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Experimental to Clinical Coronary Physiology

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Current Clinical Coronary Physiology

Current clinical coronary physiology is based on coronary pressure and flow or perfusion in experimental animals that first demonstrated coronary flow reserve (CFR) for physiological stenosis severity,[1] the fluid dynamic pressure flow equations for coronary stenosis in intact awake canines,[2] pharmacological stress initially experimentally then clinically,[3] pressure-derived fractional flow reserve (FFR) from these 2 steps,[4] cardiac positron emission tomography (PET) with N-13 ammonia in canine coronary stenosis[3] then with generator produced Rb-82 experimentally and clinically,[5] classification of microvascular angina or small vessel disease,[6] and currently quantitative PET-guided revascularization that significantly reduces myocardial infarction (MI) and death.[7] These initial concepts from experimental studies comprise the knowledge base for physiologically guided clinical management that assures ongoing evolution of coronary physiology formerly possible only experimentally.

Based on randomized trials,[8] pressure-derived FFR is now the invasive standard for objective, physiologically defining coronary artery disease (CAD) severity to guide revascularization. However, although pressure measurements are precise, FFR is physiologically imprecise with major physiological limitations. Randomized trials of FFR guided revascularization analyzed by intention to treat show no reduction in death or MI[8]; it is invasive and measured at a single point in the coronary tree rather than defining the entire coronary artery system with multiple stenoses, diffuse epicardial, and small vessel disease; it fails to account for mass of myocardium at risk; FFR particularly fails to quantify down stream perfusion or low-risk subendocardial ischemia causing angina versus transmural ischemia associated with high risk of death or MI that is reduced by revascularization.[7]

However, like coronary flow meters and microspheres in experimental animals, PET is the best-documented tool for studying human physiology of the entire coronary artery tree.[6,7,9–12] No other imaging technology has the proven record of quantitative PET as extensively detailed in recent reviews, literature, and cardiology textbooks[6,7,9,10] summarized here.

Precision Clinical Coronary Physiology

PET defined coronary flow capacity (CFC) integrates all quantitative perfusion measurements of rest and stress perfusion in cc/min per gram, CFR (ratio of stress to rest perfusion), relative stress perfusion in cc/min per gram[6,7,9–12] that is exquisitely sensitive to subendocardial ischemia.[6,9] This integration is essential for incorporating regional heterogeneity of rest and stress perfusion and CFR because of endothelial dysfunction, atherosclerosis, and myriad other pathologies that impair quantitative diagnostic value of CFR alone.[6,7,9–12] CFC per pixel integrates all of these measurements per pixel, color codes their infinite range of values and combinations into 5 well defined clinical categories by receiver operating curve analysis in 6000 patients with methodology test-retest precision in the same subject of ±10%,[12] paralleling experimental microsphere measurements of perfusion.

Each CFC pixel color coded for integrated severity is back projected to its spatial position in the left ventricular image with percent of left ventricle (LV) determined for each range of CFC severity as follows[6,7,9–12]: Red is normal, defined by 125 healthy young volunteers <40 years old with no risk factors (CFR >2.9 and stress perfusion >2.17 cc/min per gram). Orange is typical or minimally reduced, defined by people with risk factors only with no known or clinically manifest CAD (CFR >2.38–2.9 and stress perfusion >1.82–2.17). Yellow is mildly reduced CFC, defined by people with documented stable CAD without angina or ST depression on ECG during dipyridamole stress (CFR >1.6–2.38 and stress perfusion >1.09–1.82). Green is moderately reduced CFC with possible ischemia defined by people with angina or ST depression ≥1 mm with a relative stress defect (CFR >1.27–1.6 and stress perfusion >0.83–1.09). Blue is severely reduced with definite ischemia defined by people with angina and ST depression ≥1 mm and a relative stress defect (CFR, 1.0–1.27 and stress perfusion ≤0.83). Dark blue is defined by myocardial steal with stress perfusion falling below rest perfusion (CFR <1.0) nearly always with angina and ST depression ≥1 mm.

