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EDITORIAL

Apples, oranges, or pears: unexpected insights in coronary pathophysiology

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This editorial refers to 'Diagnostic value of longitudinal flow gradient for the presence of haemodynamically significant coronary artery disease', by M.J. Bom *et al.*, pp. 21–30.

Bom *et al.*[1] compare longitudinal perfusion gradients with fractional flow reserve (FFR) of angiographic stenosis as a substudy of the superb PACIFIC trial proving quantitative perfusion superior to anatomy for defining physiologic severity of coronary artery disease (CAD).[2]

This substudy determined variously defined longitudinal base to apex perfusion gradients compared with pressure derived FFR ≤0.8 for proximal and distal angiographic coronary stenosis. The authors report that 'significant and relatively strong correlations were found between hyperaemic longitudinal myocardial blood flow gradient and FFR ($r = 0.57$, $P < 0.001$) in non-proximal lesions', but not for proximal stenosis. For all stenosis combined, longitudinal perfusion gradients were inferior to absolute stress perfusion correlations with FFR. Therefore, distal stenosis associated with or behaved like diffuse narrowing in contrast to discrete proximal stenosis limiting downstream hyperaemic flow and hence precluding longitudinal pressure or perfusion gradients. Of 160 stenosis with FFR ≤0.8, the 69 with non-proximal stenosis (43%) had good correlations between distal FFR and the longitudinal perfusion gradient *Figures 2C, D, 5B* and *D* of the report by Bom *et al.*[1]

This meticulous data supports several conclusions with unexpected insights into clinically relevant pathophysiology of CAD, FFR, and quantitative perfusion imaging. First, this esteemed lab proved frequent occurrence of base to apex longitudinal perfusion gradients correlating with distal arterial FFR ≤0.8, while proximal FFR ≤0.8 for proximal stenosis did not have longitudinal perfusion gradients. Second, stress perfusion [and likely coronary flow reserve (CFR)] are better than longitudinal perfusion gradients for identifying focal FFR ≤0.8.

Since the original concept of longitudinal perfusion gradients was based on relative images only, its proof and 43% prevalence by quantitative perfusion is gratifying with additional unexpected important insights developed below. Of course, absolute stress perfusion or CFR for identifying segmental stenosis is better than longitudinal perfusion gradients for identifying flow limiting stenosis since it was never proposed for that purpose but rather is observed in some patients but not others, differences needing physiologic explanation.

Physiologic basis for longitudinal perfusion gradients

Longitudinal perfusion gradients require three combined conditions: 'diffuse epicardial' narrowing with adequate small vessel vasodilation for 'increased perfusion'[3] that generates a pressure gradient along arterial length[4] and coronary branches interacting with the longitudinal pressure gradient causing 'coronary branch steal'.[5] It is one physiologic manifestation of CAD, originally quantified as the first derivative of activity over length of left ventricle to explain apical myocardial steal in the absence of focal angiographic stenosis, occlusion or collaterals.[3]

Figure 1 illustrates coronary flow capacity (CFC)[6–9] for focal stenosis (*Figure 1A*), diffuse small vessel disease (*Figure 1B*), a longitudinal perfusion gradient due to diffuse epicardial artery narrowing (*Figure 1C*) with preserved vasodilatory capacity (red) tapering to moderately reduced at the apex with subendocardial ischaemia and ≥1 mm ST-depression during dipyridamole stress. Segmental stenosis, small vessel disease, severe endothelial dysfunction, caffeine, branch occlusion, even severe diffuse coronary narrowing sufficient to prevent flow increase preclude longitudinal perfusion gradients. Chronic total occlusion with distal to proximal retrograde collateral flow causes a 'reverse distal to proximal longitudinal gradient' in *Figure 1D* with good apical stress perfusion, tapering proximally to subendocardial ischemia (light green) to myocardial steal (blue) at the base due to collateralized chronic total occlusion of right coronary artery.

The opinions expressed in this article are not necessarily those of the Editors of *EHJCI*, the European Heart Rhythm Association or the European Society of Cardiology.

