Coronary physiology and prognosis – what does pressure-bounded Coronary Flow Reserve add?

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Forget about shortcuts. Instead, enjoy the wonders of your path.

Paolo Coello

The coronary circulation is unique in its ability to autoregulate to metabolic demand. The ratio of maximal to resting blood flow was first called the coronary flow reserve (CFR) by Lance Gould in 1974.[1] The practical challenges measuring CFR invasively add time and complexity to routine physiological lesion assessment. On the other hand, invasively measured CFR provides additional prognostic information in the 40% of patients who have discordance between fractional flow reserve (FFR) and CFR. This discrepancy occurs because of fundamental differences in coronary pathophysiology in focal CAD and diffuse CAD.[2] For example, an older diabetic patient with a diffusely diseased vessel, microvascular dysfunction but only minor focal stenosis may have a preserved FFR but impaired CFR (Figure 1). Both indices provide complementary information. Even amongst patients with preserved FFR (>0.8), abnormal CFR denotes those at higher risk of adverse events.[3] Determination of CFR using only pressure measurements (FFR & Pd/Pa) is thus an attractive concept.

1. Predicting CFR using the change between resting and hyperaemic pressure gradients

Early correlation studies systematically underestimated true CFR by neglecting the important contribution of frictional forces to pressure drop.[4] More recently the concept of "pressure-bounded CFR" (pb-CFR) was introduced. pbCFR uses Gould's pressure-velocity relationships[5] for a coronary stenosis to compute minimum and maximal values of CFR (Figure 1C – pressure gradient-velocity relationship). In

essence, pb-CFR is a confidence interval of true CFR values. It examines the change between resting gradient (Pd/Pa or iFR) and hyperaemic lesion gradients (FFR). If the bounds (confidence intervals) of pb-CFR are under 2 it is categorised as reduced. Previous work has shown that low pb-CFR is associated with cardiac death and myocardial infarction (1.5% v 3%, adjusted HR 3.8; 95% CI 1.04-13.7). However, when revascularisation was included in a composite end-point, low pb-CFR was not predictive of major adverse cardiac events.[6] Unfortunately, not all patients can be categorised as normal or abnormal. Around 40% of patients have 'indeterminate pb-CFR' where the bounds cross the threshold of significance.

2. What is the prognostic significance of indeterminate pb-CFR?

Lee et al present a succinct article addressing the significance of 'grey zone' pb-CFR values by investigating outcomes according to the true (thermodilution-derived) CFR in a cohort with indeterminate pbCFR. They provide useful insights into the topical area of FFR/CFR discordance in their study with median follow up approaching 4 years.

This skilled group of coronary physiology researchers used their multicenter Korean registry to retrospectively analyse whether thermodilution-derived CFR (thermo-CFR) was predictive of events in 170 patients (179 lesions) with indeterminate pb-CFR. The vast majority of patients had stable angina with preserved FFR (>0.8) and at least one coronary artery with intermediate stenosis. The primary end-point was patient-oriented composite outcomes (POCO - a composite of all-cause mortality, myocardial infarction, and ischemia-driven revascularization). Roughly a quarter of the indeterminate pb-CFR group had a measured thermo-CFR that was abnormally reduced (<2). Known associates of reduced CFR were observed – the low thermo-CFR group were significantly older

with functionally and anatomically more severe disease (lower FFR, higher SYNTAX & Gensini scores and lower minimum lumen diameter on angiography). They had a non-significant trend towards more diabetes and higher microvascular resistance. Unsurprisingly, the unadjusted risk of POCO was increased in this group. Notably, all-cause mortality was also far greater in this low thermo-CFR group (13.9% v 1.5%, 95% CI 1.5-18.5, p=0.011). Even after adjustment for age, FFR and diabetes, there was still a striking increase in events amongst those with low thermo-CFR (aHR 9.8, 95% CI 3.0-32.5, p<0.001). The authors themselves acknowledge the limitations of this modestly sized retrospective unblinded study. This may introduce bias as the physicians may have been aware of CFR and pb-CFR influencing the decision to revascularise driving POCO. Another limitation of pb-CFR relates to assessment of lesions with small gradients at rest. The ratio of pb-CFR is likely to be inaccurate where the resting gradient is less than 5mmHg because of larger relative error from typical pressure wire imprecision (+/- 2mmHg).

