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EDITORIAL COMMENT

Same Lesion, Different Artery, Different FFR!?*

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If we could excise a stenosed epicardial vessel from 1 patient and implant it in another patient with a larger or a smaller heart (e.g., as a result of body size), would the fractional flow reserve (FFR) value change? Because FFR was designed to be a *lesion-specific* metric of relative hyperemic flow (1), we might expect that distal myocardial mass would not affect its value. In other words, if the coronary stenosis stayed the exactly the same but was attached to a different amount of muscle with the same ability to vasodilate, we might at first glance anticipate that we would measure the same FFR value. The report by Yang et al. (2) in this issue of *iJACC* provides an important opportunity to retrain our intuition because epicardial FFR does indeed depend on the amount of distal mass.

The normal relationship between the epicardial vessels and the amount of distal myocardial mass reflects 2 physiological principles (3). First, endothelial cells must avoid injury by ensuring that the shear stress does not exceed damaging limits. Second, the structure of the epicardial vessels seeks to minimize the required energy to move the blood along the conduits (viscous friction loss) in relation to the energy content of the blood (potential energy). These principles, along with basic considerations of dimensional analysis, imply that epicardial coronary artery area equals distal myocardial mass raised to the two-thirds power. These theoretical considerations have been verified experimentally using invasive angiography in human subjects (3).

As disease develops, this normal relationship changes in 2 important ways. First, the epicardial vessel undergoes positive or negative remodeling in response to atherosclerosis. Second, the distal myocardium can become hypertrophied in response to hypertension or reduced by myocardial infarction. Therefore, the slightly higher area-versus-mass exponent seen in a human cohort with varying atherosclerotic burden versus the normal expectation (roughly 0.75 to 0.80 vs. 0.67) reflects the net effect of these pathophysiological processes, with scatter about the average as a result of unique balances in an individual patient (3), as summarized in **Figure 1**, panel 1.

What does the observed epicardial area versus myocardial mass relationship tell us about coronary artery development? Because endothelial cells sense shear stress via mechanoreceptors, vessel dimensions can adapt naturally at a local level during embryological maturation. Indeed, other "design parameters," such as constant flow velocity (leading to an exponent of 1.0 between coronary area and distal mass) and constant pressure gradient per unit length (leading to an exponent of 0.5 via the Hagen-Poiseuille equation), do not offer plausible, local mechanisms for vessel adjustment during development. **Figure 1**, panel 2 summarizes these alternative hypotheses and their supporting evidence.

The exponent of 0.5 between coronary area and myocardial mass proposed by Yang et al. (2) therefore disagrees with both theoretical expectations and prior experimental results. The data in their Figure 1B should have been fit with a power law area $\propto$ mass^c to find the exponent c. Its confidence interval would help us understand how far their cohort had "moved"

