Preserved hyperaemic response in (distal) string sign left internal mammary artery grafts

Joost Hartman a,b,*, Hans Kelder c, Rob Ackerstaff d, Henry van Swieten e, Freddy Vermeulen b, Ad Bogers a

Abstract

Objective: To correlate supraclavicular ultrasonography at rest and in hyperaemic response with angiographically patent and (distal) 'string sign' left internal mammary artery (LIMA) to left anterior descending (LAD) area grafts. Methods: Fifty-three patients with LIMA to LAD area grafting were prospectively entered in a follow-up study. Arteriography (native and LIMA) was performed at 1.4 ± 0.8 years postoperatively and ultrasonography was performed at rest, in hyperaemic response and 2 min after hyperaemic response at 1.8 ± 0.8 years postoperatively and was compared to arteriography. Ultrasonographic parameters analysed were systolic and diastolic peak velocity, systolic and diastolic velocity integral, diastolic/systolic peak velocity ratio and diastolic/total velocity integral ratio. Results: One patient was excluded because obesity hampered ultrasonography. Arteriography demonstrated functional grafts in 43 patients (group I), sequential distal 'string sign grafts' in 4 patients (group II) and total 'string sign grafts' in 5 patients (group III). Between the groups all ultrasonographic velocities showed a significant linear relation (p ≤ 0.013) at rest and during maximal hyperaemic response all velocities increased significantly within all groups (p ≤ 0.018). A significant decrease was found 2 min after hyperaemic response and diastolic velocities showed a significant linear relation (p ≤ 0.032). Conclusions: String sign LIMA grafts' were found in 9/52 (17.3%) patients. All patent and all 'string sign grafts' showed a shift towards a coronary flow profile in the proximal segment postoperatively. The study revealed the 'functionality' of the patent and the (distal) 'string sign LIMA graft' in regard to myocardial oxygen demand. 'String sign grafts' are 'recruitable' on demand.

Keywords: Duplex; LIMA; Bypass; String sign

1. Introduction

The use of internal mammary arteries (IMAs) is accepted as the best choice in coronary artery bypass grafting (CABG) because of the longer graft patency and patient survival than venous grafts [1–3]. It is well known that postoperative left internal mammary artery (LIMA) graft velocity patterns are typically biphasic with lower antegrade systolic and higher antegrade diastolic values compared to preoperative values. This velocity pattern is due to the IMA grafts adaptation to the coronary artery stream bed with an increasingly diastolic flow portion.

IMA grafts can develop into 'string sign grafts' or can occlude and the causes of these findings are still discussed. It remains unclear how and when patent LIMA grafts become 'string sign LIMA grafts' and their behaviour at rest and in hyperaemic response is still unknown. Studies have suggested that using this conduit in mild to moderate stenosis in the target vessel lead to decreased antegrade flow in the arterial bypass and may cause 'string sign IMA grafts' or disuse atrophy [4–7]. Moreover, there is still no consensus in the assessment of the severity of the left anterior descending (LAD) stenosis related to the IMA conduit patency [8–10].

Control arteriography is the current gold standard method for the assessment of the IMA conduit patency especially for patients at rest. Analysing the functionality or adaptability of the patent, 'string sign'- or occluded LIMA grafts in myocardial hyperaemic tests with control angiography has not been performed or described to our knowledge. Limitations of

[Received 30 August 2006; received in revised form 24 October 2006; accepted 14 November 2006; Available online 11 December 2006]
control arteriography are its costs, its risks in clinically stable patients of 0.7—4.0% [11,12] and the possible disruption of baseline haemodynamics by contrast injection [13].

Echo Doppler ultrasonography is nowadays a frequently used non-invasive method for preoperative IMA screening and postoperative assessment of the LIMA graft function. This method can be used at rest and in contrast to angiography also during hyperaemic response. In this study we evaluate the patency and functionality of the patent, partial- and total ‘string sign LIMA graft’ at rest and during hyperaemic myocardial response. To our knowledge, this is the first report analysing LIMA ‘string sign grafts’ versus patent LIMA grafts by supraclavicular Doppler.

