Left main coronary artery (LMCA) disease is prevalent, occurring in 4% to 7% of patients undergoing coronary angiography.1,2 Several studies have highlighted the inadequacies of coronary angiography in the assessment of intermediate LMCA stenosis,3–5 leading to the use of other modalities to determine LMCA stenosis severity.

Fractional flow reserve (FFR) is now considered the gold standard technique to determine the functional significance of epicardial coronary stenoses in the cardiac catheterization laboratory,6,7 and the use of FFR to guide revascularization of multivessel epicardial disease results in improved outcomes.8 Several studies have demonstrated the usefulness of measuring FFR to guide the decision for revascularization of intermediate LMCA disease.9,10 However, LMCA stenosis is usually associated with downstream disease in the epicardial vessels.11,12 The effect of downstream epicardial disease in the left anterior descending (LAD) or left circumflex (LCX) arteries on the FFR assessment of LMCA stenosis remains unclear.

Disease in the LAD will certainly affect FFR assessment of the LMCA when the pressure-sensor wire is in the LAD.13,14 For this reason, it is recommended to position the pressure sensor in an artery that is free of significant stenosis. However, in theory, LAD disease might also affect FFR assessment of the LMCA when the pressure sensor is positioned in a nondiseased LCX. Blood flow across the LMCA is dependent on the outflow to the LAD and LCX. Therefore, significant LAD stenosis may decrease flow across the LMCA and could falsely elevate the FFR.

The goal of this study is to explore the effect of downstream disease in either the LAD or the LCX on FFR assessment of intermediate LMCA disease with the pressure wire in a nondiseased downstream vessel using an in vitro sheep model.

Background—Several studies have shown that fractional flow reserve (FFR) measurement can aid in the assessment of left main coronary stenosis. However, the impact of downstream epicardial stenosis on left main FFR assessment with the pressure wire in the nonstenosed downstream vessel remains unknown.

Methods and Results—Variable stenoses were created in the left main coronary arteries and downstream epicardial vessels in 6 anaesthetized male sheep using balloon catheters. A total of 220 pairs of FFR assessments of the left main stenosis were obtained, before and after creation of a stenosis in a downstream epicardial vessel, by having a pressure-sensor wire in the other nonstenosed downstream vessel. The apparent left main FFR in the presence of downstream stenosis ($\text{FFR}_{\text{app}}$) was significantly higher compared with the true FFR in the absence of downstream stenosis ($\text{FFR}_{\text{true}}$; 0.80±0.05 versus 0.76±0.05; estimate of the mean difference, 0.035; $P<0.001$). The difference between $\text{FFR}_{\text{true}}$ and $\text{FFR}_{\text{app}}$ correlated with composite FFR of the left main plus stenosed artery ($r=−0.31$; $P<0.001$) indicating that this difference was greater with increasing epicardial stenosis severity. Among measurements with $\text{FFR}_{\text{app}} >0.80$, 9% were associated with an $\text{FFR}_{\text{true}}$ of <0.75. In all instances, the epicardial lesion was in the proximal portion of the stenosed vessel, and the epicardial FFR (combined FFR of the left main and downstream stenosed vessel) was ≤0.50.

Conclusions—A clinically relevant effect on the FFR assessment of left main disease with the pressure wire in a nondiseased downstream vessel occurs only when the stenosis in the other vessel is proximal and very severe. (Circ Cardiovasc Interv. 2013;6:161-165.)

Key Words: fractional flow reserve ■ left main coronary artery ■ stenosis
was given via endotracheal intubation. An 8F sheath was placed in the femoral artery and a 6F sheath was placed in the femoral vein. Heparin was administered (200 U/kg) intravenously before cardiac catheterization.

**Experimental Protocol**

An 8F guiding catheter was used to engage the LMCA. Two pressure-sensor wires (Certus Pressure Wire, St. Jude Medical, St. Paul, MN) were then advanced into the downstream epicardial arteries with the pressure sensors placed in the distal third of the LAD and LCX respectively. Angioplasty balloon catheters were used to create variable stenoses in the LMCA (4- to 6-mm diameter balloons) and proximal segments of the LAD or LCX (2- to 4-mm diameter balloons) by varying the sizes of the balloons used and the atmospheric pressure applied using insufflators. We ensured that the LMCA balloon did not encroach on the LMCA bifurcation and allowed it to hang out of the LMCA ostium when necessary. In 3 sheep, an adequate FFR drop could not be created despite using balloons, which were larger than the diameter of the LMCA probably because of the elasticity of normal sheep LMCA. It was found that the use of a second guiding catheter in these 3 sheep enabled creation of a stable FFR in the required range. Care was taken to disengage the guiding catheter carrying the pressure wires from the LMCA during pressure measurements.

