia.

Systolic time intervals (STI) were performed the day before catheterization and two weeks after surgery. Propranolol was stopped the day before the measurement. A previous study has shown that the negative inotropic effect of propranolol has disappeared by 12 hours. In 16 patients who were on no drugs, the STI were also repeated at three months postsurgery. The STI were determined by the method previously described from our laboratory. The pre-ejection period/left ventricular ejection time (PEP/LVET) was used as the primary measure of left ventricular performance. The electromechanical systole (QSJ) was used as a measure of adrenergic tone.

In the last five patients studied, 24-hour urinary excretion of epinephrine and norepinephrine was also determined the day before the pre and postoperative STI measurements. None of these patients had postoperative myocardial infarction. None were taking drugs known to interfere with the elimination or excretion of catecholamines. The epinephrine and norepinephrine were measured by a modification of the trihydroxyindole fluorometric technique. The normal range obtained from 35 hospitalized subjects with normal cardiorenal function and no obvious emotional or physical stress is 38.6 ± 22.5 (1 sd) for combined excretion of epinephrine and norepinephrine. A creatinine clearance was calculated during each urinary collection period and any subject with a clearance of less than 60 ml/min during the day of the study was excluded.

Statistical analyses were performed with the aid of a Hewlett-Packard 9100B computer-calculator employing both the two group and paired t-tests.

Results

The patients were divided into two groups on the basis of the presence or absence of a postoperative myocardial infarction. There were no significant differences between these two groups in the preoperative period in terms of anginal pattern, prior infarction, or left ventricular performance judged angiographically.

Group I included 29 patients in whom no postoperative infarction could be diagnosed on the basis of serum enzyme studies or electrocardiographic evidence. The graft patency rate in 17 patients studied postoperatively from this group was 85%.

Group II consisted of 11 patients in whom there was a strong suspicion of postoperative infarction. In four (10% of the series) there was classic electrocardiographic evidence of a new transmural infarction with Q waves greater than 40 msec. In seven (18% of the series) persistent ST and T abnormalities were the only signs suggestive of ischemic injury and not explicable by metabolic abnormalities, pericarditis, or drugs. In addition, there was a persistent elevation of the serum glutamic oxaloacetic transaminase (SGOT) greater than 100 units on the third postoperative day. The graft patency rate in five patients studied postoperatively from this group was 20%.

The mean values of the various STI for each group are shown in figures 1 and 2. All values are shown in terms of mean ± SEM. The postoperative values of one group were compared with those of the other by analysis of variance and Newman-Keuls multiple range test. A normal increase in the STI after surgery is shown in figure 1. None of the STI was significantly reduced following surgery (p>0.05).

Figure 1. Mean values of the various systolic time intervals (STI) before and after surgery (SVG). All values are shown in terms of their deviation (Δ) from the mean normal value (±1 SEM). The P value refers to differences between pre and postoperative values. NS = nonsignificant.
their deviation from the mean normal value. Preoperatively the QS1 was significantly shorter than normal for each group. Although the QS1 shortened further after surgery in both groups, the change was significant only in group I. Of note, the preoperative QS1 was significantly shorter in group II compared to group I (P < 0.05).

The LVET index (I) was significantly shortened from normal before surgery in both groups and shortened significantly further after surgery in both groups. The PEPI was slightly but significantly prolonged in group I preoperatively and shortened significantly after surgery. The PEPI was within the normal range both before and after surgery in group II. Not shown is the change in heart rate after surgery. There was a significant increase (P < 0.01) in both groups I and II (19 and 21 beats/min respectively). All patients were in sinus rhythm with heart rate less than 110 beats per minute during the study.

The PEP/LVET was significantly increased from normal preoperatively in group I and showed a small but significant deterioration after surgery. In group II, on the other hand, the preoperative PEP/LVET was normal and showed a marked increase after surgery. The PEP/LVET was increased significantly more in group II than in group I (P < 0.001).

