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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

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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