3. What can we learn from this study by Lee et al?

There are two important highlights. First, the authors have shown that attempting to estimate CFR using pressure only measurements (pb-CFR) will miss around a quarter of patients with truly low CFR. This figure is greater than the validation study where the indeterminate pb-CFR group was excluded (sensitivity of 95.5% without the indeterminate group).[7] It seems there is no easy shortcut when measuring CFR invasively. Second, this work supports the evolving literature regarding the incremental prognostic value of CFR even amongst patients without functionally significant epicardial stenosis. Full physiological assessment with both indices provides insights into the complex mechanisms of ischaemia in the individual patient.

4. CFR/FFR discordance gives insight into what causes the patient's ischemia

There is a clear relationship between high risk clinical variables (e.g. diabetes and advancing age) with a reduced CFR. Lesions with significant resting gradients (Pd/Pa, iFR® and diastolic resting indices) often have downstream compensatory microvascular dilation that maintains resting coronary flow at the expense of a reduced CFR.[8] pb-CFR will highlight the clinician to some patients in this group. But what should we do with this information? These patients may have a worse prognosis and potentially more angina, but the pathophysiology in this group is varied and not specific to the focal epicardial lesion. Indeed, coronary physiology pioneers Lance Gould and Nils Johnson coined the phrase "physiological stenosis severity" which considers the in vivo transmural myocardial pressure gradient.[9] As clinicians, we need to think outside the model of fixed epicardial physiology to consider the myriad of other contributors to reduced CFR and ischaemia. Factors including the vasomotor lesion 'tone', ventricular hypertrophy and myocardial compression, subendocardial viability ratio (Buckberg index), microvascular dysfunction, endothelial impairment and others.[10] The pathophysiology in patients with reduced CFR is varied, but the natural history of these high risk patients with angina, diffuse atheroma and reduced CFR may be best improved with CABG.[11] FFR may not be a panacea, but its strong correlation with relative coronary flow reserve[12] lends methodological support for it to remain the gold standard. It identifies the relative significance of a focal stenosis that is more amenable to PCI than diffuse disease.

5. Future perspectives: stratified trials to direct treatment

A stratified approach to coronary artery disease would personalise revascularisation decisions based on physiological patterns and mechanisms of

coronary disease. The goal being to maximally reduce symptoms, morbidity and mortality. Proving this hypothesis will require large randomised controlled trials using the patient (clinical events) as the gold standard. We need to think beyond fixed epicardial assessment. Appraising the change in translesion gradient between rest and hyperaemia, pb-CFR allows a better understanding of the pathophysiology (in some patients) although lacks accuracy to direct therapy. Ongoing studies that may provide insights into the utility of pressure and flow measurements in symptom relief and prognosis include the Ischemia trial, physiology outputs from the ORBITA trial as well as the DEFINE-FLOW (NCT02328820) study.

Revascularisation decisions are only one part of treatment - there is a pressing need for improved medical treatments targeting diffuse and microvascular coronary disease. Like many things in life, there are no shortcuts here. Lee et al's study on pb-CFR reminds us that appreciating the underlying processes and the journey are key.

Figure Legend –

pb-CFR calculation worked example from pressure wire assessment of a 68-year-old female diabetic with angina and no obstructive coronary disease (ANOCA).

