Value of fractional flow reserve in making decisions about bypass surgery for equivocal left main coronary artery disease


Abstract
Objective—To investigate the value of coronary pressure derived fractional flow reserve (FFR) measurements in supporting decisions about medical or surgical treatment in patients with angiographically equivocal left main coronary artery stenosis.
Design—A two centre prospective single cohort follow up study.
Interventions—FFR of the left main coronary artery was determined in 54 consecutive patients with angiographically equivocal left main coronary artery disease. If FFR was ≥ 0.75, medical treatment was chosen; if FFR was < 0.75, surgical treatment was chosen.
Main outcome measures—Freedom from death, myocardial infarction, or any coronary revascularisation procedure.
Results—In 24 patients (44%), FFR was ≥ 0.75 and medical treatment was chosen (medical group). In the remaining 30 patients (56%), FFR was < 0.75 and bypass surgery was performed (surgical group). Mean (SD) follow up was 29 (15) months (range 12–65 months). Survival among patients at three years of follow up was 100% in the medical group and 97% in the surgical group. Event-free survival was 76% in the medical group and 83% in the surgical group.
Conclusions—FFR supports decision making in equivocal left main coronary artery disease. If FFR is below 0.75, the decision for bypass surgery is supported. If FFR is above 0.75, a conservative approach is justified.

Keywords: coronary artery disease; left main coronary artery; fractional flow reserve; coronary artery bypass

The presence of left main coronary artery stenosis may have serious implications and it is often decisive in the choice of surgical versus non-surgical treatment.1 However, in clinical practice patients are sometimes encountered with only mild or moderate left main coronary artery stenosis on the angiogram. Although such patients are intuitively at increased risk, it is unclear whether their prognosis will be improved by bypass surgery. On the one hand if there is rupture of an anatomically insignificant left main plaque, the result could be fatal. On the other hand it is conceivable that too early an operation could lead to inappropriate use of available grafts and premature occlusion of either the native vessel or the graft, leaving the future risk of acute occlusion unaffected.2 This problem is exacerbated in several ways. First, reliable angiographic assessment and quantitative coronary angiography of a left main coronary artery stenosis is often difficult; second, it is not uncommon for left main coronary artery disease to be suspected but hard to quantify from the angiogram; and third, classical non-invasive tests are often incapable of discriminating between inducible ischaemia caused by the left main coronary artery steno sis itself or by other abnormalities elsewhere in the coronary system.3 In case of doubt, surgical treatment is often chosen, encouraged by the widespread and generalised fear of under treating patients.

Fractional flow reserve (FFR), calculated from coronary artery pressure measurement, has been shown to be an accurate and lesion specific index for determining if an intermediate stenosis is functionally significant and responsible for reversible ischaemia. A threshold value of 0.75 clearly distinguishes lesions responsible (FFR < 0.75) or not responsible (FFR ≥ 0.75) for reversible ischaemia during exercise.4,5 Our aim in this study was to investigate the clinical value of pressure derived FFR measurements in supporting decisions about whether to perform or defer bypass surgery in patients with equivocal left main coronary artery disease.

Methods

PATIENT POPULATION
All patients were eligible for this study who underwent diagnostic catheterisation in our hospitals between 1994 and 1999 and in whom a left main coronary artery stenosis of 40–60% was present by visual estimation, or in whom left main coronary artery disease was visible but could not be quantified from the angiogram. Patients were only eligible if no other angiographic abnormalities were present that warranted bypass surgery—for example, if as well as equivocal left main coronary artery stenosis there was also three vessel disease requiring bypass surgery, the patient was not eligible for the study. If on the other hand concomitant disease was present elsewhere in the coronary tree that was suitable for percutaneous transluminal coronary angioplasty (PTCA), the patient was eligible for the study.

Department of Cardiology, Catharina Hospital, 5602 ZA Eindhoven, Netherlands
G J W Bech
H Droste
N H J Pijls
J J R M Bonnier
H R Michels
K H Peels
J J Koolen

Department of Cardiology, Cardiovascular Centre, Aalst, Belgium
B De Bruyne

Correspondence to: Dr Pijls
cardiologie.catharina.zks@wxs.nl

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After informed consent had been obtained, coronary artery pressure measurements and calculations of FFR associated with the left main coronary artery stenosis were performed. The decision on whether to perform surgery or to choose conservative treatment was then based upon FFR measurements below or above 0.75, respectively.

