Intense Exercise and Native Collateral Function in Stable Moderate Coronary Artery Disease
Incidental, Causal, or Clinically Important?

K. Lance Gould, MD

In the report by Möbius-Winkler et al\(^1\) in this issue of Circulation, 60 patients with coronary artery disease (CAD) by angiogram and fractional flow reserve (FFR) ≤0.75 were randomly assigned to supervised high- or moderate-intensity exercise or a sedentary group for 4 weeks at specialized rehabilitation centers. At angiogram, a coronary artery was occluded by low-pressure balloon occlusion for 1 minute without therapeutic percutaneous coronary intervention (PCI). The coronary pressure beyond the occlusion as a ratio to aortic pressure is an index of collateral back perfusion distal to the occlusion termed the collateral flow index (CFI), although flow is not measured, only pressure. Both high- and moderate-intensity training significantly improved CFI and exercise threshold for angina in comparison with the sedentary subjects. Although collaterals on angiogram were not expressly addressed, the moderate, nonocclusive stenosis did not cause reported visible collaterals on the angiogram, thereby implying improved native microcollaterals as the mechanism attributed to improved exercise performance.

This article by Möbius-Winkler et al\(^1\) exemplifies carefully done classical hypothesis testing, experimental design, complex invasive and noninvasive data, and statistically significant differences in CFI and exercise capacity between trained and sedentary groups. Implementation of the 3-way randomized interventions with no crossovers and strict adherence to intense exercise or sedentary regimens is impressive.

However, sometimes, we (authors, reviewers, editors, and readers) want to believe a nice idea supported by limited selective data that hold our critical judgment in abeyance, thereby accepting causal conclusions that we want to believe despite the lack of hard specific cause and effect data. Our deferring critical demands of the data are particularly likely when many aspects of a study are perfect, including statistically significant differences between associations we want to believe as causal. However, if we critically demand of ourselves the hard evidence of causality rather than association, the conclusions that we wish to be true are often proven untrue or without causal association despite perfect study design.

Showing that exercise training increases native collateral perfusion as the causal basis for increased exercise performance in patients with moderate coronary stenosis requires the following causal associations in the data that were not reported:

1. Improved CFI should correlate with improved exercise performance by multivariate regression analysis or by tertile group association that is essential for individual causal association.
2. Total transient balloon occlusion with CFI <0.22 to 0.3 indicates poor collateral perfusion that often produces angina and ST change.\(^2\) The average baseline CFI in this study was 0.146±0.07, so that one might expect angina and ECG changes during the 1-minute occlusion. After exercise training, CFI increased to 0.2±0.09, which remains in the poor collateral range. If collateral function improved enough to enhance exercise performance, then the frequency or time to angina and ST depression after balloon occlusion should be longer after training and correlate directly with CFI increase, with increased exercise capacity and reduction of angina/ST change during occlusion.
3. Myocardium tolerates perfusion pressure to <30 to 35 mm Hg without ischemia.\(^3\) The moderate stenosis of this study had FFR averaging 0.63±0.1 during adenosine hyperemia that causes maximal pressure gradient more than exercise. With an average systolic pressure of 136±23 mm Hg, the FFR of 0.63 indicates a coronary perfusion pressure of 86 mm Hg during adenosine hyperemia. Consequently, with either adenosine hyperemia or exercise stress (not balloon occlusion stress), the average coronary pressures during adenosine or exercise did not approach this level of low 30 to 35 mm Hg pressure that causes the ischemia necessary for stimulating collaterals. Ischemia sufficient to stimulate collateral growth typically requires, and is associated with, total occlusion or subtotal occlusion with slow forward flow.
4. The average lowest hyperemic coronary pressure of 86 mm Hg is much higher than the 35 mm Hg threshold causing ischemia.\(^3\) In comparison, after training, the increased coronary occlusion pressure was 5 mm Hg in the high-intensity group (17±7 to 22±10 mm Hg, \(P=0.001\)) and 2 mm Hg improvement in the moderate-intensity group (17±6 to 19±6 mm Hg, \(P=0.14\)) with their CFI increasing from 0.14±0.07 to 0.2±0.09 (change of 0.06±0.05, \(P=0.001\)). Although statistically significant, such small 2 to 5 mm Hg occlusive pressure...
changes would likely have little physiological effect on improving exercise tolerance in patients averaging 86 mm Hg hyperemic coronary pressures that are far above the 35 mm Hg ischemic threshold.

5. The whisker plots fail to show individual patient data points that, given the wide scatter, would likely indicate a minority of ≈25% of subjects having native collaterals as previously reported2,6,7 with increased CFI in comparison with more patients with little or no increased CFI. In contrast, a greater proportion of patients appear to have improved exercise performance, thereby suggesting poor individual correlation of CFI with exercise improvement or time to angina/ST change after balloon occlusion.

6. No angiogram data are reported even if only to report that no collaterals were observed on angiogram.

7. Regular exercise improves everything – hypertension, diabetes mellitus, lipid profile, endothelial function, heart failure, diastolic dysfunction, weight loss, catechol regulation, mobility, balance, strength, endurance, and mental function. Moreover, the increased exercise capacity of training and training bradycardia is mediated by peripheral adaptation, including increased vagal tone of bradycardia in athletes, all of which have little to do with the heart or collaterals. Like these associations in which exercise improves much, this article reports a slightly increased CFI and increased exercise capacity that is statistically significant. However, given the lack of causal associative data and a realistic view of collateral physiology, a causal relation between the 2 observations appears physiologically unlikely. Rather, the lack of causal associative data contravenes the authors’ causal conclusions that native collaterals are the basis for improved exercise capacity after intense training.

