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The Impact of Downstream Coronary Stenoses on Fractional Flow Reserve Assessment of Intermediate Left Main Disease

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Objectives The aim of this study was to assess the validity of measuring fractional flow reserve (FFR) of the left main (LM) coronary artery in the setting of concomitant left anterior descending (LAD) or left circumflex (LCX) stenoses.

Background The theoretical impact of a stenosis in the LAD on the FFR assessment of intermediate LM disease with the pressure wire in an unobstructed LCX is currently unknown.

Methods A previously validated in vitro model of the coronary circulation was used to create a fixed intermediate stenosis of the LM and a variable downstream LAD or LCX stenosis. The true LM FFR ($FFR_{LM\ true}$), with no concomitant downstream disease, was compared to the apparent LM FFR ($FFR_{LM\ apparent}$), with concomitant downstream disease measured with different degrees of LAD or LCX disease. Additionally, an equation based on a resistors model was derived to predict the effect of downstream stenosis on LM FFR ($FFR_{LM\ predicted}$).

Results In the setting of isolated moderate LM disease (FFR 0.72 ± 0.08), mild to moderate proximal LAD or LCX lesions did not significantly affect LM FFR. Lesions with a composite FFR (LM + downstream disease) ≥0.65 resulted in an $FFR_{LM\ apparent}$ that was not significantly different from $FFR_{LM\ true}$ (0.76 ± 0.06 vs. 0.76 ± 0.05, $p = 0.124$). Our equation for $FFR_{LM\ predicted}$ accurately modeled the effects of concomitant disease ($r = 0.95$, $p < 0.001$).

Conclusions These data suggest that in the presence of proximal mild to moderate LAD or LCX disease, LM FFR can be reliably measured with the pressure wire placed in the uninvolved epicardial artery. (J Am Coll Cardiol Intv 2012;5:1021–5) © 2012 by the American College of Cardiology Foundation

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Multiple studies have highlighted the limitations of the angiographic assessment of intermediate left main (LM) coronary artery disease (1). Fractional flow reserve (FFR) is a well-accepted invasive technique for determining the functional significance of epicardial coronary artery disease (2–4). Although a number of reports have demonstrated the usefulness of measuring FFR to assess intermediate LM

See page 1026

disease, the effect of downstream epicardial disease in the left anterior descending artery (LAD) on the FFR assessment of the LM remains unclear (5,6). Disease in the LAD will certainly affect FFR assessment of the LM when the pressure wire is in the distal LAD. However, in theory, LAD disease might also affect the FFR assessment of the LM when the pressure wire is positioned in a non-diseased left circumflex artery (LCX). The flow across the LM depends on the outflow to the LAD and LCX, and therefore the LAD stenosis impairs maximal flow across the LM, which will falsely elevate the FFR.

The goal of this study is to explore the effect of increasingly severe downstream disease in either the LAD or the LCX on FFR assessment of intermediate LM disease when the pressure wire is positioned in the nondiseased epicardial vessel.

Abbreviations and Acronyms

FFR = fractional flow reserve

$FFR_{LM\ apparent}$ = left main FFR in the setting of a concomitant left anterior descending or left circumflex stenosis

$FFR_{LM\ predicted}$ = predicted true fractional flow reserve of the left main stenosis in the setting of concomitant left anterior descending or left circumflex stenosis

$FFR_{LM\ true}$ = true fractional flow reserve of left main stenosis

LAD = left anterior descending coronary artery

LCX = left circumflex coronary artery

LM = left main coronary artery

P_a = mean aortic pressure

$P_{d\ LAD}$ = mean distal left anterior descending artery pressure beyond all stenoses