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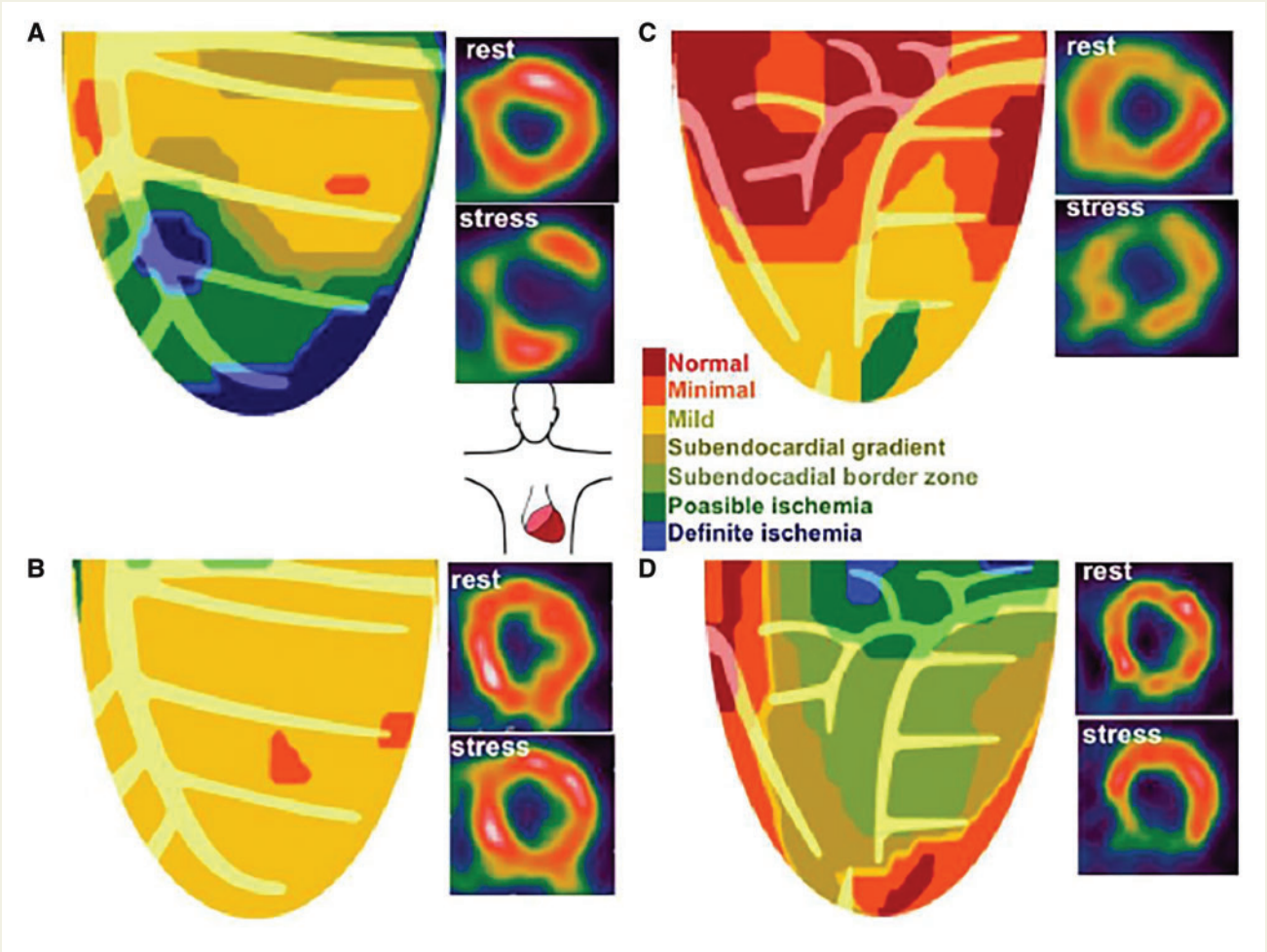

Figure 1 CFC in single views with rest stress relative tomographs. (*A*) Focal stenosis. (*B*) Small vessel disease. (*C*) Diffuse narrowing with base to apex longitudinal perfusion gradient. (*D*) Right coronary artery occlusion with retrograde collateral perfusion causing reversed apex to base longitudinal perfusion gradient.

Apples, oranges, or pears

The combined distal angiographic stenosis, distal low coronary pressure ≤0.8, and longitudinal pressure gradient confirm in 43% of cases the exact conditions above reflecting diffuse disease associated with distal stenosis. Thus, longitudinal perfusion gradients characterize a significant proportion of cases with FFR ≤0.8 hence is not expected to predict severe CAD generally but rather to describe one common face of CAD.

Apples or oranges or pears as three faces of fruit allude to stress perfusion, CFR and the longitudinal perfusion gradient as three faces of CAD. Competitively comparing one of these metrics against the other obscures the truth and beauty of their combination for understanding integrated coronary pathophysiology and its power in clinical management. More importantly and unexpectedly, the three fruit analogy also alludes to FFR as a single point measurement that fails to reveal three essential distal physiologic phenomenon—distal myocardial mass, distal absolute perfusion, perfusion or pressure gradients, and associated subendocardial or transmural perfusion gradients caused by low perfusion pressure. Ironically, while FFR was the 'gold standard' to which longitudinal perfusion gradients were compared, the results demonstrate these three fundamental flaws in single, arbitrarily located FFR values based on visual angiographic stenosis.