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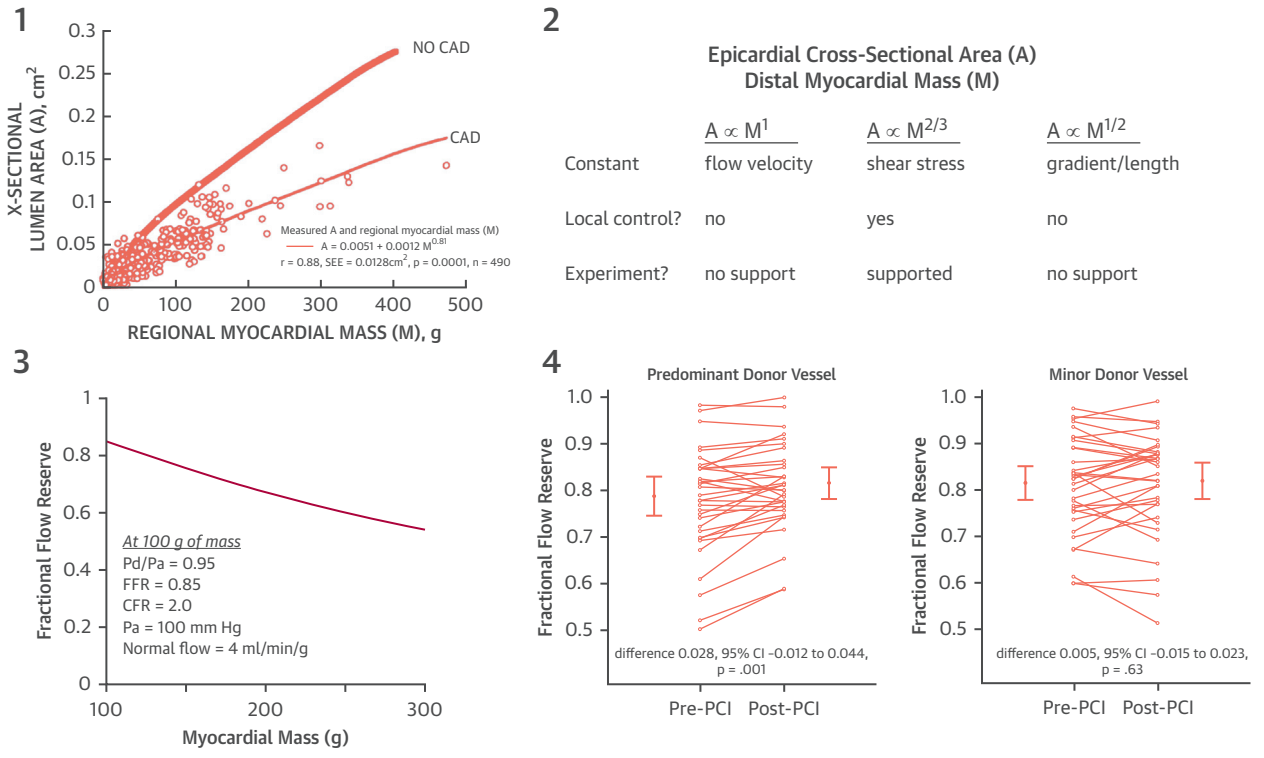
FIGURE 1 **Clinical Implications of Structure and Function Relationships**



(1) Experimental data from a human cohort with and without coronary artery disease (CAD) demonstrated a curvilinear relationship between epicardial cross-sectional area (A) and distal myocardial mass (M) with a coefficient of about 0.8. Reprinted with permission from Seiler et al. (3). **(2)** On the basis of proposed design constants, the coefficient for the relationship between A and M can assume values of 1, two-thirds, or one-half. Constant shear stress, which can be controlled at a local level, receives support from both theory and experimental data. **(3)** Simulation of the effect of mass on the fractional flow reserve (FFR) of a stenosis when keeping the friction and separation coefficients constant. **(4)** Clinical data measuring fractional flow reserve (FFR) in the donor vessel before and after revascularization of a recipient chronic total occlusion shows an average increase of +0.03 even with a large donor vessel **(left)** and a smaller increase with a minor donor vessel **(right).** However, large increases can be seen in individual cases. Reprinted with permission from Ladwiniec et al. (17). CFR = coronary flow reserve; CI = confidence interval; Pa = aortic pressure; PCI = percutaneous coronary intervention; Pd = distal coronary pressure; SEE = standard error of the estimate.

from the 0.67 "baseline" as a result of epicardial remodeling and myocardial disease. If the exponent were stratified by epicardial atherosclerotic burden (for which FFR provides an integrative, hemodynamic metric), we would anticipate values farther from 0.67 with increased disease. Furthermore, because each subject in the study by Yang et al. (2) had both simulated FFR and volume and mass measurements, a "paired" comparison using a McNemar test would have provided objective evidence of differential diagnostic performance versus invasive FFR. The wide scatter in their Figure 1C suggests that volume and mass parameters contribute too little for clinical decisions in an individual.

Two other recent papers have refocused attention on using deviations from normal structure and function relationships for clinical diagnosis via coronary computed tomography (4,5). Although the finding that smaller coronary volume relative to myocardial mass indicates insufficient supply, and hence lower FFR values (4), has logic, the claim that myocardial flow depends on mass to the three-fourths power contradicts basic notions of flow continuity. Similarly, the notion of "fractional myocardial mass" demands that myocardial mass and cumulative epicardial vessel length have a four-thirds power law (5), in contradiction both to continuity and to experimental evidence of a linear relationship (6). Both these attempts underscore that allometric scaling laws *among* species need not hold *within* a species (7).