$P_{d\ LCX}$ = mean distal left circumflex artery pressure beyond all stenoses

Methods

Procedure. A previously validated in vitro model of the coronary circulation was used to simulate the LM with a distal bifurcation into the 2 daughter vessels representing the LAD and LCX (Fig. 1) (7). This model simulates pulsatile cardiovascular flow using a piston pump in conjunction with mechanical mitral and aortic valves. The microvascular resistance in the distal LAD and LCX can be independently adjusted to tune the model to approximate both appropriate volume of flow for those perfusion territories, as well as flow velocity characteristics approximating human coronary flow (typically 400 ml/min for the LAD). A mechanical occluder was attached to the LM to create a variable stenosis. Perivascular flow probes (Transonic Systems Inc., Ithaca, New York) were fitted onto each branch vessel along with mechanical occluders distal to each probe. A fluid-filled pressure transducer was attached to the proximal aorta to measure mean aortic pressure (P_a). A pressure wire (St. Jude Medical, St. Paul, Minnesota) was advanced distally to each daughter vessel to measure distal LAD pressure ($P_{d\ LAD}$) and distal LCX pressure ($P_{d\ LCX}$). Absolute flow in the LAD and LCX was measured at each step using a flow meter (Transonic Systems Inc.) These data were simultaneously acquired with an analog-to-digital converter and a custom LabVIEW application (National Instruments, Austin, Texas) sample rate of 1,000 Hz. To account for difference in distal myocardial perfusion territory and flow between the LAD and LCX, the model was tuned to approximate human physiological conditions during maximal coronary hyperemia with a LAD/LCX flow of 2:1. An isolated moderate LM stenosis was created and P_{dLCX}/P_a was termed true FFR of the LM ($FFR_{LM\ true}$). A progressive LAD stenosis was created from mild to severe and the apparent FFR value of the LM ($FFR_{LM\ apparent}$) was also calculated as P_{dLCX}/Pa (but in the presence of a stenosis in the LAD). The same was repeated with a concomitant stenosis in the LCX and $FFR_{LM\ apparent}$ was in this case calculated as P_{dLAD}/P_a. We define "composite FFR" as the LM lesion plus the downstream lesion with the pressure wire distal to both lesions. Mild to moderate LAD/LCX lesions were arbitrarily defined as a composite FFR of ≥0.65 and severe lesions as <0.65.

Prediction of LM FFR. The severity of the true FFR value of the LM is underestimated in the presence of concomitant coronary artery disease. Therefore, an equation to predict the FFR value of the LM ($FFR_{LM\ predicted}$) was developed based on a resistance model of the coronary circulation. These equations were applied to predict the true FFR of the LM (Online Appendix). FFR values of <0.15 were excluded since these values are not physiological.

Statistics. $FFR_{LM\ true}$ was compared with $FFR_{LM\ apparent}$ and $FFR_{LM\ predicted}$ using paired *t* tests. Linear correlation was performed with $FFR_{LM\ apparent}$ versus $FFR_{LM\ true}$, and $FFR_{LM\ predicted}$ versus $FFR_{LM\ true}$. The Pearson correlation was calculated and a *Z* test was applied to assess for differences between dependent correlations (8).

A plot was constructed to assess the accuracy of the predictive equation across the range of distal stenosis severity. A 2-sided p value <0.05 was considered statistically significant.

Results

FFR was measured in LM lesions with progressive LAD or LCX stenoses (n = 75). $FFR_{LM\ true}$ was 0.72 ± 0.08 and ranged from 0.57 to 0.82. $FFR_{LM\ apparent}$ had a moderate correlation with $FFR_{LM\ true}$ ($r = 0.73$, $p < 0.001$). The divergence of $FFR_{LM\ apparent}$ from $FFR_{LM\ true}$ was minimal for mild to moderate LAD or LCX disease and became significant only for severe disease (Fig. 2). $FFR_{LM\ apparent}$ was significantly higher than $FFR_{LM\ true}$ (0.78 ± 0.08 vs. 0.72 ± 0.08, $p < 0.001$) in the entire cohort (Fig. 3A). Lesions with a composite FFR (LM + downstream LAD