In other literature, claims of stress perfusion in mL/min/g as 'better than' CFR reflects the same 'splitter' physiologic thinking since either may best characterize some individuals but not others. Integrating all perfusion metrics as for CFC in *Figures 1* and *2*[6–9] (FDA 510K171303) with subendocardial border zones is a universal physiologic measure for the spectrum of microvascular disease[7] or CAD severity predicting high risk of death or myocardial infarction and their significant reduction after revascularization[8] based on evolving experimental physiology to clinical management.[9]

'Splitters' relying on CFR alone (*Figure 2A*) or stress perfusion alone (*Figure 2B*) may erroneously suggest severe diffuse CAD (*Figure 2A* and *B*) or regional disease (*Figure 2C*) due to regional heterogeneity without flow limiting stenosis as confirmed by CFC incorporating all perfusion metrics for every pixel.[6–9] Commonly reported

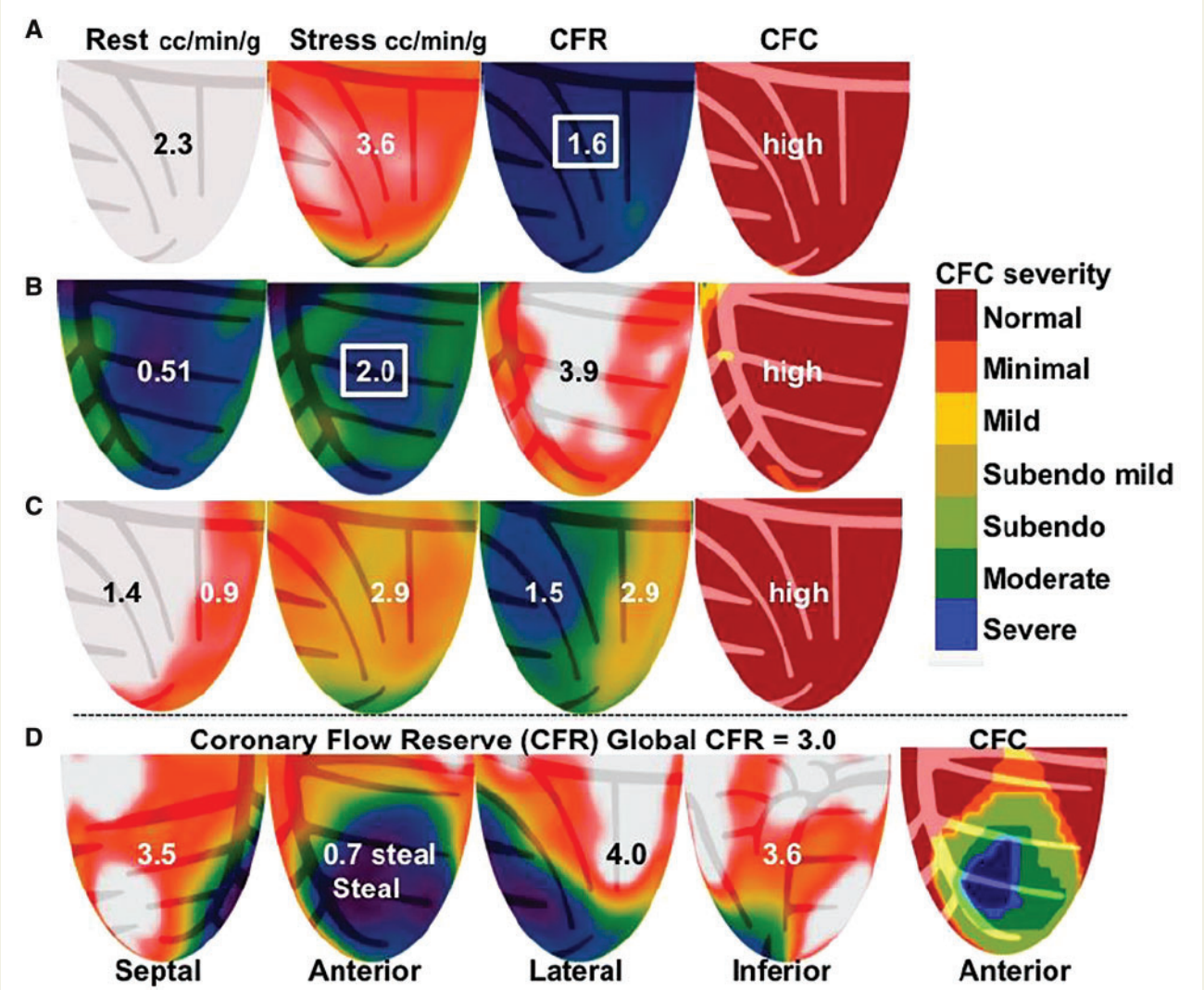

Figure 2 Single views of global (*A* and *B*) and regional perfusion heterogeneity (*C*), all with excellent normal CFC integrating pixel values of stress perfusion with CFR. Global perfusion fails to identify regional stenosis (*D*).

global CFR also fails to indicate clinically important regional versus diffuse pathophysiology, illustrated in *Figure 2D*.[6–9]

Experimental to clinical coronary physiology

Historically, experimental coronary physiology averages specific perfusion metrics in grouped subjects to establish physiologic principles in animal models without CAD.[9] Clinical coronary physiology applies these principles integrating all perfusion metrics to account for and quantify great variability among individuals with CAD or risk factors for optimal highly personalized management.[6–9] In this study, for FFR ≤0.8, 43% had substantially different downstream or distal pathophysiology than the balance of comparable low FFR, thereby demonstrating its incompleteness as a physiologic metric of severity. Therefore, clinical coronary physiology must integrate all physiologic measurements into a synthesis that best describes individuals for their optimal care rather than the opposite competitive splitting measurements thereby causing methodologic conflicting views that retard understanding and clinical management.