A balloon was advanced to the proximal LMCA, and a separate balloon was advanced to the proximal LAD. Intracoronary nitroglycerin was administered (100–200 µg), and continuous hyperemia was induced using an adenosine infusion via the femoral venous sheath (140 µg/kg per minute). The LMCA balloon was inflated to create a stable FFR reading. The true left main FFR (FFR<sub>true</sub>) was defined as the distal coronary pressure measured in the LCX divided by the aortic pressure with the LAD balloon deflated. The balloon in the LAD was then inflated. The apparent left main FFR (FFR<sub>app</sub>) was defined as the distal coronary pressure measured in the LCX divided by aortic pressure during LAD balloon inflation. The epicardial FFR (FFR<sub>epicardial</sub>) was defined as the distal pressure measured in the LAD divided by the aortic pressure during LAD balloon inflation and represented the composite FFR of the left main and downstream epicardial stenosis. The LAD balloon was then deflated, and we ensured that the FFR<sub>true</sub> remained the same as before LAD balloon inflation.

By varying the LMCA stenosis aiming for LMCA FFR between 0.65 and 0.90, and varying the downstream epicardial stenosis, paired measurements of FFR<sub>true</sub> and FFR<sub>app</sub> were obtained. To evaluate the effect of LCX stenosis on LMCA FFR measurement, the LAD balloon was then repositioned to the proximal LCX, and another set of measurements was collected for each animal. To compare the effect of proximal versus mid segment stenosis, measurements were obtained in the mid segment of the LAD as well.

**Statistical Analysis**

Values are presented as mean±SD unless otherwise stated. Pearson analyses were used to assess the correlation between variables. A plot of the difference between FFR<sub>true</sub> and FFR<sub>app</sub> versus FFR<sub>epicardial</sub> was used to investigate the effect of distal epicardial lesion severity on change in LMCA FFR. Mixed effects models were used to estimate the difference between FFR<sub>true</sub> and FFR<sub>app</sub> to account for the correlation between repeated measurements and the variability between individual sheep. Mixed effects models were also used to compare the difference between FFR<sub>true</sub> and FFR<sub>app</sub> in different groups including LAD versus LCX, and proximal segment versus mid segment.

**WHAT IS KNOWN**

- Fractional flow reserve (FFR) can be used to guide the decision for revascularization in the setting of intermediate left main coronary disease.
- The effect of downstream epicardial stenosis on the fractional flow reserve measurement of left main coronary lesions remains unclear.

**WHAT THE STUDY ADDS**

- This study shows that a clinically relevant effect on the fractional flow reserve assessment of left main disease with the pressure wire in a nonstenosed downstream artery occurs only when the stenosis in the other downstream artery is proximal and very severe.

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**Figure 1.** Schematic example of physiological measurements. A, True fractional flow reserve (FFR<sub>true</sub>) of the left main coronary artery obtained during left main balloon inflation and no stenosis in the left anterior descending (LAD) artery (FFR<sub>true</sub>=distal pressure [P<sub>d</sub>] in the left circumflex [LCX] artery divided by proximal arterial pressure [P<sub>a</sub>]). B, FFR<sub>app</sub> obtained during balloon inflation in the LAD (FFR<sub>app</sub>=LCX/P<sub>d</sub>/P<sub>a</sub> during downstream balloon inflation). FFR<sub>epicardial</sub> represents FFR of left main plus LAD (FFR<sub>epicardial</sub>=LAD/P<sub>a</sub> during LAD balloon inflation).
A two-sided P value of 0.05 was considered significant. Statistical calculations were performed using SPSS (v. 15, SPSS, Chicago, IL), and graphs were constructed using Graphpad Prism v. 5.01 (Graphpad Software, La Jolla, CA).

Results
A total of 220 sets of physiological measurements were obtained in 6 sheep. Mean baseline FFRtrue was 0.76±0.04 (range, 0.63–0.94). Mean composite FFRepicardial was 0.51±0.15.

Relationship Between FFRtrue and FFRapp
FFRtrue correlated with FFRapp (r=0.81; P<0.001) but FFRtrue was lower than FFRapp for the whole cohort (0.76±0.05 versus 0.80±0.05; estimate of the mean difference, 0.035; 95% confidence interval, 0.031–0.039; P<0.001). The difference between FFRapp and FFRtrue correlated with FFRepicardial (r=−0.31; P<0.001) indicating that the difference between FFRtrue and FFRapp became greater with increasing downstream epicardial stenosis severity (Figure 2).

The effect of different levels of epicardial stenosis severity on the difference between FFRtrue and FFRapp is shown in Figure 3. The difference between FFRtrue and FFRapp was similar for LAD stenosis compared with LCX stenosis (estimate of the mean difference, 0.005; 95% confidence interval, −0.003 to 0.014; P=0.216; Figure 4).

In the group with LAD stenoses, the difference between FFRtrue and FFRapp was greater for proximal lesions versus mid lesions (estimate of the mean difference, 0.014; 95% confidence interval, 0.001–0.027; P=0.03; Figure 5).

Effect of Downstream Epicardial Stenosis on FFR Cutoffs
Among measurements with FFRapp >0.80, 9% were associated with an FFRtrue of <0.75. In all instances, the epicardial lesion was in the proximal portion of the stenosed vessel and...
the epicardial FFR (combined FFR of the left main and stenosed epicardial vessel) was ≤0.50 (Figure 6). Among measurements with FFR_{app} >0.85, none were associated with an FFR_{true} of <0.75.

