Coronary Blood Flow After Acute MI

Alternative Truths*

K. Lance Gould, MD, Nils P. Johnson, MD

Rarely do editorialists have the opportunity to address a technically nearly perfect paper on human coronary physiology, particularly, when alternative truths leap out of superb data viewed without preconceptions of what data “should show.” Such data have their own power and their own purity that resist obfuscation, even by the author’s well-intended but narrow, and likely incorrect, interpretation. The purview of hypothesis testing includes letting data talk to us, telling us a different story, perhaps an even more profound one than hypothesized, as with this study reported by de Waard et al. (1) in this issue of JACC: Cardiovascular Interventions. de Waard et al. (1) measured resting and hyperemic coronary flow velocity and coronary flow reserve (CFR) in patent culprit and nonculprit arteries of patients after emergent percutaneous coronary intervention (PCI) for acute myocardial infarction (AMI). Similar measurements were made in control patients with coronary artery disease (CAD) without AMI. In a parallel porcine model, the same flow velocity measurements were obtained before and after AMI by balloon occlusion of the left circumflex coronary artery.

Resting and hyperemic flow velocities and CFR were comparable in culprit and nonculprit arteries and significantly lower than in control patients. Infarct size by AMI correlated with reduced CFR with great scatter about the mean correlation; endothelin-1 levels peaked at 3 h after PCI and decreased to baseline at 24 h. In the porcine model, resting and hyperemic coronary flow velocities before and after AMI showed a nonsignificant trend, although their ratio for CFR was significantly lower after MI. The extent of porcine myocardial hemorrhage and infarct size correlated with reduced CFR.

The authors conclude that “the decreased CFR after AMI in culprit and nonculprit vessels is not a result of pre-existent microvascular dysfunction, but represents a combination of post-occlusive hyperemia, myocardial necrosis, hemorrhagic microvascular injury, compensatory hyperkinesis, and neurohumoral vasoconstriction.”

WHAT FAILS TO FIT THE AUTHORS’ CONCLUSIONS?

The data are meticulously gathered and analyzed in this superb clinical and parallel experimental protocol. The striking aspect of Figures 2A and 3 shows that the culprit and reference arteries of the same patient have similar CFR and resting and hyperemic flow velocities. All differences are highly significant between control patients without MI and patients with AMI for CFR and resting and hyperemic flow velocities. The visual parallel of Figure 2B for the controlled experimental pig model does not strictly carry over to its statistics, where the differences between primary data, pre- and post-AMI resting and hyperemic flow velocities, are not significant, whereas their ratio for CFR is.
In essence, the primary flow velocity data of the controlled pig model fail to give statistically valid support paralleling the statistically significant clinical data. That disparity is a signal suggesting alternative explanations. Moreover, high resting flow may misleadingly reduce CFR despite adequate or high stress flow, thereby failing to reflect true physiological stenosis severity.

In contrast to the controlled pig model, CFR and hyperemic flow velocity are significantly different from those in control patients without AMI. **Figure 1** of this editorial offers a visual explanation. The left ventricular maps before and after elective PCI show regional quantitative rest and stress perfusion in ml/min/g, CFR, and their integration into coronary flow capacity by positron emission tomography, as previously reported (2-4). The severe stress defect (shown in blue) disappears after stenting but diffusely reduced coronary flow capacity remains, as indicated by the yellow color-coded regions with CFR of ~2.3 and stress flow of ~1.4 ml/min/g on the color scale. Stress perfusion and CFR of the stented artery...

**FIGURE 1** Coronary Flow Capacity Before and After Percutaneous Coronary Intervention

The large blue areas indicate severely reduced stress flow and coronary flow reserve in ischemic ranges associated with angina and >1 mm ST depression on ECG during dipyridamole stress according to the color scales (3,4). Green indicates moderately reduced, yellow mildly reduced, and orange minimally reduced stress flow and coronary flow reserve above ischemic levels associated with diffuse CAD. The percent of the left ventricle in each range of coronary flow capacity is shown in the color-coded text below each image. Generic coronary artery distributions are overlaid on the perfusion images. AV = atrioventricular node coronary artery branch; CAD = coronary artery disease; D1 = first diagonal branch off the left anterior descending coronary artery; D2 = second diagonal branch off the left anterior descending coronary artery; ECG = electrocardiogram; LAD = left anterior descending artery; LCx = left circumflex artery; OM1 = first obtuse marginal artery off the left circumflex coronary artery; OM2 = second obtuse marginal artery off the left circumflex coronary artery; RCA-PDA = right coronary artery-posterior descending artery; RI = Ramus Intermedius coronary artery; STΔ = ST-segment depression on ECG.
and the remainder of the left ventricle are all similar, reflecting residual diffuse disease just as observed in the AMI patients reported by de Waard et al. (1).