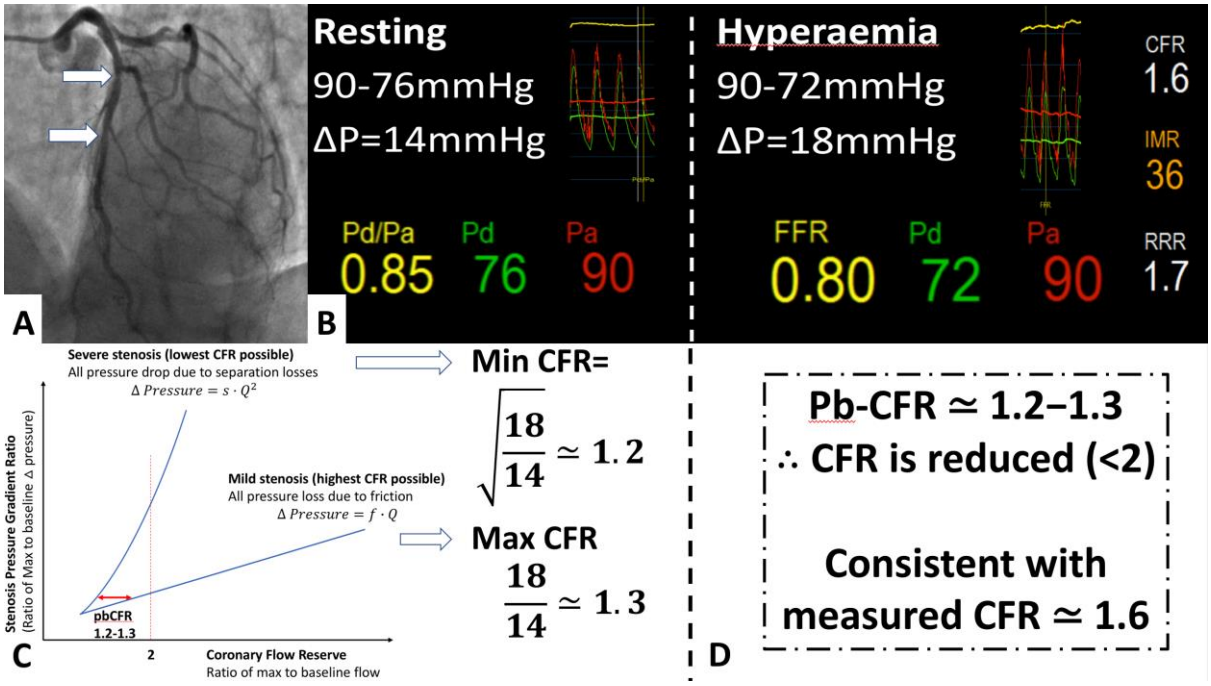
A – Coronary angiography showing mild tandem stenoses in the left anterior descending artery.

B – Notable resting translesion gradient (ΔP=14mmHg) with only minimal further pressure drop at hyperaemia (ΔP=18mmHg), symptoms of full adenosine effect were noted by the patient.

C – Change in flow (CFR) plotted against change in translesional gradient based on Gould's pressure gradient-velocity curves[5] $(\Delta P = f Q + s Q^2)$. Q represents flow, f is frictional losses whilst s represents separation losses before and after the stenosis. If all the pressure drop across a lesion relates to friction (mild/no stenosis) then the CFR will be higher and is calculated as hyperaemic ΔP divided by the resting ΔP. This is the upper bound of the CFR – in this case 1.3. The minimum possible CFR occurs where all the pressure drop relates to flow separation losses (severe stenosis) thus the lower bound of CFR is the square root of the figure above ($\sqrt{1.3}$) ≃ 1.2.

D – pb-CFR in this worked example is categorised as reduced (<2) because the bounds (intervals) are under this threshold. In this case the actual measured CFR (by thermodilution) was 1.6 and the pb-CFR correctly predicted the reduced CFR. The microvascular resistance was elevated (IMR 36) and was an important contributor to the reduced CFR. This lady was randomised to full disclosure of coronary physiology results to help her physician stratify her treatment in the BHF CorMicA study (NCT03193294). The angina responded to stratified medical therapy including beta-blockers, calcium channel blockers, aspirin and a statin.

Figure 1


A
B
Resting
90-76mmHg
ΔP=14mmHg
Pd/Pa
0.85
Pd
76
Pa
90
Hyperaemia
90-72mmHg
ΔP=18mmHg
FFR
0.80
Pd
72
Pa
90
CFR
1.6
IMR
36
RRR
1.7
Severe stenosis (lowest CFR possible)
All pressure drop due to separation losses
$\Delta\ Pressure = s \cdot Q^2$
Mild stenosis (highest CFR possible)
All pressure loss due to friction
$\Delta\ Pressure = f \cdot Q$
Stenosis Pressure Gradient Ratio
(Ratio of Max to baseline Δ pressure)
pbCFR
1.2-1.3
2
Coronary Flow Reserve
Ratio of max to baseline flow
C
Min CFR=
$\sqrt{\frac{18}{14}} \simeq 1.2$
Max CFR
$\frac{18}{14} \simeq 1.3$
Pb-CFR ≃ 1.2–1.3
∴ CFR is reduced (<2)
Consistent with
measured CFR ≃ 1.6
D

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