2. Material and methods

Fifty-three patients (40 M), with a mean age of 61±7 years were scheduled for LIMA bypass grafting to the LAD area and prospectively entered in a follow-up study.

Control arteriography was performed at 1.4±0.8 years and mid-term supraclavicular ultrasonography follow-up at 1.8±0.8 years.

The angiograms were analysed by two observers and assessed for native coronary artery stenoses, stenosis of coronary anastomoses and the patency of LIMA grafts. The LIMA grafts and the native coronary arteries were studied by selective injections in order to assess the patency and run off of the LIMA grafts and the stenoses of the native coronary system. LIMA patency and contrast run off were classified into three categories: group I: patent and functional LIMA grafts (Fig. 1d); group II: sequential LIMA distal ‘string sign graft’; no narrowing of the LIMA graft and high flow of contrast from the origin to the first anastomosed branch with narrowing and no or very low contrast flow into the distal graft segment (Fig. 2d); group III: total LIMA ‘string sign graft’; narrowing of the LIMA graft and no or very low flow of contrast into the LIMA graft (Fig. 3d).

In order to analyse differences between fully patent sequential LIMA grafts to the LAD area and sequential LIMA distal ‘string sign grafts’ of group II we constituted a subgroup of group I with only the sequential LIMA grafts (group IB).

The LIMA origin ultrasonographic parameters were analysed by two independent observers. The observers were blinded for the angiography results. Ultrasonography was performed at rest, during a stress test using 0.14 mg/kg min infusion of adenosine [14] for 6 min and 2 min after the stress test. All patients were monitored electrocardiographically.

Fig. 1. Mid-term follow-up supraclavicular duplex of a patent LIMA graft at angiography (d) at rest (a), during hyperaemic response (b) and 2 min after hyperaemic response (c). Note the scale: (d) patent LIMA graft (A) to the LAD (B). sy: systolic; di: diastolic.

Fig. 2. Mid-term follow-up supraclavicular duplex of a distal LIMA ‘string sign graft’ at angiography (d) at rest (a), during hyperaemic response (b) and 2 min after hyperaemic response (c). Note the scale: (d) LIMA jump graft (A) to the diagonal branch (B) with distal LIMA ‘string sign graft’ (C) to the LAD (D). sy: systolic; di: diastolic.

Fig. 3. Mid-term follow-up supraclavicular duplex of a total LIMA ‘string sign graft’ at angiography (d) at rest (a), during hyperaemic response (b) and 2 min after hyperaemic response (c). Note the scale: (d) total LIMA ‘string sign graft’ (A) to the LAD (B). sy: systolic; di: diastolic.
during ultrasonography. Informed consent was obtained from all patients.

3. Duplex ultrasonography technique

Initially a Sonos 2000 (Hewlett Packard, Andover, Mass.) and later a Sonos 2500 (Hewlett Packard, Andover, Mass.) duplex scanner was used that combined both B-mode imaging and pulsed Doppler ultrasound to evaluate blood velocity parameters of the LIMA. Duplex ultrasound investigations and recordings were performed by two trained and experienced technicians. The ultrasound investigation was performed in supine position of the patients under continuous electrocardiographic control. A 7.5 MHz sector scanner was positioned in the supraclavicular fossa and duplex velocities were measured and recorded at an angle of approximately 60° distal to the origin of the LIMA. Software with correction for insonation angle was used. Spectral analysis of LIMA duplex velocity recording was performed during 3–5 consecutive cardiac cycles and data were analysed off-line and interpreted by two physicians. The intraobserver variability was 1.9%. The following velocity parameters were analysed: peak diastolic and peak systolic velocity (DPV and SPV), diastolic and systolic velocity time integral (DVI, SVI), peak diastolic/peak systolic velocity ratio (DSVR) and diastolic/total (diastolic+systolic) velocity integral ratio (DTVIR). The velocity–time integral is the integral of the instantaneous velocity (V) over the time interval (T).

3.1. Statistical analysis

Data entry and univariate statistical analyses were performed with the use of Epi Info 6.04c (CDC, Atlanta, Georgia). Data within groups were tested by paired t tests and between groups by unpaired t tests and ANOVA tests. All data were expressed as mean ± standard deviation. Data were considered statistically significant when the p-value was 0.05 or less.