**Discussion**

In the present study, FFR of the LMCA was measured in a nonstenosed downstream epicardial vessel before and after inducing stenosis in the other downstream epicardial vessel. The results of this study show that LMCA FFR measurement may be overestimated in the presence of downstream epicardial disease despite measuring FFR in a nondiseased epicardial vessel. However, the effect seems to be modest, and awareness of the extent of this effect can help guide the use of FFR to aid in making clinical decisions in this setting.

Several studies have proposed the use of FFR to guide management in intermediate LMCA disease.9,10 These studies, although small, consistently show that deferral of LMCA FFR >0.75 is not associated with increased risk of future adverse events.10 In a recent study of 213 patients treated either with medical therapy or with coronary artery bypass grafting based on LMCA FFR, the use of FFR to guide revascularization resulted in an excellent outcome when LMCA revascularization was deferred based on an FFR ≥0.80.9 Put together, these studies suggest that LMCA lesions with FFR >0.8 should not be revascularized, and lesions with FFR <0.75 should be revascularized. We have chosen to focus on the occasions where FFR_{app} >0.8 is associated with FFR_{true} of <0.75 in the current study. This is because these situations represent the times when the FFR_{app} may underestimate the severity of LMCA lesions to the extent that it changes the clinical decision from medical management to revascularization.

It is important to note that significant LMCA stenosis is nearly always associated with downstream disease in the epicardial vessels,11,12 and this may affect LMCA FFR measurement. Previous studies involving serial stenosis within 1 coronary artery showed that downstream stenosis within the same artery, in the absence of large vessel branching, will reduce flow in the artery and lessen the pressure gradient across the proximal lesion.13,14 In theory, significant disease in the LAD will also impact the FFR assessment of the LMCA, even if the pressure wire is positioned in a nondiseased LCX. In this case, stenosis in the LAD will theoretically increase resistance to flow distal to the LMCA and decrease total blood flow across the LMCA and hence increase the FFR measurement in the LCX. Although flow was not directly measured in this study, the results obtained are consistent with this hypothesis. The observations that the difference between FFR_{true} and FFR_{app} increased with increasing downstream stenosis severity and was higher for proximal lesions compared with mid lesions are also consistent with this theory. The results of this study also show that even mild epicardial disease may cause a statistically significant but numerically small difference between FFR_{app} and FFR_{true}.

The impact of downstream epicardial disease on LMCA FFR was modest compared with the effect of having downstream stenosis within the same artery in previous studies.13,14 This is likely because of the effect of having a large branch vessel in between the 2 stenoses. The nonstenosed branch vessel would be expected to divert flow away from the stenosed downstream vessel and, therefore, lessen the impact of the downstream stenosis on LMCA flow.13,14

Because the LAD, in general, subtends a greater mass of myocardium, one would expect disease in the LAD to have a greater impact on the assessment of LMCA FFR with the pressure wire in the LCX than the opposite scenario. In our study, there was no significant difference in the effect of LAD and LCX lesions. However, there was a small numeric difference,
Lesions with FFR_{app} >0.8.

Figure 6. True fractional flow reserve (FFR_{true}) in instances where FFR_{app} >0.8.

and the lack of significance may have been a result of a type 2 error caused by inadequate numbers for this subgroup analysis. Alternatively, it may be a result of the fact that the sheep LCX is quite large in general and may supply a similar amount of myocardium as the LAD.

Clinical Implications

The results of this study suggest that measurement of LMCA FFR in the presence of downstream stenosis is feasible by placing the pressure sensor in the nonstenosed downstream vessel. Because downstream disease will generally cause overestimation and not underestimation of the FFR, an FFR result of <0.75 should indicate the need for revascularization regardless of whether downstream disease in the other vessel exists. The results of the current study suggest that the scenario of having FFR_{app} >0.80 and FFR_{true} <0.75 only occurs when the downstream disease in the stenosed vessel is proximal and very severe (combined FFR of the LMCA and the stenosed vessel ≥0.50). On the basis of previous data showing that deferral of FFR ≥0.75 is safe, an FFR of >0.85 would almost certainly indicate that the LMCA lesion is not functionally significant despite the presence of downstream stenosis.

Limitations

A limitation of this study is that blood flow was not directly measured to verify that LMCA flow decreased in the presence of downstream stenosis. However, flow across a stenosis is equivalent to the pressure gradient across the stenosis divided by the resistance to flow caused by the stenosis. Resistance across a given LMCA stenosis remains the same. Therefore, a decrease in pressure gradient with increased LMCA FFR implies decreased flow. Another limitation is the use of an animal model and acutely created stenoses to simulate coronary lesions. However, higher collateral flow and microvascular resistance would be expected in human coronary circulations with chronic stenoses, which would likely lessen the difference between FFR_{true} and FFR_{app}. The principle that only severe proximal epicardial lesions would affect LMCA FFR assessment should be applicable to humans. However, the specific FFR_{epicardial} cutoff demonstrated in this article requires validation in a human study.

Conclusions

A clinically relevant effect on the FFR assessment of left main disease with the pressure wire in a nonstenosed downstream artery occurs only when the stenosis in the other downstream artery is proximal and very severe.

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