CORONARY CATHETERISATION AND CORONARY PRESSURE MEASUREMENT

After diagnostic catheterisation had been performed, a 6 or 7 French guiding catheter was advanced into the ostium of the left coronary artery. After an intravenous injection of 10 000 units of heparin and an intracoronary injection of 200–300 µg glyceryl trinitrate, control angiography was done. A pressure monitoring guide wire (Radi Medical Systems, Uppsala, Sweden) was then set to zero, calibrated, and introduced into the guiding catheter. The pressure wire was advanced to the tip of the guiding catheter, and it was verified that the pressure measured by the pressure wire was equal to the pressure measured by the guiding catheter. Next, the pressure wire was advanced further into the left coronary artery until the pressure sensor was located just distal to the left main coronary artery segment. Maximum myocardial hyperaemia was then induced by a continuous infusion of adenosine in a femoral vein at an infusion rate of 140 µg/kg per min for 2–4 minutes. If damping of the aortic pressure signal was observed, the guiding catheter was retrieved from the ostium while leaving the pressure wire distal to the left main coronary artery segment. During maximum hyperaemia, left main coronary artery FFR was calculated from the ratio of the simultaneously recorded mean aortic pressure (P_a) and mean coronary artery pressure (P_d) [FFR = P_d / P_a], as described previously. Measurements were performed with the pressure sensor located in all large branches of the left coronary artery. Some examples of angiograms and pressure recordings of patients in this study are shown in figs 1 and 2.

If FFR of the left main coronary artery was \( \geq 0.75 \), indicating that in itself the stenosis was unlikely to be physiologically significant, no bypass surgery was performed. If appropriate, PTCA of a concomitant lesion elsewhere in the coronary tree was done and medical treatment was continued with aspirin and statins if indicated (medical group). If FFR of the left main coronary artery was < 0.75, indicating that the lesion had physiological significance and that the left main coronary artery stenosis was most probably associated with inducible ischaemia, coronary artery bypass grafting (CABG) was undertaken (surgical group).

Quantitative coronary arteriographic analysis was done on control cineangiograms obtained just before the intracoronary pressure measurements.

FOLLOW UP AND CLINICAL EVENTS

All patients were closely followed for an average of 2.5 years (range 12–63 months), with clinical visits at least once a year. Data on angina frequency and drug use were obtained at all follow up visits. Major adverse events were mutually exclusive and defined in the following...
STATISTICS

Continuous data are reported as mean (SD). Differences within and between subgroups were tested by use of paired or unpaired Student’s t tests. Categorical differences between subgroups were tested for using Fisher’s exact test or the χ² test. Patient survival curves and curves for freedom of death or major adverse cardiac events were constructed according to Kaplan and Meier. A probability value of p < 0.05 was considered significant. All tests were two tailed.

Results

BASELINE CHARACTERISTICS AND PROCEDURAL OUTCOMES

Table 1 shows baseline clinical and angiographic data of the two groups. Except for smoking and a family history of coronary heart disease, no significant differences were present between the groups. No complications occurred during catheterisation or coronary pressure measurement. Pressure recordings of two patients are shown in figs 1 and 2.

In 24 of the 54 patients, FFR of the left main coronary artery stenosis was 0.75 or more, making inducible ischaemia from left main coronary artery stenosis highly unlikely, so bypass surgery was not performed (medical group). In this group 16 patients were treated with drugs alone, seven underwent PTCA for a concomitant lesion, and one underwent aortic valve replacement without bypass surgery. In the remaining 30 patients FFR of the left main coronary artery stenosis was below 0.75, indicating that the lesion was haemodynamically significant. CABG was performed in these patients within a few days (surgical group).

Although baseline left main coronary artery per cent diameter stenosis was similar between the medical and surgical groups, the mean reference diameter and minimum lumen diameter were significantly larger in the medical group, but with substantial overlap (table 1; fig 3).

FOLLOW UP

Follow up was obtained in all patients. Mean (SD) follow up was 29 (15) months (range 12–63 months). Events during follow up are detailed in table 2.