4. Results

4.1. Control arteriography

The mean time intervals between operation and control arteriography (group I: 1.5 ± 0.9 years; group II: 1.0 ± 0.04 years; group III: 1.7 ± 1.4 years, p = 0.64) and between control arteriography and mid-term follow-up ultrasonography (group I: 0.33 ± 1.4 years; group II: 0.53 ± 0.4 years; group III: 0.67 ± 0.8 years, p = 0.91) did not differ significantly between the groups.

In 17.3% of the patients (distal) ‘string sign LIMA grafts’ were observed.

Group I consisted of 43 patients (35 M, 62 ± 8 years), with 10 single LIMA to LAD and 33 sequential LIMA grafts to the LAD area (82.7%). Subgroup IB consisted of the 33 patients (28 M, 60 ± 7 years) with all patent sequential LIMA grafts.

Group II contained four patients (2 M, 66 ± 4 years), all with LIMA sequential grafts to the LAD area (7.7%). Group III contained five patients (4 M, 66 ± 5 years), with three single LIMA to LAD and two LIMA sequential grafts to the LAD area (9.6%).

The degree of stenosis of the left anterior descending arteries and diagonal branches at control arteriography are shown in Table 1. No stenoses of the distal anastomoses could be detected either at selective LIMA graft arteriography or native coronary arteriography. No patient presented angina and no electrocardiographic changes appeared.

4.2. Ultrasonography mid-term follow-up of the LIMA origin

One patient was excluded from the study because obesity hampered ultrasonography. In 52 patients (98%) ultrasonographic detection of the origin of the LIMA was successful and all registrations could be used for analysis. The time interval between surgery and mid-term follow-up did not differ significantly between groups (group I: 1.87 ± 0.99 years; group II: 1.5 ± 0.4 years; group III: 1.8 ± 0.7 years, p = 0.52). Neither the heart rate nor the systolic or diastolic blood pressure was significantly different between the groups. All patients were in sinus rhythm. Parameters were statistically

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Degree of native coronary vessel stenosis of the anterior wall at control arteriography</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Group I</td>
</tr>
<tr>
<td>LAD stenosis</td>
<td>88 ± 16</td>
</tr>
<tr>
<td>LAD stenosis</td>
<td>—</td>
</tr>
<tr>
<td>First diagonal branch stenosis</td>
<td>83 ± 16</td>
</tr>
<tr>
<td>First diagonal branch stenosis</td>
<td>—</td>
</tr>
<tr>
<td>Second diagonal branch stenosis</td>
<td>91 ± 11</td>
</tr>
</tbody>
</table>

LAD, left anterior descending artery; group I, patent and functional LIMA grafts; group II, distal LIMA string sign grafts; group III, total LIMA string sign grafts; group IB, patent and functional sequential grafts; p, ANOVA p-test for differences between groups; p*, unpaired p-values for differences between groups. Data are mean ± standard deviation.

LIMA to LAD and two LIMA sequential grafts to the LAD area (9.6%).

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Postoperative supraclavicular LIMA duplex velocities at rest in mid-term follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Group I (n = 43)</td>
</tr>
<tr>
<td>DPV (cm/s)</td>
<td>38 ± 14</td>
</tr>
<tr>
<td>DVI (cm²)</td>
<td>13 ± 5</td>
</tr>
<tr>
<td>SPV (cm/s)</td>
<td>51 ± 15</td>
</tr>
<tr>
<td>SVI (cm²)</td>
<td>11 ± 4</td>
</tr>
<tr>
<td>DSVR</td>
<td>0.7 ± 0.2</td>
</tr>
<tr>
<td>DTVIR</td>
<td>0.6 ± 0.1</td>
</tr>
</tbody>
</table>

DPV, diastolic peak velocity; DVI, diastolic velocity integral; SPV, systolic peak velocity; SVI, systolic velocity integral; DSVR, diastolic/systolic peak velocity ratio; DTVIR, diastolic/total (diastolic + systolic) velocity integral ratio. Groups I–III as described in Table 1. p, differences between groups I and II; p*, differences between groups I and III; p**, differences between groups II and III; p***, values for linear relation between the three groups. Data are mean ± standard deviation. NS: not significant.
studied in order to analyse the differences and relationships between the groups.