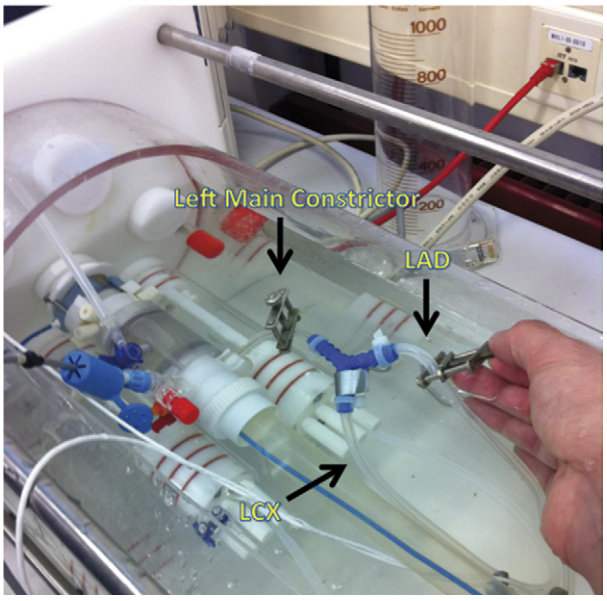

Figure 1. In Vitro Model of the Coronary Circulation

An in vitro model of the coronary circulation with a left main artery (LM) that bifurcates into the left anterior descending (LAD) and left circumflex (LCX) branches with independently adjustable microcirculatory resistance. There are variable resistance constrictors around the LM and LAD.

or LCX disease) ≥0.65 resulted in an $FFR_{LM\ apparent}$ that was not significantly different from $FFR_{LM\ true}$ (0.76 ± 0.06 vs. 0.76 ± 0.05, p = 0.124) (Fig. 3B) and lesions with a composite FFR <0.65 resulted in a higher $FFR_{LM\ apparent}$ than $FFR_{LM\ true}$ (0.79 ± 0.09 vs. 0.70 ± 0.08, p < 0.001) (Fig. 3C). LCX disease appeared to have less impact than LAD disease did on the FFR assessment of intermediate LM disease with the pressure wire in the nondiseased epicardial vessel (0.77 ± 0.09 vs. 0.69 ± 0.09, p < 0.001 for $FFR_{LM\ apparent}$ vs. $FFR_{LM\ true}$ with LAD disease and 0.78 ± 0.07 vs. 0.73 ± 0.06, p < 0.001 for $FFR_{LM\ apparent}$ vs. $FFR_{LM\ true}$ with LCX disease) (Figs. 4A and 4B).

Using the equation for $FFR_{LM\ predicted}$, the correlation with $FFR_{LM\ true}$ was much stronger (r = 0.95, p < 0.001). The linear regression equation for $FFR_{LM\ predicted}$ versus $FFR_{LM\ true}$ was y = 1.02x + 0.01, indicating the prediction model not only correlated with $FFR_{LM\ true}$, but was physiologically sound as the regression approximated the line of identity. Our equation for $FFR_{LM\ predicted}$ was accurate through the range of downstream disease from mild to severe (Fig. 5). The correlation with $FFR_{LM\ true}$ was significantly stronger for $FFR_{LM\ predicted}$ in comparison with $FFR_{LM\ apparent}$, z = 8.26, p < 0.01.

Discussion

In patients with intermediate LM coronary artery disease, accurate determination of functional significance is critical. Isolated LM disease is rare, occurring in <10% of cases (9). Therefore, a better understanding of the utility and potential limitations of FFR in the setting of moderate LM disease with concomitant downstream stenoses is critical to revascularization decision making. The primary finding of our study was that in the setting of moderate LM plus concomitant mild to moderate LAD disease, assessment of LM FFR with the pressure sensor placed in the LCX artery is reliable. We found that in the setting of LM plus downstream disease, the assessment of FFR LM with the pressure sensor in the nondiseased vessel is not significantly affected until the composite of the LM and downstream disease with the pressure sensor in the distal diseased epicardial vessel is severe (FFR <0.65).

LM plus LCX disease would be expected to affect LM FFR to a lesser extent than the reverse situation with LM plus LAD disease because the LCX receives less outflow than the LAD. Indeed, in our in vitro model, we found this trend as the model was tuned to approximate human LAD and LCX perfusion territories with a 2:1 flow ratio. This suggests that LCX lesions are even less likely to affect LM FFR when measured with the pressure wire in an unobstructed LAD.

A second major finding was that applying our equation based on a resistors model accounted for the effect of downstream disease and allowed for more accurate assessment of LM FFR. FFR can be defined based on flow, as traditionally calculated, by the ratio of pressure, as used in clinical practice, or as microcirculatory and epicardial resistances (Online Appendix). By calculating FFR using resistance, we can "virtually" remove an LAD or LCX stenosis to estimate the isolated LM FFR.