In the medical group, five patients experienced an event during follow up—after 3, 4, 16, 28, and 42 months, respectively. In all of these, chest pain developed or worsened, accompanied by a positive exercise test in four cases. In two cases, progression of left main coronary artery disease was present, both angiographically and physiologically. These two patients both underwent bypass surgery. In the three other patients, progression of disease in other coronary branches was observed, requiring bypass surgery in one and PTCA in two.

In the surgical group five patients also experienced an event during follow up: one patient died 29 days after surgery because of respiratory failure from acute respiratory distress syndrome and pneumonia; in one patient a large anterior wall myocardial infarct occurred perioperatively; in the three other patients early
**Table 1 Baseline clinical and angiographic data**

<table>
<thead>
<tr>
<th></th>
<th>Medical group, FFR &gt; 0.75</th>
<th>Surgical group, FFR &lt; 0.75</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n=24)</td>
<td>(n=30)</td>
</tr>
<tr>
<td>Sex</td>
<td>Male 18 (75%)</td>
<td>26 (87%)</td>
</tr>
<tr>
<td></td>
<td>Female 60 (9)</td>
<td>63 (9)</td>
</tr>
<tr>
<td>Risk factors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>4 (17%)</td>
<td>9 (30%)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>8 (33%)</td>
<td>6 (20%)</td>
</tr>
<tr>
<td>Raised cholesterol</td>
<td>8 (33%)</td>
<td>14 (47%)</td>
</tr>
<tr>
<td>Smoking</td>
<td>7 (29%)</td>
<td>19 (63%)</td>
</tr>
<tr>
<td>Family history</td>
<td>4 (17%)</td>
<td>16 (53%)</td>
</tr>
<tr>
<td>Previous PTCA</td>
<td>2 (8%)</td>
<td>4 (13%)</td>
</tr>
<tr>
<td>Previous infarction</td>
<td>8 (33%)</td>
<td>5 (16%)</td>
</tr>
<tr>
<td>CCS class</td>
<td>2.8 (1.0)</td>
<td>3.4 (0.9)</td>
</tr>
<tr>
<td>Stress test performed</td>
<td>13 (54%)</td>
<td>10 (33%)</td>
</tr>
<tr>
<td>Positive/negative/inconclusive</td>
<td>8/1/4</td>
<td>7/1/2</td>
</tr>
<tr>
<td>Ejection fraction (%)</td>
<td>55 (8)</td>
<td>57 (6)</td>
</tr>
<tr>
<td>Additional disease</td>
<td>One/two vessel disease 10/6</td>
<td>10/13</td>
</tr>
<tr>
<td>Duration of follow up (months)</td>
<td>28 (15)</td>
<td>29 (14)</td>
</tr>
<tr>
<td>Angiographic data</td>
<td>Reference diameter (mm) 4.06 (0.67)</td>
<td>3.45 (0.59)*</td>
</tr>
<tr>
<td></td>
<td>Minimum lumen diameter (mm) 2.35 (0.46)</td>
<td>1.95 (0.39)*</td>
</tr>
<tr>
<td></td>
<td>Diameter stenosis (%) 42 (9)</td>
<td>43 (10)</td>
</tr>
<tr>
<td>Pressure data</td>
<td>P&lt; (mm Hg) 10 (13)</td>
<td>95 (18)</td>
</tr>
<tr>
<td></td>
<td>P&gt; (mm Hg) 81 (10)</td>
<td>63 (14)*</td>
</tr>
<tr>
<td></td>
<td>Fractional flow reserve 0.90 (0.06)</td>
<td>0.67 (0.09)*</td>
</tr>
</tbody>
</table>
| Values are n (%) or mean (SD). *
P < 0.05.
CCS, Canadian Cardiovascular Society; FFR, fractional flow reserve; P<, aortic pressure; P>, mean hyperaemic coronary pressure just distal to the left main coronary artery; PTCA, percutaneous transluminal coronary angioplasty.