No ischemia could be detected electrocardiographically during ultrasonography and no patient had complaints of angina.

4.3. At rest

All velocities of the functional LIMA grafts (Fig. 1a) are higher than LIMA 'string sign grafts' (Fig. 3a) and differ significantly (Table 2). By comparing the velocities of the functional grafts with the distal LIMA 'string sign grafts' a clear tendency can be noticed (Figs. 1a and 2a). All functional LIMA graft velocities are higher but do not differ significantly except for peak systolic velocity (Table 2). Comparing the velocity parameters of distal LIMA 'string sign grafts' with total LIMA 'string sign grafts' it was found that only the DVI is significantly higher whereas all velocities in group II are higher. The linear relations for all velocities between the three groups are highly significant (Table 2).

As expected, the subgroup IB shows higher velocities than group II (Table 5).

4.4. Hyperaemic response

Nor the heart rate or the systolic or diastolic blood pressure differs significantly between the three groups during 6 min of hyperaemic response.

In all groups, in contrast to values at rest, the DSVR is >1. Within all groups, a highly significant increase of all velocities is present (PI, PII and PIII in Table 3). Remarkably, total 'string sign LIMA grafts' do respond and velocities and time integrals increase significantly. However, maximal velocities in this group remain lower compared to the other groups (Table 3).

Comparing the hyperaemic responses between all groups, only the diastolic values differ significantly between groups I and III (p1, p** and p*** in Table 3). However, these parameters increase significantly during hyperaemic response within all groups (PI, PII and PIII in Table 3). Analysing the subgroup IB versus group II only the diastolic parameters differ significantly although a significant increase is clear within both groups (Table 5).

4.5. 2 min after hyperaemic response

There are no significant differences in heart rate, systolic or diastolic blood pressure between the groups. All velocities decrease within the three groups in 2 min. In group I and III all values decreases significantly and in group II all but the peak systolic velocity decrease significantly (p1, p** and p*** in Table 4).

In group I, velocities decreased to values at rest whereas velocities in group II and group III are still higher compared to values at rest. The linear relation between the three groups for differences of maximal hyperaemic response versus values after 2 min is significant for diastolic parameters. All values in group IB decrease as well. In contrast to the hyperaemic response diastolic velocities do not differ significantly compared to group II (Table 5).

Table 3
Maximal hyperaemic response values during 6 min of adenosine

<table>
<thead>
<tr>
<th>Group I (n = 43)</th>
<th>Group II (n = 4)</th>
<th>Group III (n = 5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DPV (cm/s)</td>
<td>103 ± 27</td>
<td>83 ± 16</td>
</tr>
<tr>
<td>DVI (cm²)</td>
<td>31 ± 10</td>
<td>22 ± 4</td>
</tr>
<tr>
<td>SPV (cm²)</td>
<td>91 ± 24</td>
<td>80 ± 13</td>
</tr>
<tr>
<td>SVI (cm²)</td>
<td>19 ± 5</td>
<td>16 ± 3</td>
</tr>
<tr>
<td>DTVIR</td>
<td>1.3 ± 0.1</td>
<td>1.3 ± 0.2</td>
</tr>
</tbody>
</table>

DVP, DVI, SPV, SVI, DSVR and DTVIR as described in Table 2. p, values for linear relation between the three groups for absolute maximal hyperaemic values; p1, differences of absolute values between groups I and II; p**, differences of absolute values between groups I and III; p***, differences of absolute values between groups II and III; PI, differences of maximum hyperaemic values versus values at rest within group I; PII, differences of maximum hyperaemic values versus values at rest within group II; PIII, differences of maximum hyperaemic values versus values at rest within group III; p1, values for linear relation of maximum hyperaemic values versus values at rest between the groups. Data are mean ± standard deviation. NS: not significant.