Regional physiological size-severity on CFC maps is essential for planning revascularization because angiograms of occluded arteries cannot quantify % of LV at risk, diffuse disease, subendocardial border zones, residual collateral perfusion, or viability (Figure 1). In this case, the right coronary artery ischemia is the largest primary revascularization target; mid to distal left anterior descending coronary artery ischemia is modest in size with diffuse CAD that may be suboptimal for bypass surgery but stentable; first diagonal branch and left circumflex

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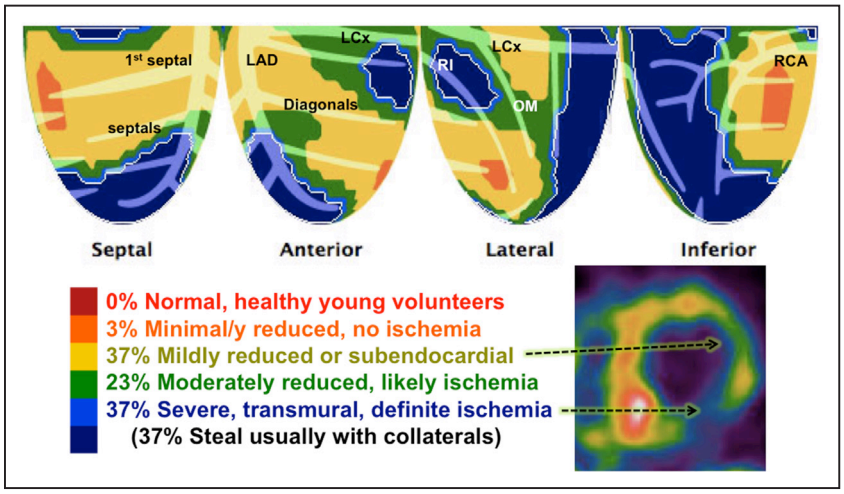

Figure 1. Illustrates routine positron emission tomography (PET)–derived coronary flow capacity (CFC) for providing essential diagnostic quantification in complex coronary artery disease beyond coronary flow reserve, coronary angiogram or any other imaging. With dipyridamole stress, CFC blue regions indicate severe ischemia with myocardial steal in a large area (20% of left ventricle) of a dominant right coronary artery (RCA), a moderate sized (13% of left ventricle) mid to distal left anterior descending coronary artery (LAD) region, a small first diagonal region (4% of left ventricle), and small distal left circumflex coronary artery (LCx) region, all indicating subtotal or total occlusions with collaterals to viable myocardium (no scar). The CFC green indicates subendocardial border zones around severe transmural ischemia (blue). Outside these regional stress abnormalities, CFC is mildly reduced diffusely (yellow) indicating additional diffuse coronary artery disease. OM indicates obtuse marginal branch; and RI, ramus intermedius branch.

coronary artery distributions are too small for revascularization, all confirmed at angiogram. Therefore, the invasive cardiologist knows beforehand what to expect at angiogram for physiologically informed decisions on PCI primarily of right coronary artery, secondarily of left anterior descending coronary artery, or later procedures depending anatomy, visual collaterals, or deciding on bypass surgery if PCI carries high risk or fails.

Heterogeneity of Resting Perfusion and CFR

CFR may be low regionally (Figure 2A, blue) because of heterogeneous high resting perfusion thereby erroneously suggesting stenosis. In contrast, CFC integrating regional resting perfusion, stress perfusion, and CFR shows excellent CFC (Figure 2A red) comparable to young, healthy, conditioned volunteers with no risk factors or medical conditions.

Severe Stenosis

Severe stenosis causes a central region of CFC blue (Figure 2B) with border zones of subendocardial ischemia (dark green) to less severe subendocardial underperfusion (light green to dark yellow) in concentric rings or target pattern of ischemia, each as a percent of LV, also reflected in single cross-sectional tomograms of relative uptake. For Figure 2, percent values are of the entire LV, although only one quadrant view is illustrated for simplicity. CFC blue is associated with high risk of death or MI that is significantly reduced by revascularization.[7]

Mild to Moderate Stenosis

Mild to moderate stenosis causes primarily subendocardial ischemia with CFC light green (Figure 2C) and epicardial layers of higher perfusion, commonly with angina and ST depression during stress. However, this degree of nonblue CFC is associated with low risk of death or MI, and revascularization does not reduce MI or death despite relieving angina.[6,7]

Small Vessel Disease

Small vessel disease from myriad pathologies reduces CFC uniformly across LV walls with diffuse regional and uniform