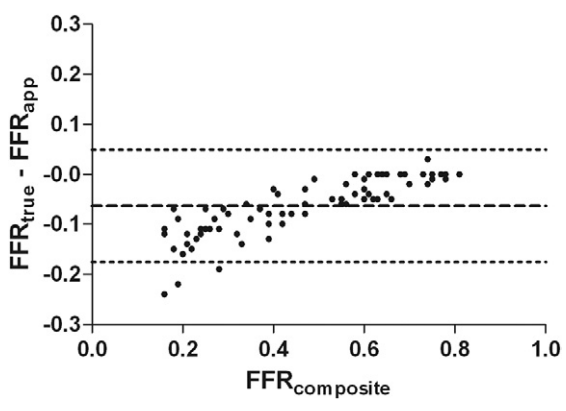

Figure 2. Effect of Downstream Stenosis on LM FFR

Plot of true FFR of LM stenosis ($FFR_{LM\ true}$) minus LM FFR in the setting of a concomitant LAD or LCX stenosis ($FFR_{LM\ apparent}$) on the y-axis as a function of downstream stenosis severity (composite LM + LAD or LCX FFR) on the x-axis. Dashed lines represent 95% confidence intervals. For a fixed LM stenosis, as the downstream stenosis becomes more severe, $FFR_{LM\ apparent}$ rises. An epicardial lesion with a downstream FFR of >0.60 is associated with a <0.05 overestimation of $FFR_{LM\ true}$. Abbreviations as in Figure 1.