Table 4
Two minutes after the adenosine hyperaemic response test

<table>
<thead>
<tr>
<th>Group I (n = 43)</th>
<th>Group II (n = 4)</th>
<th>Group III (n = 5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DPV (cm/s)</td>
<td>47 ± 17</td>
<td>42 ± 13</td>
</tr>
<tr>
<td>DVI (cm²)</td>
<td>14 ± 5</td>
<td>13 ± 3</td>
</tr>
<tr>
<td>SPV (cm²)</td>
<td>56 ± 21</td>
<td>45 ± 17</td>
</tr>
<tr>
<td>SVI (cm²)</td>
<td>10 ± 4</td>
<td>8 ± 1</td>
</tr>
<tr>
<td>DSVR</td>
<td>0.9 ± 0.3</td>
<td>1 ± 0.2</td>
</tr>
<tr>
<td>DTVIR</td>
<td>0.6 ± 0.1</td>
<td>0.6 ± 0.0</td>
</tr>
</tbody>
</table>

DPV, DVI, SPV, SVI, DSVR and DTVIR as described in Table 2. p, values for linear relation between the three groups; p1, differences of maximal hyperaemic response and 2 min after the response test within group I; p**, differences of maximal hyperaemic response and 2 min after the response test within group II; p***, differences of maximal hyperaemic response and 2 min after the response test within group III; p1, values for linear relation for differences of maximal hyperaemic response minus values 2 min after the response test between groups. Data are mean ± standard deviation. NS: not significant.
5. Discussion

Takagi et al. [15] tested and compared the ultrasonographic method from the supraclavicular fossa with Doppler catheter measurements and found significant correlations in SPV (p < 0.01), DPV (p < 0.01), and the diastolic to systolic peak flow velocity ratios (p < 0.01) between the methods. Therefore, we can assume that ultrasonography from the supraclavicular fossa permits assessment of the LIMA graft patency.

Patent LIMA grafts and their transthoracic ultrasonographic patterns have been widely described. LIMA grafts can develop into ‘string sign grafts’ and it is interesting to study the response in velocity patterns of these ‘string sign LIMA grafts’. In total LIMA ‘string sign’ velocities in all grafts. Some explanations may be put forward in this regard. First, there is no difference in the degree of stenosis of the LAD but there is a significant difference in stenosis of the diagonal branch. However, there were only two patients with sequential LIMA grafts in the ‘string sign’ group. Secondly, we already reported [17] that at multivariate analyses the diagnostic velocity time integral of less than 0.60 in all grafts.

A (partial) LIMA ‘string sign graft’ was observed in 17.3% (9 patients) of our study population (52 patients). At rest, in all groups the DSVR was < 1.0, this confirms that peak systolic velocities were higher than peak systolic velocities in the proximal part of the LIMA graft. In all groups, the DTVIR was equal to or higher than 0.5 which implicates a more pronounced coronary flow reserve in the systolic peak velocity and the diastolic fraction becomes increased significantly. The diastolic peak velocity equals to the systolic peak velocity and the diastolic fraction becomes predominant (DTVIR > 0.5) as in the patent — and partial ‘string sign’ — LIMA grafts. However, the diastolic values remained significantly lower compared to the patent LIMA grafts. Some explanations may be put forward in this regard. First, there is no difference in the degree of stenosis of the LAD but there is a significant difference in stenosis of the diagonal branch. However, there were only two patients with sequential LIMA grafts in the ‘string sign’ group. Secondly, we already reported [17] that at multivariate analyses the maximal diastolic peak velocity in hyperaemic response correlated significantly with the LIMA run-off areas. These LIMA run-off areas can also contribute to the findings but we did not take these in account. Nevertheless, the LIMA grafts do respond in the stress test demonstrating to be a ‘reactive conduit’.

After the stress test, all velocities within groups I and III decreased significantly and DSVR became equal to or lower than 1. Adenosine is rapidly metabolized [14] and all LIMA grafts, even the total ‘string sign LIMA grafts’, responded well and immediate to their function on demand of the decreased myocardial stress circumstances. After 2 min, all diastolic values were lowered by 50% in all groups. So, this finding enhanced the statement that string sign LIMA grafts can be considered as ‘living conduits’.