What clinical consequences arise from these seemingly abstract structure and function relationships

in the epicardial vessels? Probably the most important impact involves the dependence of FFR on the amount of distal myocardial mass. Clinical data have shown falling FFR values when moving from smaller vessels such as the right coronary artery (RCA) and left circumflex coronary artery to larger vessels such as the proximal left anterior descending (LAD) coronary artery (8,9), as well as an inverse relationship between the myocardial jeopardy index (an angiographically derived estimate of relative subtended myocardium) and FFR (9). Similarly, FFR values were lower in parent LAD vessels than in their diagonal daughter branches (0.67 vs. 0.71 on average; $p = 0.02$) (10). Finally, the higher average FFR values observed in women (0.75 with body surface area 1.78 m^2) versus men (0.71 with body surface area 2.01 m^2) also support a mass dependence (11).

Although these clinical observations could reflect sampling bias (perhaps operators were more likely to perform FFR measurements on angiographically worse proximal lesions than on milder distal lesions), fluid dynamic considerations support the association. Because normal hyperemic flow remains relatively constant around 3 ml/min/g over the entire left ventricle (12), the absolute volume of blood flow depends on the mass of distal muscle supplied by a particular epicardial conduit. A 50% difference in mass between the RCA and LAD, coupled with the 30% coefficient of variation in absolute myocardial size, as shown by Yang et al. (2) in their Table 1, implies that an RCA in a small patient versus an LAD in a large patient could easily have 2-fold differences in absolute flow (95 vs. 191 ml/min from $111 \times 1.06 \times 0.27 \times 3$ vs. $143 \times 1.06 \times 0.42 \times 3$ on the basis of their Table 1 and assuming a myocardial density of 1.06 g/cc). Therefore, even without a coronary artery stenosis, the viscous pressure loss along a fixed length of the same epicardial vessel could vary by 2-fold because of distal mass alone.

In the setting of a stenosis, the combination of viscous and exit or separation effects makes the impact of mass even more interesting. Formally, the pressure gradient along the vessel (ΔP) equals $v \times Q + s \times Q^2$ where Q represents absolute flow in milliliters per minute and v and s are coefficients that "depend on the stenosis geometry, blood viscosity and density, vessel diameter, and the shape of the pulsatile wave form" (13). Crucially, it is the absolute flow (ml/min) not perfusion (ml/min/g) that ultimately drives pressure loss. Hence for the same stenosis (fixed coefficients v and s), a larger distal mass (more grams of tissue) requires increased absolute flow (ml/min) despite the same perfusion (ml/min/g), thus leading to a greater pressure loss. Stability of minimal myocardial resistance independent of epicardial stenosis is a fundamental assumption of the FFR model validated in animals (1) and humans using thermodilution (14) and Doppler velocity (15) techniques. Although normal flow increases in proportion to mass, as detailed earlier, stenotic flow reaches a lower, mass-dependent limit imposed by reaching minimal resistance earlier. **Figure 1**, panel 3 shows an example of how FFR depends on mass, although the exact shape will vary for each patient, depending on details of pressure loss versus flow curve shape, myocardial mass, and minimal myocardial resistance (as well as collateral resistance from donor to recipient vessel not accounted for in this simplified model).

Two systematic studies (16,17) and several case reports clearly demonstrate that FFR values in the donor artery to a chronic total occlusion increase after successful reopening of the recipient vessel. Although the average increase in FFR remains a modest +0.03 (17), as shown in **Figure 1**, panel 4, extreme changes up to +0.14 (16) have been reported. Whereas qualitative factors (size of chronic total occlusion territory, severity of donor stenosis, extent of collaterals) can offer visual clues to the predicted FFR increase, quantitative prediction would require measurement of the exact donor and recipient masses, as well as construction of a pressure loss versus flow curve for the donor vessel—all impractical for routine clinical practice.

In conclusion, the work by Yang et al. (2) reminds us that basic structure and function relationships of the epicardial coronary circulation carry clinical consequences, both for the diagnosis of lesion severity and for the impact of chronic total occlusion recanalization on donor vessel physiology. Although FFR is a lesion-specific metric, its value does depend on the amount of distal myocardium supplied by the vessel. Because both "depth" (18) and "extent" (physiological severity and amount of myocardium) affect outcomes, FFR provides a prognostic metric that incorporates both aspects simultaneously. *Same* lesion, *different* vessel, *different* FFR!

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