There were 16 patients in whom STI measurements were also available at three months after surgery. None were receiving cardiovascular drugs throughout the study period. The data from this subgroup of patients is shown in figure 3 and table 1. There were nine patients from group I and seven from group II. The STI of these samples were very similar to the larger groups except that the small postoperative deterioration in PEP/LVET noted in group I was not found in the subgroup. Of note is the fact that the QS1 returned to the normal range by three months postsurgery in each subgroup. The PEP/LVET also improved in the group II sample but was still significantly increased when compared to the preoperative value.

The data from the five group I patients in whom 24-hour urinary catecholamine excretion was also measured are shown in figure 4 and table 2. The QS1 values for this sample were similar to the mean values for group I before and after surgery. Again in this subgroup there was no significant change in the PEP/LVET after surgery. The combined excretion of epinephrine and norepinephrine was significantly increased over normal preoperatively (P < 0.01). Postoperatively there was a significant further increase in catecholamine excretion (P < 0.01). The E + NE was obtained at three months in three patients and had returned to normal (41 ± 5.5 μg/24 hrs).

Discussion

Recent studies have demonstrated the high incidence of

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**Figure 3.** Serial changes in QS1 and PEP/LVET in nine group I patients (solid line) and seven group II patients (dashed line). The QS1 is shown in terms of deviation from normal while the PEP/LVET is expressed in absolute values. Note the parallel changes in QS1 in both groups and the significant deterioration in the PEP/LVET after surgery in group II.

**Figure 4.** Twenty-four hour urinary excretion of epinephrine (E) and norepinephrine (NE) and QS1 before and after surgery in five patients from group I. Although the preoperative value of QS1 was short and the excretion of E and NE increased, there was a further increase in catecholamine excretion and shortening of the QS1 after surgery.

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**Table 1. Serial Changes in STI after SVG**

<table>
<thead>
<tr>
<th></th>
<th>Group I (N = 9)</th>
<th>Group II (N = 7)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>QS1 (msec)</td>
<td>LVET (msec)</td>
</tr>
<tr>
<td>Preop</td>
<td>524 ± 5</td>
<td>388 ± 4</td>
</tr>
<tr>
<td>2 wks postop</td>
<td>512 ± 5</td>
<td>382 ± 3</td>
</tr>
<tr>
<td>P</td>
<td>&lt;0.005</td>
<td>NS</td>
</tr>
<tr>
<td>3 mos postop</td>
<td>538 ± 4.5</td>
<td>404 ± 6</td>
</tr>
<tr>
<td>P†</td>
<td>&lt;0.001</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>P‡</td>
<td>&lt;0.05</td>
<td>&lt;0.025</td>
</tr>
</tbody>
</table>

*Preop compared to 2 wks postop.
†2 wks postop compared to 3 mos postop.
‡Preop compared to 3 mos postop.
NS = not significant.
Abbreviations: QS1 = total electromechanical systole; LVET = left ventricular ejection time index; PEPI = pre-ejection period index.
ischemic injury to the left ventricle in all types of cardiac surgery involving cardiopulmonary bypass.\textsuperscript{24-27} However, the effect of this injury on left ventricular function is not well established. The data from our study indicates that only a mild deterioration of left ventricular performance occurs unless there is peri-operative infarction. The infarction produces significant deterioration of left ventricular performance which is only partially improved three months later. The incidence of postoperative myocardial infarction and graft occlusion (the two were not necessarily related) in our series is similar to that reported by others.\textsuperscript{24, 25}

A common feature in both group I and II was a shortening of the QS\textsubscript{I} both before and after surgery. A previous study of patients with acute myocardial infarction showed a high correlation between the extent of shortening of the QS\textsubscript{I} and level of urinary catecholamine excretion.\textsuperscript{20} Consequently we hypothesized that the short QS\textsubscript{I} in our patients was related to excessive adrenergic activity. This was directly confirmed in five group I patients. We excluded group II patients from the catecholamine analysis since the presence of infarction would of itself be expected to result in excessive adrenergic stimulation.\textsuperscript{20, 28-32}