**Table 2 Patients with an event during follow up**

<table>
<thead>
<tr>
<th>Patient/sex</th>
<th>Age (years)</th>
<th>RD (mm)</th>
<th>MLD (mm)</th>
<th>DS (%)</th>
<th>FFR LM</th>
<th>Initial treatment</th>
<th>Event, treatment of event (days to event)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medical group (FFR &gt; 0.75)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1/M</td>
<td>61</td>
<td>4.30</td>
<td>2.61</td>
<td>40</td>
<td>0.85</td>
<td>Medical treatment</td>
<td>Medical test positive, CAG, disease progression proximal LAD, PTCA (82)</td>
</tr>
<tr>
<td>2/F</td>
<td>70</td>
<td>4.01</td>
<td>2.10</td>
<td>48</td>
<td>0.96</td>
<td>PTCA LAD</td>
<td>CAG, restenosis LAD, re-do PTCA (118)</td>
</tr>
<tr>
<td>3/M</td>
<td>42</td>
<td>4.51</td>
<td>1.93</td>
<td>57</td>
<td>0.95</td>
<td>Medical treatment</td>
<td>Medical test positive, CAG, disease progression LM, CABG (482)</td>
</tr>
<tr>
<td>4/F</td>
<td>49</td>
<td>2.98</td>
<td>2.18</td>
<td>27</td>
<td>0.95</td>
<td>Medical treatment</td>
<td>Medical test positive, CAG, disease progression LM, CABG (845)</td>
</tr>
<tr>
<td>5/M</td>
<td>68</td>
<td>5.57</td>
<td>2.45</td>
<td>56</td>
<td>0.96</td>
<td>PTCA LCX</td>
<td>Medical test positive, CAG, new stenosis LAD and RCA, CABG (1293)</td>
</tr>
<tr>
<td>Surgical group (FFR &lt; 0.75)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6/F</td>
<td>70</td>
<td>4.48</td>
<td>2.76</td>
<td>38</td>
<td>0.50</td>
<td>LITA LAD</td>
<td>Postoperative ischaemia, redo thoracotomy, SVG LAD (0)</td>
</tr>
<tr>
<td>7/M</td>
<td>61</td>
<td>2.41</td>
<td>1.80</td>
<td>25</td>
<td>0.62</td>
<td>Left main reconstruction, SVG RCA</td>
<td>Postoperative ischaemia, anterior myocardial infarction (0)</td>
</tr>
<tr>
<td>8/F</td>
<td>75</td>
<td>3.89</td>
<td>2.68</td>
<td>31</td>
<td>0.72</td>
<td>LITA LAD, SVG RCA, SVG LCx, AVR</td>
<td>Postoperative mitral regurgitation, valve replacement (0)</td>
</tr>
<tr>
<td>9/M</td>
<td>66</td>
<td>3.02</td>
<td>1.54</td>
<td>49</td>
<td>0.73</td>
<td>LITA LAD</td>
<td>Postoperative ischaemia, redo thoracotomy, SVG LAD (0)</td>
</tr>
<tr>
<td>10/M</td>
<td>81</td>
<td>3.92</td>
<td>1.65</td>
<td>58</td>
<td>0.63</td>
<td>LITA LAD, SVG jump D1-LCx-RCA</td>
<td>Postoperative ARDS and pneumonia, death (29)</td>
</tr>
</tbody>
</table>

ARDS, acute respiratory distress syndrome; AVR, aortic valve replacement; CABG, coronary artery bypass grafting; CAG, coronary angiography; DS, diameter stenosis; D1, first diagonal branch; F, female; FFR, fractional flow reserve; LAD, left anterior descending coronary artery; LCx, left circumflex coronary artery; LITA, left intercostal artery; M, male; MLD, minimum lumen diameter; PTCA, percutaneous transluminal coronary angioplasty; RCA, right coronary artery; RD, reference diameter; SVG, saphenous vein graft.
Left main coronary artery disease and fractional flow reserve

In itself, main coronary artery disease is not without risk of acute occlusion unaccompanied by other stenoses elsewhere in the coronary tree. Therefore, differentiation between ischaemia caused by the left main coronary artery itself or that accompanying other stenoses elsewhere in the coronary tree is necessary. In the case of equivocal left main coronary artery disease, this clinical dilemma is aggravated for three reasons. First, reliable angiographic assessment of FFR is useful in making decisions about whether or not to proceed to bypass surgery. In patients with significant left main coronary artery stenosis, coronary bypass surgery prolongs life. Thus it is generally accepted that a bypass operation should be performed in patients with left main coronary artery stenosis which is significant at angiography, or unequivocally associated with reversible ischaemia on non-invasive stress testing.