DIFFUSE CAD: THE ICEBERG ASSOCIATED WITH ADVERSE EVENTS

Residual diffuse disease underlies most focal stenosis and virtually all acute coronary syndromes (ACS) (5–7). From our expanded previously published data (2,3), 1,257 patients with documented CAD had global stress perfusion in ml/min/g of 1.82 ± 0.66 compared with 2.73 ± 0.49 for 125 healthy young volunteers without risk factors or blood caffeine levels (p = 0.001). In CAD patients, global CFR was 2.65 ± 0.86 compared with 4.3 ± 0.72 (p = 0.001) in volunteers. Globally impaired flow capacity reflects the global burden of diffuse CAD. Because ACS are associated with a high burden of diffuse disease compared with patients without ACS (5–7), the control patients in this study are controlling for less extensive diffuse disease, not for purely functional or hemodynamic mechanisms invoked by the authors.

Residual diffuse disease also explains why the primary flow velocity data of the pig model failed to achieve the statistical significance comparable to the patient data because the pigs had no diffuse disease. With diffuse disease narrowing arterial lumens, resting flow velocity increases as normal resting perfusion is maintained (8). Therefore, the authors’ clinical data best fit with residual diffuse disease of culprit and nonculprit arteries rather than primary functional or hemodynamic changes playing secondary roles as in the pigs in which primary flow velocity changes were not statistically significant.

Finally, a small correction is needed on the control of coronary blood flow attributed to adenosine based on a 1973 paper: “This may be caused by reactive hyperemia, in which metabolites with vasodilatory properties, such as endogenous adenosine, build up due to prolonged ischemia (reference 16 in the de Waard et al. paper).” More recent literature elegantly proves that regional coronary blood flow is exquisitely controlled by the release of adenosine triphosphate from red blood cells in the local hypoxic myocardium, not by endogenous myocardial adenosine release (9).

CLINICAL IMPLICATIONS

The clinical implications for assessing physiological stenosis severity are substantially different from the authors’ conclusions that low hyperemic flow velocity post-MI will underestimate severity of nonculprit stenosis by making FFR too high. With diffuse disease, FFR will be high with either high or low stress perfusion (10) associated with well-documented FFR-CFR discordance (11) and low FFR in the absence of significant angiographic stenosis (12). Therefore, whole-vessel FFR in the setting of diffuse disease does not correctly predict the increase in maximal flow after PCI (10,13). Moreover, future risk after primary PCI of AMI returns to a relatively low level comparable to that in patients without AMI undergoing adequate medical treatment. Consequently, assessing severity of nonculprit coronary arteries or their PCI has not consistently reduced subsequent MI or death in randomized trials.

Alternative truths enhance and extend the profound shift from anatomic to physiological severity of focal and diffuse CAD incurred by the paradigm-changing randomized trials of FFR. As the lucky instigator of CFR, vasodilator stress, in vivo stenosis pressure flow relations, and senior author on the experimental origins of FFR, these editorialists see coronary physiology as the saving guide for rational, quantitative, evidenced managed CAD. That commitment demands that we let physiology talk to us, tell us its reality, particularly the reality of diffuse disease underlying all stenosis that dominates patient outcomes more than generally realized in the pursuit of stenosis, as reflected in these superb data.

REPRINT REQUESTS AND CORRESPONDENCE: Dr. K. Lance Gould, Weatherhead P.E.T. Center for Preventing and Reversing Atherosclerosis, University of Texas Medical School, 6431 Fannin, Room 4.256MSB, Houston, Texas 77030. E-mail: k.lance.gould@uth.tmc.edu.

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