We did not perform our data into flow because of the poor correlation of the diameter at angiography versus ultrasonography [17]. We agree with Driever et al. [18] that calculations of the diastolic flow values contain errors especially in determining the diameter of the LIMA which is a significant part of the flow calculation. We used the supraclavicular approach and although Driever et al. [18] assessed LIMA graft patency through the second intercostal space both approaches showed a DSVR of < 1.0. So, systolic peak velocity remained higher than diastolic peak velocities in the proximal part of the LIMA as also described by Bach et al. [19]. They mentioned a diastolic/systolic peak velocity ratio of 0.6 ± 0.2.
Gaudino et al. [20] showed the increase of the systolic and diastolic peak velocity in myocardial stress conditions with a decrease of the systolic/diastolic peak velocity ratio to 0.85 ± 0.28 compared to 1.51 ± 0.33 at rest. Mauric et al. [21] described the significant increase of the diastolic peak velocity after leg exercise compared to values at rest whereas the systolic peak velocity was unchanged.

Katz et al. [22] described the dominant diastolic flow pattern in patent grafts at transthoracic Doppler. Occluded grafts had absent flow or a dominant systolic pattern. Adenosine induced increase of LIMA diastolic peak velocity from 48 to 105 cm/s. He did not measure adenosine effects in occluded LIMA vessels.

There are only a few reports describing the 'string sign' or no flow LIMA graft to the LAD area. Akasaka et al. [6] described, using a guide wire, that the no flow state in IMA grafts at rest were temporary and that these IMA grafts functioned as conduits during hyperaemic states.

In our opinion, a non-invasive method – as the supraclavicular ultrasonography — to assess LIMA graft patency would be useful for clinical diagnosis and long-term follow-up of graft outcome.

6. Limitations

First, the number of patients with (partial) LIMA 'string sign graft' is small which hampers statistical analyses. Secondly, no control group with an occluded and non-responding LIMA graft was present.

7. Conclusions

Our findings suggest that LIMA 'string sign grafts' are in a 'low functional state' at rest and can adapt to myocardial stress conditions when myocardial oxygen demand is increased. So, in our opinion, LIMA 'string sign grafts' are 'living conduits'.

References


Appendix A. Conference discussion

Dr P. Sergeant (Leuven, Belgium): I was somewhat surprised by the rather high prevalence of the string sign in this unselected population. Did you ever go back to the original angios and identify the degree of stenosis of the lesions?

Dr Hartman: We did. The angiograms were studied by two cardiologists and by two cardiac surgeons. It is a high amount of string sign LIMA grafts. I agree. We analysed the preoperative- and control angiograms again and confirmed the previous analysed severity of the stenosis in the coronary arteries. I agree it is a high percentage of string sign LIMA grafts.

Dr Sergeant: Excuse me, but I want to refine your answer. Can you give us some idea what the average degree of stenosis was or the range of stenosis?

Dr Hartman: 80% of stenosis with a range of 30–35%.

Dr Sergeant: So some of these patients had only a 50% stenosis of the LAD if you give a range of 30%?

Dr Hartman: That is correct.
Dr Sergeant: There has been casual evidence of return of recruitability of these string signs, but this is well presented.

Dr M. Irarrazaval (Santiago, Chile): There are strings and strings. How thick were your strings here? Have you categorized the thickness of the strings? And also is there a time frame? Is there a reversibility of this recruitable condition as time goes or is it vice versa?

Dr Hartman: To answer your first question, with reference to the angiographical findings, we classified the LIMA grafts in three categories. We selected the string sign LIMA grafts by very low or no contrast flow into the left internal mammary artery. That was the criteria. We didn’t rely on the duplex measurements because of the poor correlation between the duplex measurements and the control angiography measurements of the LIMA graft diameter. We classified the patients only by analyzing the no or low contrast flow into the LIMA graft.

Dr Irarrazaval: Did you see any pattern on the time following these patients, whether this recruitable condition remained for a time many years after or it was only initially or was it something related with time?

Dr Hartman: We didn’t analyse that. We analysed the velocity patterns 1.6 years after the operation in a one-time setting. I agree with you, it would be interesting to analyse the ratios in these patients within 10 or 15 years.