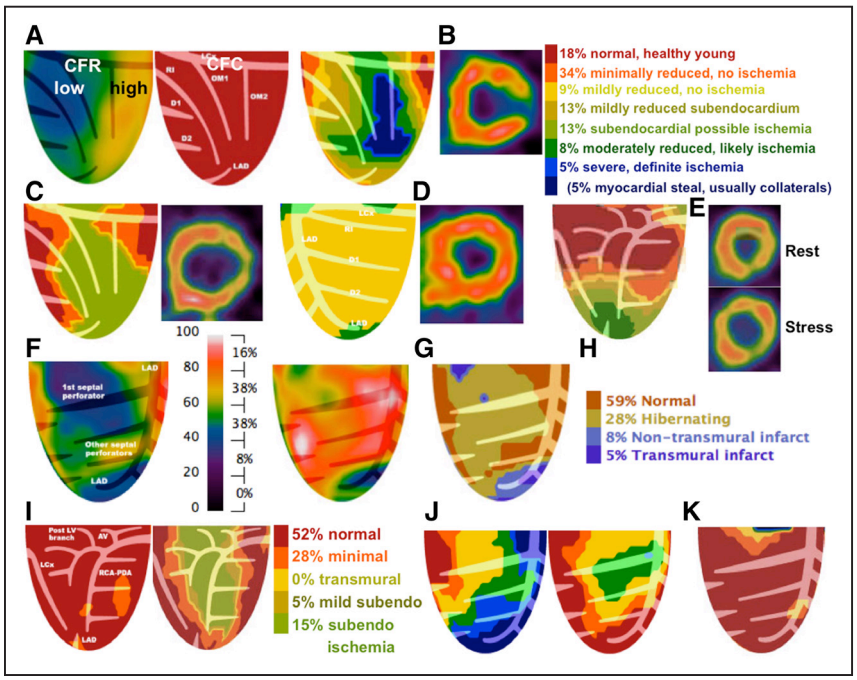

Figure 2. Illustrates coronary flow capacity (CFC) for every cardiac diagnosis related to coronary function[6,7,9–12] in single quadrant views for efficiency. AV indicates atrioventricular; CFR, coronary flow reserve; D1, first diagonal branch; D2, second diagonal branch; LAD, left anterior descending coronary artery; LCx, left circumflex coronary artery; LV, left ventricle; OM, obtuse marginal branch; PDA, posterior descending coronary artery; RCA, right coronary artery; and RI, ramus intermedius branch.

transmural reduction of stress perfusion, CFR, and relative uptake on tomograms (Figure 2D) seen with diabetes mellitus, hypertension, hyperlipidemia, obesity without flow-limiting stenosis usually without angina.[6]

Diffuse Epicardial Atherosclerosis

Diffuse epicardial atherosclerotic narrowing reduces CFC that may show a base to apex longitudinal perfusion gradient from good (red) to orange to yellow to green at the apex and reduced subendocardial perfusion during dipyridamole stress compared with resting relative tomogram (Figure 2E).[6,7,9] This pattern requires and reflects adequate small vessel function to increase coronary blood flow sufficient to reduce distal pressure causing low subendocardial perfusion.[6,7,9] Commonly, combined stenosis plus diffuse epicardial narrowing cause mild to moderately reduced CFC diffusely and severely reduced segmental CFC, as in Figure 1.

Hibernating Myocardium

Chronically under perfused myocardium (Figure 2F relative topogram) that takes up fluoro-deoxy-glucose indicates viable myocardium (Figure 2G) that recovers contractile function after revascularization where the mismatch topogram (Figure 2H) shows percent of LV with normal resting perfusion, hibernating, nontransmural or transmural scar.[9]

Progression of CAD

Normal CFC (red) in patients with uncontrolled risk factors may progress by small repetitive plaque ruptures to mild or moderate stenosis with subendocardial ischemia (panel I); progressive repetitive small ruptures lead to severe stenosis and acute coronary syndromes.[9] Vigorous risk factor control prevents, stabilizes, or even reverses this process to some extent.[9]

Effects of Revascularization

Although revascularization is the commonest coronary procedure justified for improving coronary blood flow, the literature is devoid of quantitative perfusion before coronary intervention or afterward to assess results. Severely reduced CFC (blue) is improved after PCI (Figure 2J) but with a residual mild CFC abnormality because of the left anterior descending coronary artery stent jailing the first septal perforator. Most stent-jailed branches have similar stress perfusion abnormalities.

