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EDITORIAL COMMENT

Coronary Pathophysiology Underlying the Obesity Paradox*

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In this issue of *JACC: Advances*, Valenta et al[1] from Thomas Schindler's positron emission tomography (PET) team report on PET perfusion imaging underlying the "obesity paradox." The data reveals interesting new coronary pathophysiology differentiating visceral obesity associated with prevalent risk factors and high coronary artery disease (CAD) risk from subcutaneous morbid obesity without risk factors with low CAD risk compared to normal weight controls. The study highlights 2 perhaps somewhat underappreciated pathophysiologic concepts about obesity reviewed in this paper. First, visceral obesity is associated with prevalent high-risk factors, coronary calcification, nonobstructive coronary diffuse CAD but no flow-limiting stenosis by PET, and a high risk of coronary events compared to the normal weight controls. In contrast, subcutaneous morbid obesity is associated with normal lipid profiles, less coronary calcium, and a low risk of clinical CAD. Second, advanced precise PET perfusion imaging quantifies and explains specific measurable coronary pathophysiology associated with this loosely defined "obesity paradox" and different outcomes.

This paper nicely reviews metabolic differences between visceral obesity vs subcutaneous morbid obesity and their differential prevalence of subclinical or manifest CAD with metabolic mechanisms proposed. Its novelty derives from the also underappreciated PET-derived base-to-apex longitudinal perfusion gradient that solidly bookends the "obesity paradox" by PET imaging, augmenting the risk-factor-outcome disparities in the literature. The novel insight may be enhanced by a brief review of the cardiac base-to-apex longitudinal perfusion gradient and its mechanism as a marker of early, mild, diffuse, nonobstructive CAD in some patients but not others with more advanced diffuse CAD without focal stenosis as ruled out by PET in this study.

Widespread diffuse nonobstructive coronary atherosclerosis was reported many years ago from the pathology of Korean War casualties and by intracoronary ultrasound. The coronary physiologic consequences and noninvasive imaging were first described as a base-to-apex longitudinal perfusion gradient along the long axis of the left ventricle by PET of stress myocardial perfusion imaging.[2] The mechanism of this longitudinal perfusion gradient is explained by experimental demonstration of coronary "branch steal," whereby low-resistant branches along a diffusely narrowed parent coronary artery shunts blood flow away from downstream flow in the parent artery.[3] Consequently, vasodilation stress with intravenous dipyridamole may cause myocardial steal at the left ventricle apex, manifesting as a fall in stress perfusion below resting levels despite a patent parent artery with no focal stenosis or collateralization.

The stress-induced base-to-apex longitudinal perfusion gradient was confirmed as a marker of diffuse CAD in several subsequent publications.[4-8] However, it was not observed in all patients with

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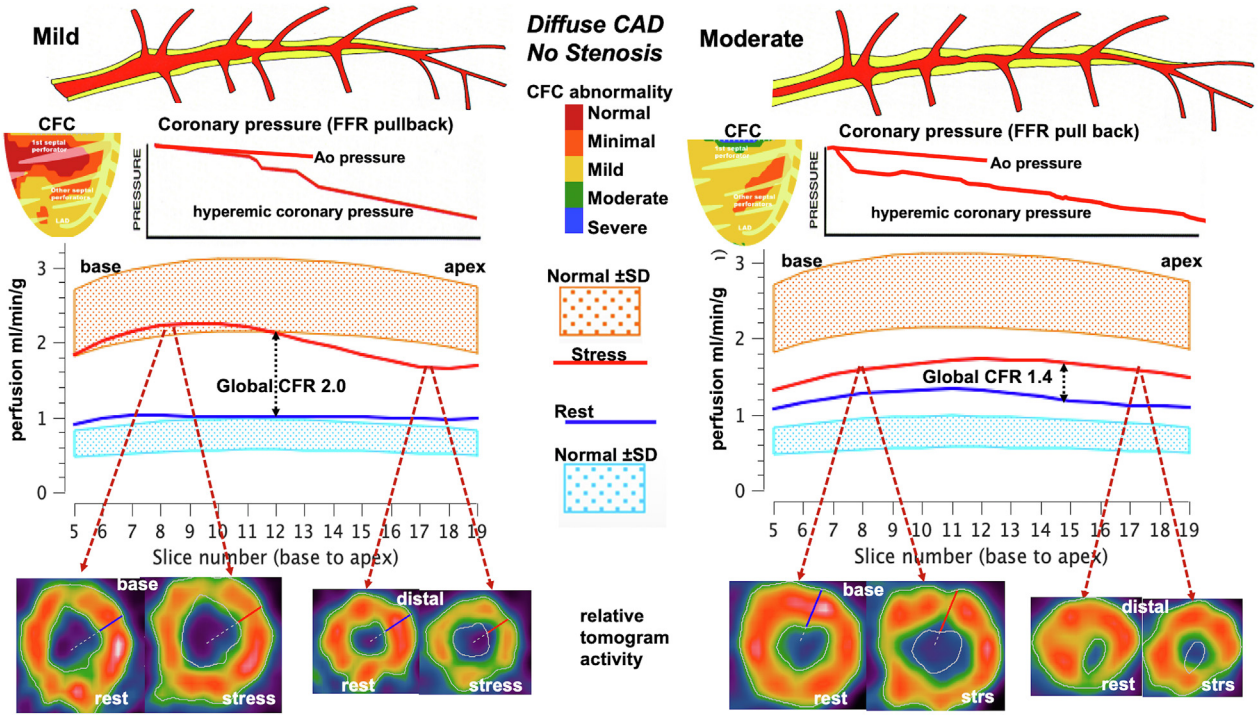
FIGURE 1 Schematic Explaining the Stress Induced Longitudinal Perfusion Gradient and Reduced Subendocardial Perfusion in Diffuse Epicardial CAD