In patients with equivocal left main coronary artery stenosis the best treatment is less obvious. On the one hand it is clear that an insignificant plaque can, if it ruptures, have dramatic consequences; on the other hand, early surgery could lead to the inappropriate use of available graft material and premature occlusion of either the native vessel or the graft, leaving the future risk of acute occlusion unaffected. In the case of equivocal left main coronary artery disease, this clinical dilemma is aggravated for three reasons.

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Discussion

Our study shows that in patients with intermediate left main coronary artery stenosis (40–60%), about half the stenoses (56%) can be considered physiologically significant, with an FFR value of < 0.75, and half (44%) cannot. In this first group, CABG was performed, on the basis of earlier studies; in the second group no surgery was performed and a medical approach was chosen. This strategy was accompanied by an excellent survival and freedom from events for up to three years of follow up, and importantly—although both groups were comparable in terms of percentage diameter stenosis—the medical group with an FFR of 0.75 or above had a similar outcome to the surgical group, with an FFR below 0.75. Furthermore, the events in the medical group were less serious (no deaths and no myocardial infarction), they were equally distributed over time, and CABG was still necessary in the patients in the following five years. All events in the surgical group occurred early.

At follow up, average CCS class decreased significantly in both groups. However, this improvement was largest in the patients with an FFR below 0.75, indicating that their complaints were associated with the left main coronary artery lesion and that subsequent CABG was in fact justified.

Another interesting observation is that, although average stenosis severity was equal in the two groups (table 1), the patients with an FFR of < 0.75 had a smaller reference diameter by quantitative coronary angiography and accordingly a smaller minimum lumen diameter (fig 3). It is likely that in those patients diffuse left main coronary artery disease was present, which was not detected by lumenography. This phenomenon of diffuse left main coronary artery disease is well known from intravascular ultrasound (IVUS) studies, which have also shown that occult left main artery disease may be more common than is generally appreciated. These studies have shown the additional value of IVUS in patients with intermediate left main stenosis.20–22
comparative studies of IVUS and FFR have not been performed so far.

Despite the lower mean reference diameter and minimum lumen diameter in patients with functionally significant stenoses, angiography was not capable of distinguishing in individual patients which stenoses were functionally significant and which were not (fig 3).

There have been few prospective studies on left main coronary artery stenosis, and in case of doubt most clinicians elect to do bypass surgery.11 12 In the present prospective non-randomised study, all consecutive patients with equivocal left main coronary artery disease in whom such a dilemma was present were included. The decision to operate or not was based entirely on the FFR. Therefore we believe that our study is representative of those patients with equivocal left main coronary artery disease and that it has direct clinical implications for decision making.

We have shown earlier that in patients with intermediate stenosis it is in general safe to defer surgical intervention if the stenosis has no physiological significance—that is, if it does not cause reversible ischaemia;21 this can now be extended to angiographic stenosis of the intermediate left main coronary artery. Finally, as with all other non-significant stenoses, there is no evidence that affected patients are at a higher risk of events than persons without any coronary artery disease. However, the issue addressed here is that the prognosis will probably not be improved by surgery unless the stenosis is physiologically significant.

LIMITATIONS
As this study was non-randomised, it is impossible to determine what the event rates would have been if CABG had been performed in patients with an FFR of > 0.75, or not performed in patients with an FFR of < 0.75. Thus we do not have any evidence that patients with angiographically equivocal left main coronary artery stenosis and an FFR of < 0.75 would definitely have benefited from CABG, as opposed to medical treatment alone. However, it has been well documented that the presence and extent of inducible ischaemia are the most important prognostic factors in coronary artery disease, so it was considered unethical not to perform surgery in patients in whom inducible ischaemia was present, and in whom it could be assumed that there was a relation between the ischaemia and the left main coronary artery stenosis.23

Routine follow up angiography was not scheduled in this study to avoid bias in the decision making process.

CONCLUSIONS
Our study shows that in patients with suspected equivocal left main coronary artery disease, intracoronary pressure measurements and calculations of the FFR are feasible and helpful in decisions about surgical versus medical treatment. In patients with an FFR of the left main coronary artery of > 0.75, CABG may be deferred, and inappropriate use of graft material