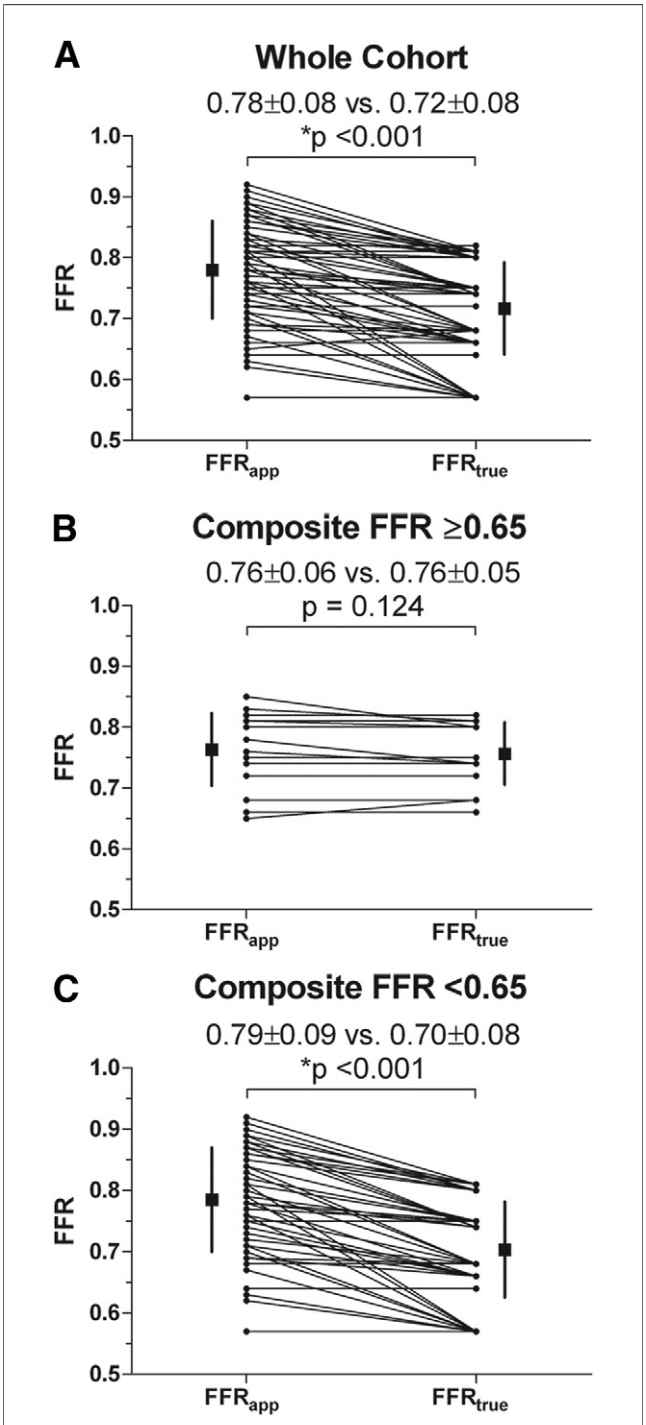

Figure 3. Impact of Epicardial Stenosis Severity on Assessment of LM FFR

(A) FFR difference between $FFR_{LM\ apparent}$ and $FFR_{LM\ true}$ for the entire cohort. **(B)** Difference between $FFR_{LM\ apparent}$ and $FFR_{LM\ true}$ for epicardial lesions with an FFR ≥0.65. **(C)** Difference between $FFR_{LM\ apparent}$ and $FFR_{LM\ true}$ for epicardial lesions with an FFR <0.65. Abbreviations as in Figure 2.

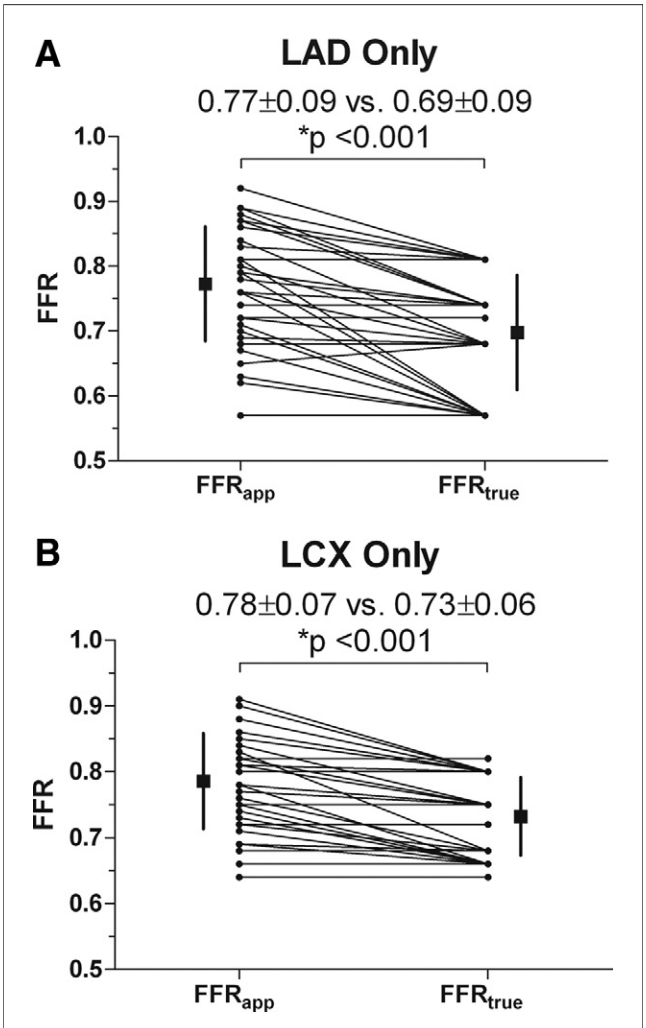

Figure 4. Effect of LAD Disease Versus LCX Disease on Assessment of LM FFR

(A) Difference between $FFR_{LM\ apparent}$ and $FFR_{LM\ true}$ for LAD stenoses. **(B)** Difference between $FFR_{LM\ apparent}$ and $FFR_{LM\ true}$ for LCX stenoses. Abbreviations as in Figures 1 and 2.