Nonischemic Cardiomyopathy

Cardiomyopathy with normal coronary arteries may be because of diabetes mellitus, hypertension, alcohol, obesity, or genetic as in this case, with excellent CFC, no scar, and an ejection fraction of 26% by ECG gated perfusion PET.

Thus, continuing evolution from experimental to precision clinical coronary physiology may reside in decisional, dynamic software that encapsulates 45 years of coronary physiology as size-severity color maps of the heart guiding receptive informed clinicians and patients for optimal management of symptoms and survival.

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References

1. Gould KL, Lipscomb K, Hamilton GW. Physiologic basis for assessing critical coronary stenosis. Instantaneous flow response and regional distribution during coronary hyperemia as measures of coronary flow reserve. *Am J Cardiol*. 1974;33:87–94.
2. Gould KL. Pressure-flow characteristics of coronary stenoses in unsedated dogs at rest and during coronary vasodilation. *Circ Res*. 1978;43:242–253.
3. Gould KL, Schelbert HR, Phelps ME, Hoffman EJ. Noninvasive assessment of coronary stenoses with myocardial perfusion imaging during pharmacologic coronary vasodilatation. V. Detection of 47 percent diameter coronary stenosis with intravenous nitrogen-13 ammonia and emission-computed tomography in intact dogs. *Am J Cardiol*. 1979;43:200–208.
4. Pijls NHJ, van Son JAM, Kirkeeide RL, Bruyne BD, Gould KL. Experimental basis of determining maximal coronary myocardial and collateral blood flow by pressure measurements for assessing functional stenosis severity before and after PTCA. *Circulation*. 1993;86:1354–1367.
5. Gould KL, Goldstein RA, Mullani N, Kirkeeide R, Wong G, Smalling R, Fuentes F, Nishikawa A, Matthews W. Noninvasive assessment of coronary stenoses by myocardial imaging during pharmacologic coronary vasodilation. VIII. Feasibility of 3D cardiac positron imaging without a cyclotron using generator produced Rb-82. *J Am Coll Cardiol*. 1986;7:775–792.
6. Gould KL, Johnson NP. Coronary physiology: beyond CFR in microvascular angina. *J Am Coll Cardiol*. 2018. In press.
7. Gould KL, Johnson NP, Roby AE, et al. Regional artery specific thresholds Of quantitative myocardial perfusion by PET associated with reduced MI and death after revascularization in stable CAD [published online August 16, 2018]. *J Nucl Med*. doi: 10.2967/jnumed.118.211953. http://jnm.snmjournals.org/content/early/recent.
8. De Bruyne B, Fearon WF, Pijls NH, et al; FAME 2 Trial Investigators. Fractional flow reserve-guided PCI for stable coronary artery disease. *N Engl J Med*. 2014;371:1208–1217. doi: 10.1056/NEJMoa1408758
9. Gould KL, Schelbert H, Narula J. Chapter 19, Positron emission tomography in heart disease and Chapter 34, Coronary blood flow. *Hurst's The Heart*. 14th ed. New York, NY: McGraw Hill; 2017:893–921.
10. Gould KL, Johnson NP, Bateman TM, et al. Anatomic versus physiologic assessment of coronary artery disease. Role of coronary flow reserve, fractional flow reserve, and positron emission tomography imaging in revascularization decision-making. *J Am Coll Cardiol*. 2013;62:1639–1653. doi: 10.1016/j.jacc.2013.07.076
11. Johnson NP, Gould KL. Integrating noninvasive absolute flow, coronary flow reserve, and ischemic thresholds into a comprehensive map of physiological severity. *JACC Cardiovasc Imaging*. 2012;5:430–440. doi: 10.1016/j.jcmg.2011.12.014
12. Kitkungvan D, Johnson NP, Roby AE, Patel MB, Kirkeeide R, Gould KL. Routine clinical quantitative rest stress myocardial perfusion for managing coronary artery disease: clinical relevance of test-retest variability. *JACC Cardiovasc Imaging*. 2017;10:565–577. doi: 10.1016/j.jcmg.2016.09.019

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