Proximal and distal coronary flow capacity (CFC), coronary flow reserve (CFR), stress ml/min/g, the base-to-apex longitudinal perfusion gradient, and relative subendocardial perfusion for mild to moderate (left) or severe (right) diffuse epicardial nonobstructive coronary artery disease (CAD) (no focal stenosis).

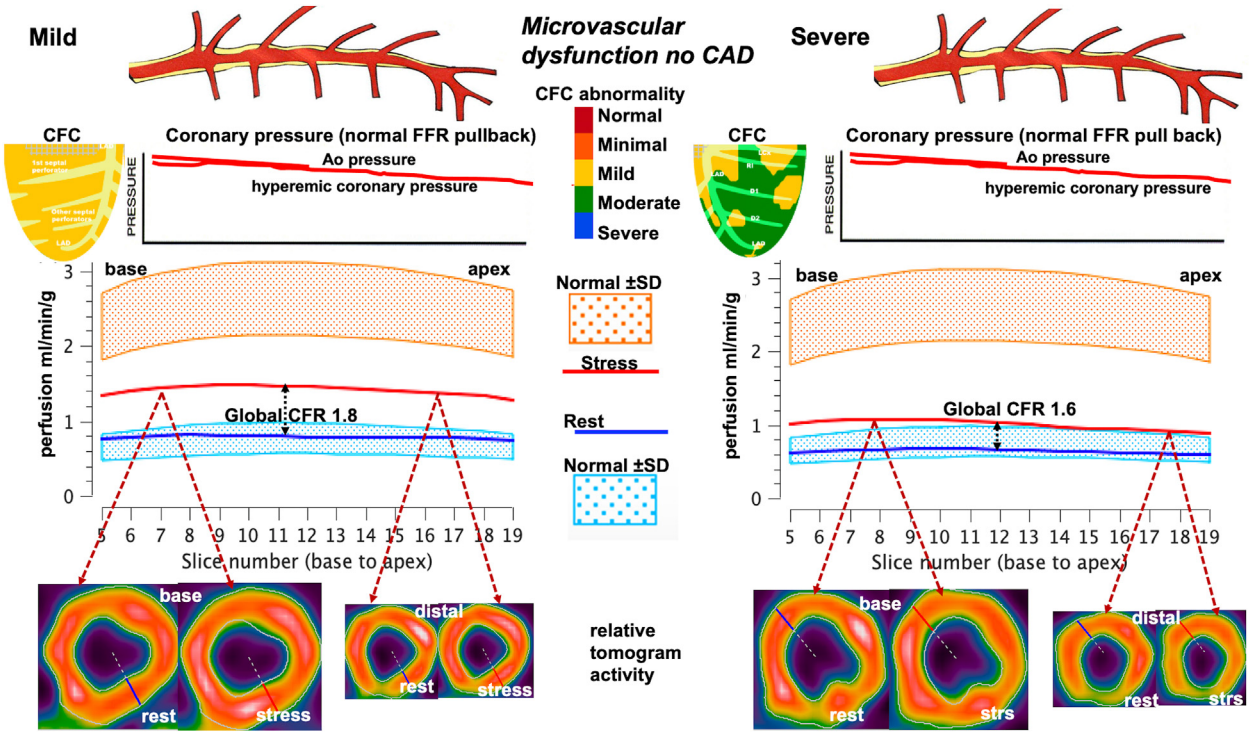
diffuse CAD,[7] an unexplained heterogeneity due to 2 factors. First, as addressed by Valenta et al,[1] are the different obesity phenotypes underlying the "obesity paradox".[1] Second is the little-recognized fluid dynamics underlying the base-to-apex longitudinal perfusion gradient explained in this editorial.