We demonstrated that an LM stenosis with concomitant LAD or LCX disease represents a special case of serial lesions, as there is a major side branch and requires a different model than that previously described by De Bruyne et al. (10). When applied to our dataset, these previously described equations for serial lesions, though an improvement over $FFR_{LM\ apparent}$, did not correlate as well with $FFR_{LM\ true}$ as the new equation for $FFR_{LM\ predicted}$ did ($r = 0.87$ vs. $r = 0.95$). In contrast to serial lesions without a major side branch in which even mild distal disease significantly affects the apparent FFR of a proximal lesion, in our model, LM FFR is not affected by mild to moderate LAD disease and is falsely elevated only in the presence of a severe proximal LAD lesion. Accordingly, our model may also be important when considering serial lesions within a major epicardial artery with a major intervening side branch.

Given these findings, it seems that FFR assessed in the proximal uninvolved branch is reliable in the setting of LM disease plus concomitant mild to moderate downstream

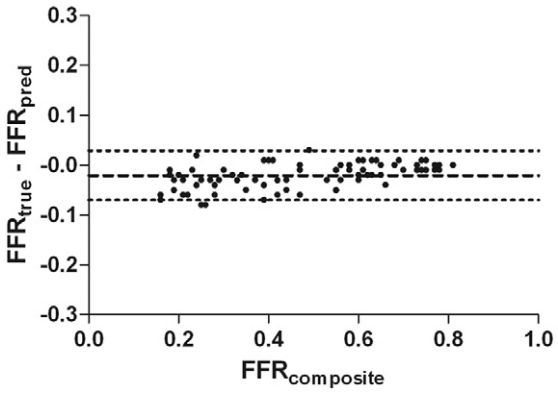

Figure 5. Results of an Equation To Predict LM FFR in the Setting of Downstream Stenosis

Plot of $FFR_{LM\ true}$ minus the predicted true FFR of the LM stenosis in the setting of concomitant LAD or LCS ($FFR_{LM\ predicted}$) on the y-axis as a function of downstream stenosis severity (composite LM + LAD or LCX FFR) on the x-axis. **Dashed lines** represent 95% confidence intervals. For a fixed LM stenosis, $FFR_{LM\ predicted}$ accurately estimates $FFR_{LM\ true}$ through the range of downstream stenosis severity. Abbreviations as in Figures 1 and 2.

stenosis. In the setting of severe downstream disease, the operator needs to be aware that the FFR may be falsely elevated, and alternative methods for assessing the left main, such as intravascular ultrasound, can be considered. From a practical perspective, if the composite FFR with the pressure sensor in the distal LAD in a patient with LM plus LAD disease is >0.65, our data suggest that assessment of the LM contribution to ischemia with the pressure sensor in the proximal LCX is accurate using the usual cutoff of 0.75 to 0.80 for FFR decision making.

Study limitations. Our method was applied to an in vitro model of the coronary circulation, which though previously validated, may harbor important differences to human coronary physiology. Notably, there is no collateral circulation, and that might affect the accuracy of our equations, although collaterals would be expected to lessen the impact of downstream disease on LM FFR. These findings will need to be confirmed in an in vivo model. We also did not test the impact of lesion location within the epicardial vessel, because of limitations of our in vitro model. All lesions in this study were considered proximal. Theoretically, a distal lesion would have even less affect on flow across the LM and less tendency to lead to an overestimation of the FFR. This will need to be confirmed in an in vivo model. A limitation of our equation for $FFR_{LM\ predicted}$ is that it requires knowledge of absolute or relative flows, which is not currently practical for clinical purposes. That being said, the purpose of testing this equation was to lend support to the physiological basis for the observed phenomenon and not to propose a clinical method for improving the interpretation of LM FFR in this setting. In the future, simplified methods for determining absolute or relative coronary flow in vivo might allow the use of our equations for adjudicating LM lesions with even severe downstream disease.

Conclusions

In an in vitro model of the coronary circulation, we found that mild to moderate proximal LAD or LCX disease did not significantly affect LM FFR when the pressure wire is positioned in the nondiseased epicardial vessel. In the setting of severe proximal downstream disease, the LM FFR may be falsely elevated. Our theoretical model for $FFR_{LM\ predicted}$ functioned well to estimate true LM FFR and validates the theoretical considerations of complex serial lesion assessment.

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Key Words: coronary artery disease ■ fractional flow reserve ■ left main coronary artery.

APPENDIX

For an explanation of the derivation of FFR in terms of coronary resistance, please see the online version of this paper.