This Editorialist looks forward to more superb data from these authors better defining distal pressure, perfusion and subendocardial gradients due to prevalent combined diffuse CAD and stenosis surpassing single visual angiographically guided FFR that has advanced clinical coronary physiology but remains incomplete. Hopefully, their measurements will be specific for diffuse disease including distal to proximal pull back pressures, angiographically diffusely narrowed arteries with or without focal stenosis and pixel distribution of stress perfusion with a proper first differential of perfusion over LV length rather than focal FFR, focal angiographic stenosis and focal regional

perfusion defects in the current study designed for focal stenosis not diffuse CAD.

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References

1. Bom MJ, Driessen RS, Raijmakers PG, Everaars H, Lammertsma AA, van Rossum AC *et al*. Diagnostic value of longitudinal flow gradient for the presence of haemodynamically significant coronary artery disease. *Eur Heart J Cardiovasc Imaging* 2019; **20**:21–30.
2. Danad I, Raijmakers PG, Driessen RS, Leipsic J, Raju R, Naoum C *et al*. Comparison of coronary CT angiography, SPECT, PET, and hybrid imaging for diagnosis of ischemic heart disease determined by fractional flow reserve. *JAMA Cardiol* 2017;**2**:1100–7.
3. Gould KL, Nakagawa Y, Nakagawa K, Sdringola S, Hess MJ, Haynie M *et al*. Frequency and clinical implications of fluid dynamically significant diffuse coronary artery disease manifest as graded, longitudinal, base-to-apex myocardial perfusion abnormalities by noninvasive positron emission tomography. *Circulation* 2000;**101**: 1931–9.
4. De Bruyne B, Hersbach F, Pijls NH, Bartunek J, Bech JW, Heyndrickx GR *et al*. Abnormal epicardial coronary resistance in patients with diffuse atherosclerosis but "Normal" coronary angiography. *Circulation* 2001;**104**: 2401–6.
5. Gould KL, Kirkeeide R, Johnson NP. Coronary branch steal: experimental validation and clinical implications of interacting stenosis in branching coronary arteries. *Circ Cardiovasc Imaging* 2010;**3**:701–9.
6. 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**:565–77.
7. Gould KL, Johnson NP. Coronary physiology: beyond CFR in microvascular angina. *J Am Coll Cardiol* 2018;72 (in press). https://doi.org/10.1016/j.jacc.2018.07.106.
8. Gould KL, Johnson NP, Roby AE, Nguyen T, Kirkeeide R, Haynie M *et al*. Regional artery specific thresholds of quantitative myocardial perfusion by PET associated with reduced MI and death after revascularization in stable CAD. *J Nucl Med* 2018; doi:10.2967/jnumed.118.211953.
9. Gould KL. From experimental to clinical coronary physiology. *Circ Res* 2018;123 (in press). doi:10.1161/CIRCRESAHA.118.313892.