**Harder Questions From Reported Data – What Else Do They Tell Us?**

Although the conclusions lack the support of essential causal associative data, the article carries some important unaddressed messages. Patients with FFR averaging 0.63±0.1 and ranging 0.34 to 0.75 with mild or no angina (Canadian Cardiovascular Society class 0 or 1) did not have PCI and had no events during 4 weeks of intense exercise training associated with increasing exercise capacity and decreasing symptoms. For whatever reasons, causal associative data are not reported to support native collaterals as the basis for improved exercise capacity with intense training. Therefore, this article raises 3 challenging unaddressed questions that are related to collaterals and exercise training.

First, the current article is consistent with previous reports suggesting that the most specific test at resting conditions for guiding PCI is total balloon occlusion – the collateral stress test.2,6,7 By comparison, coronary/aortic pressure at resting conditions is inadequate for defining stenosis severity for guiding PCI in comparison with hyperemic indices or FFR. One viewpoint considers the concept of an occlusion collateral stress test to be unethical, whereas others have performed and published such studies with the approval of committees for protection of human research,2,6,7 including the current article that passed peer review and the ethical standards of Circulation. Given such a loaded topic, long-term follow-up on these patients is important for follow-up PCI or events to validate medical management of patients with a FFR of 0.63.

Second, does a high CFI with total balloon occlusion indicate who will develop large epicardial collaterals that prevent myocardial infarction or even symptoms on complete coronary artery occlusion? Is such information a basis for deferring PCI? A collateral stress test with CFI during balloon occlusion will not likely be a widespread diagnostic test despite its safe use for assessing native collaterals in research protocols. And, fast forward, because many total coronary occlusions are asymptomatic with normal left ventricular function because of well-developed collaterals, what are reasonable guidelines for revascularization that should be used clinically or tested in a randomized trial?

Finally, in view of the average FFR of 0.63 in exercising patients doing well without short-term events, is the FFR threshold of 0.8 for PCI too high in view of Fractional Flow Reserve Versus Angiography for Guidance of PCI in Patients With Multivessel Coronary Artery Disease (FAME 2) study failing to reduce myocardial infarction or mortality by intention-to-treat analysis?9 Meta-analyses of FFR and outcomes show a continuum of risk versus FFR with balance of benefit versus risk of major adverse cardiovascular events at an FFR threshold of 0.67,9 similar to the initial threshold of 0.65 in DEFER10,11 and relative coronary flow reserve (CFR) by positron emission tomography (PET) imaging in patient with angina and significant ST depression during dipyridamole PET perfusion imaging.12,13

**Complexity of Collateral Perfusion and CAD of Supply Arteries**

By virtue of their names, pressure-derived Collateral Flow Index and Fractional Flow Reserve are substitutes or indirect measures of absolute CFR and stress flow in milliliters per minute per gram. Regardless of forward or collateral flow, CFR reduced to 1.5 to 1.7 and stress perfusion of 0.9 mL·min⁻¹·g⁻¹ for 10% to 20% of the left ventricle during dipyridamole stress is an ischemic threshold associated with symptoms and high risk of adverse events for which revascularization may be appropriate for reducing myocardial infarction and cardiac mortality that, however, remains unproven by a randomized trial.12,13

However, treating even these proven thresholds for ischemia depends on how patients present with nonacute coronary syndromes, as illustrated in the Figure. Case 1 is an asymptomatic 64-year-old man with the same stress PET perfusion defect for 17 years attributable to an occluded left anterior descending artery on angiogram with excellent flow capacity of other coronary arteries supplying the collaterals and free of obstructive focal or diffuse disease. His left ventricular function was normal at rest and stress with no procedure indicated. Case 2 is a 67-year-old man with diabetes mellitus with 2 months of progressive fatigue, dyspnea on exertion, and mild chest discomfort. He previously had 6 stents; 2 stents each in left anterior descending artery, left circumflex artery, and right coronary artery; the last was in 2011, which caged and occluded most secondary branches in addition to severe diffuse disease of
coronary arteries supplying the collaterals. He had >1 mm ST depression but no angina on dipyridamole stress. His rest and stress ejection fraction by ECG gated perfusion PET was 46%. Because of the size and severity of his stress defects, multi-branch coronary bypass surgery is a valid option. Despite both patients having well-developed collaterals, disease of the supply arteries is the critical factor determining their fate. Thus, human physiology is complex at any moment and even more complex over time, particularly with diffuse disease, and possibly too complex for any test to predict future collateral function with or without focal or diffuse CAD, particularly for only 2 to 5 mmHg coronary pressure end points.

**Beyond Coronary Pressure – How Bad, How Big, How Fast, and Where Else?**

As these examples illustrate, the critical measurements beyond coronary pressure are (1) size and severity of quantitative perfusion abnormalities at or below the ischemic threshold, (2) the severity of diffusely impaired coronary flow capacity reflecting the global burden of diffuse CAD of arteries supplying collaterals, and (3) the duration and rate of symptom and collateral development. Therefore, the Coronary Flow Capacity Map integrating stress flow and CFR provides objective personalized insights into the severity of CAD and nearly always tells what an individual patient needs – more exercise, healthier food, medications for maximal risk factor control, or, in a minority of patients, whether PCI or bypass surgery is indicated when 15% to ≥20% of the heart color-codes blue associated with new, progressive or limiting symptoms or impaired left ventricular function. Hence, regional quantitative perfusion integrating stress perfusion in milliliters per minute per gram and CFR largely eliminates the need for invasive indirect measures of relative flow reserve derived from hyperemic or occlusive coronary pressures.

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