Figure 1 illustrates the "classical" base-to-apex longitudinal perfusion gradient during dipyridamole stress due to diffuse epicardial CAD without focal stenosis. During hyperemic stress, the coronary perfusion pressure falls as measured experimentally[9] or clinically as fractional flow reserve (FFR)[10] or as a long pull-back FFR along the length of a coronary artery.[11,12] This fall in hyperemic coronary pressure impairs subendocardial perfusion experimentally[13] and clinically as a parallel pathophysiologic marker of diffuse CAD first imaged clinically by PET with or without clinical angina or ECGST-segment depression.[14]

For mild, diffuse, no-stenosis CAD during vasodilatory stress, the proximal coronary flow, pressure, and subendocardial perfusion are normal but decrease distally, paralleling the distal to proximal FFR pullback. Note that the transmural perfusion gradient to low subendocardial perfusion must be conceptually distinguished from the base-to-apex longitudinal perfusion gradient of mean transmural perfusion. The hyperemic reduced subendocardial perfusion by noninvasive PET indicates reduced hyperemic coronary pressure. In addition, the reduced hyperemic subendocardial perfusion indicates sufficient coronary microvascular function responding to dipyridamole, which rules out predominant microvascular dysfunction defined as failure to increase coronary blood flow or perfusion in response to vasodilator stress.

However, for moderate to severe, diffuse, nonstenostic, epicardial CAD during vasodilatory stress, there is no longitudinal base-to-apex perfusion gradient due to more severely reduced both proximal and distal low coronary pressure and subendocardial perfusion throughout its length that uniformly lowers mean transmural perfusion (**Figure 1**) (coronary flow capacity [CFC] yellow). Therefore, a base-to-apex longitudinal perfusion gradient indicates mild, diffuse, no-stenosis, and epicardial CAD, but not

FIGURE 2 Schematic Explaining the Absence of Stress Induced Longitudinal Perfusion Gradient and Normal Subendocardial Stress Perfusion in Microvascular Disease



Proximal and distal coronary flow capacity (CFC), coronary flow reserve (CFR), stress ml/min/g, the base-to-apex longitudinal perfusion gradient, and relative subendocardial perfusion for mild to moderate (left) or severe (right) microvascular dysfunction without diffuse epicardial coronary artery disease (CAD) or focal stenosis.

moderate to severe diffuse CAD. In contrast, moderate to severe diffuse CAD reduces global proximal and distal coronary pressure and subendocardial perfusion during hyperemic stress, thereby precluding the base-to-apex longitudinal and explaining its heterogeneous relation to pressure derived FFR in the literature.[7] These examples illustrate the precision, technologically optimized, PET perfusion imaging combined with knowledge of coronary pathophysiology and fluid dynamics for insights into the quantifiable coronary pathophysiology characterizing different obesity phenotypes underlying the "obesity paradox."

Visceral obesity associated with high-risk factors shows the coronary pathophysiology of early heterogeneous nonobstructive epicardial CAD manifested as a base-to-apex longitudinal perfusion gradient. More advanced nonobstructive CAD may manifest as uniform proximal and distal reduced subendocardial perfusion without the longitudinal base-to-apex perfusion gradient. Both degrees of diffuse nonobstructive epicardial CAD need intense medical-lifestyle management to prevent progression to plaque rupture and coronary events.

As reviewed in this paper, morbid subcutaneous obesity with normal or low-risk factors does not have the longitudinal base-to-apex perfusion gradient with less coronary calcification, less manifest CAD, and less risk of coronary events compared to normal weight controls. However, in the absence of subendocardial perfusion imaging by PET, this study cannot determine whether the absence of the longitudinal perfusion gradient in morbid obesity is due to severe or no diffuse epicardial CAD, both of which may lack a base-to-apex longitudinal perfusion gradient.

Since morbid subcutaneous obesity incurs more heart failure than acute coronary events compared to the opposite for visceral, less severe obesity, the authors appropriately ascribe the higher risk of congestive heart failure in the morbidly obese to metabolic effects on the myocardium. They rule out the common wastebasket attribution of congestive heart failure to

microvascular dysfunction by their Figures 1B and 2B and Table 2, row 3,[1] showing normal hyperemic stress perfusion of 2.26 ± 0.4 ml/min/g for the morbid obese vs 2.35 ± 0.32 ml/min/g for the normal weight group ($P = 0.30$). Coronary flow reserve in morbid obesity (1.99 ± 0.38) is slightly lower than normal weight (2.29 ± 0.53) due to rest perfusion in morbid obesity (1.17 ± 0.25 ml/min/g) being higher than normal weight controls (1.07 ± 0.24 ml/min/g). In this study, the definition of microvascular dysfunction is the inability of the microvasculature to vasodilate, thereby impairing the stress perfusion that is normal in morbid obesity.

Figure 2 defines the parallel proximal and distal CFC, coronary pressure, and subendocardial perfusion for diffuse microvascular disease in contrast with diffuse nonobstructive epicardial CAD. When mild or moderate to severe predominant microvascular dysfunction prevents increased coronary blood flow and perfusion, the proximal and distal coronary pressure and subendocardial perfusion are normal.[15] Therefore, reduced CFC or coronary flow reserve with a base-to-apex longitudinal perfusion gradient identifies diffuse epicardial CAD with adequate microvascular function, thereby excluding microvascular disease in morbid obesity in this study. This precise coronary pathophysiology by PET supports the author's conclusion that the heart failure of the morbidly obese is most likely due to primary myocardial dysfunction, such as nonischemic cardiomyopathy or severe diastolic dysfunction, but not CAD or microvascular dysfunction.

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