The genesis of the adrenergic hyperactivity is not clear. This phenomenon has been previously reported in patients with angina pectoris.\textsuperscript{33-35} Previous studies have also shown that cardiopulmonary bypass results in marked sympathetic overactivity in the immediate postoperative period.\textsuperscript{36-40} Our study indicates this is still present two weeks after surgery but has disappeared by three months. The study of Johnson also demonstrated marked shortening of the QS\textsubscript{I} early after saphenous vein bypass which cleared by three months.\textsuperscript{41}

As is the case in spontaneous myocardial infarction, it is not clear whether the adrenergic excess is always desirable.\textsuperscript{30-31} Indeed, left ventricular function was not severely compromised in any of our subjects so the excessive sympathetic stimulation was probably not required to maintain circulatory dynamics. Recent experimental animal studies suggest adrenergic overactivity may produce myocardial injury via microcirculatory aggregation of platelets.\textsuperscript{42-44} This is in addition to the increase in myocardial oxygen consumption induced by catecholamines and the greater likelihood of serious arrhythmia.\textsuperscript{20, 40} It is of interest that the preoperative QS\textsubscript{I} was significantly shorter in those patients who developed a peri-operative infarction. The question of preoperative beta blockade is raised by these results and obviously requires further study.

Based upon our study we feel that some of the controversy in the literature concerning the effect of saphenous vein bypass upon left ventricular performance is related to the variable of adrenergic tone. Saltzman showed a dose-related shortening of the QS\textsubscript{I} and fall in the PEP/LVET as the concentration of infused epinephrine was increased in normal subjects.\textsuperscript{19} In contrast to these normal subjects, our postoperative patients exhibited an increase rather than a decrease in the PEP/LVET even when no obvious myocardial injury had occurred. Thus the over-all effect of surgery upon the ventricle was more deleterious than our results suggested.

The excessive adrenergic tone in the early postoperative period can mask the presence of left ventricular dysfunction. This, of course, is true regardless of the nature of the test used to assess left ventricular function. Conversely an apparent improvement in left ventricular performance could be solely related to increased positive inotropic stimulation. Finally the worsening of left ventricular performance, whether related to obvious infarction or not, can be expected to improve over the ensuing three months. It would therefore seem more appropriate that evaluation of the effect of saphenous vein bypass upon left ventricular performance be carried out at least three months after surgery rather than in the immediate postoperative period. Indeed the majority of studies which have demonstrated improvement in left ventricular function after surgery were performed shortly after surgery whereas those suggesting no net improvement were performed in the late postoperative period.

In conclusion, the STI appear to have a useful role in both the pre and postoperative evaluation of patients undergoing saphenous vein bypass. The PEP/LVET is a useful guide to effects of surgery on left ventricular performance. Perhaps equally important, the STI are the only measurement which also provides an index of adrenergic tone. As such they may prove useful in the future in guiding therapy with beta-adrenergic blocking agents.

Acknowledgment

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| Table 2. Changes in STI and 24-hour Urinary Excretion of E and NE before and after SVG in Five Group I Patients |
|-----------------|-----------------|-----------------|-----------------|
|                 | QS\textsubscript{I} | LVETI | PEPI | PEP/LVET |                  |
| Preop           | 522 ± 4          | 389 ± 5 | 133 ± 5 | 0.39 ± 0.02 | 61 ± 8          |
| 2 wks postop    | 508 ± 5          | 381 ± 4 | 127 ± 8 | 0.38 ± 0.03 | 114 ± 14        |
| P               | <0.01            | <0.05   | NS    | NS       | <0.01           |

Abbreviations: STI = systolic time intervals; SVG = saphenous vein graft; QS\textsubscript{I} = total electromechanical systole; LVETI = left ventricular ejection time index; PEPI = pre-ejection period index; E = epinephrine; NE = norepinephrine; NS = not significant.
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