Deconstructing the idol of fractional flow reserve using the IDEAL report

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This editorial refers to ‘Coronary pressure and flow relationships in humans: phasic analysis of normal and pathological vessels and the implications for stenosis assessment. a report from the Iberian–Dutch–English (IDEAL) collaborators’, by S.S. Nijjer et al., on page 2069.

Introduction

Percutaneous coronary intervention (PCI) in patients with chronic stable coronary artery disease (CAD) has not yet been proven to reduce the incidence of myocardial infarction or death.1 The outcome after PCI is, however, dependent on the amount of myocardial ischemia,2 which is—among others—influenced by the tightness and proximity of the coronary atherosclerotic lesion. Invasive ischemia testing is relevant, because only a minority of patients with stable CAD undergo non-invasive stress testing for ischemia detection prior to elective PCI; it guides ad-hoc PCI or its deferral. The latter aims at preventing adverse effects of a PCI, which would be ineffective on symptoms in the absence of ischemia. Invasive ischemia testing does not, however, detect ECG-derived ischemia, nor does it assess the amount of ischemia or systematically account for the proximity of the stenotic lesion, i.e. for the ischemic area at risk for infarct. However, most often it provides a mere estimate of the stenosis tightness, and, rarely,3 coronary pressure-derived hyperaemic fractional flow (fractional flow reserve, FFR) for the description of the functional relevance of the stenosis.4

This practical but idolized reference for invasive functional coronary stenosis assessment (FFR) is challengeable by the presently published IDEAL report,5 which translates—at least in part—the original experimental coronary constriction protocols,6 and the coronary circulation reduced to an epicardial artery with various degrees of narrowings, but, surprisingly, without the ultimate narrowing—coronary occlusion—which would have manifested the relevance of arterio-arterial anastomoses (Figure 1C). From the mentioned experimental setting, the (patho-) physiological behaviour of coronary pressure and flow was derived, which served as the basis of human coronary physiological performance.

Coronary structural inventory

There is more to coronary (patho-) anatomy than (atherosclerotic) epicardial coronary arteries. In the context of the clinically relevant translation from structural features of CAD into functional relevance, the long known list of coronary anatomical components should be checked for obligatory vs. negligible traits (Figure 1A).5 In general, every one of the shown anatomical components for which there is evidence of functional influence on myocardial ischemia should be, at least theoretically, accounted for. Negatively exemplified and considering the embryological cardiac development with its myocardial compaction, myocardial sinusoids and arterio-sinusoidal vessels can be safely neglected as functionally relevant regarding post-natal myocardial perfusion. On the other hand, the coronary sinus with its size and (back-) pressure has to be at least considered since the recently published evidence of its relationship to myocardial ischemia.7,8 Arterio-left ventricular cavity vessels or Thebesian veins are frequently encountered during coronary angiography, but, from a coronary physiological point of view, they are quite elusive. The coronary arteriolar and capillary bed is physiologically highly relevant as the principal resistor to flow and as distensible capacity, respectively.9 Recently, extracardiac sources of the coronary circulation (i.e. natural internal mammary artery, IMA, bypasses) have been shown to mitigate myocardial ischemia when transiently occluded on the ipsilateral side and downstream of the IMA—pericardiophrenic feeding branch10 (Figure 1B).

For the mostly understandable reason of simplicity, the majority of these long known anatomical facts (Figure 1A) were not accounted for in the original experimental coronary constriction protocols,11 and the coronary circulation reduced to an epicardial artery with various degrees of narrowings, but, surprisingly, without the ultimate narrowing—coronary occlusion—which would have manifested the relevance of arterio-arterial anastomoses (Figure 1C). From the mentioned experimental setting, the (patho-) physiological behaviour of coronary pressure and flow was derived, which served as the basis of human coronary physiological performance.

Structure–function translational research: the IDEAL report

Given this situation, the authors of the IDEAL report have to be commended for their effort to describe functional coronary and
myocardial behaviour relative to structural stenosis severity in a sizeable population of CAD patients under resting conditions and during hyperaemia. Nijjer and co-workers performed a piece of structure–function translational research, whereby they found human coronary autoregulation. Autoregulation is defined as the conservation of coronary blood supply to the myocardium under resting conditions (1 mL/min/g) over a wide range of coronary perfusion pressures. It is, however, not unprecedented that constant myocardial perfusion at a mean distal coronary pressure of 60 mmHg has been documented in patients with CAD. Nijjer and co-workers confirmed autoregulation using Doppler-derived flow velocity as obtained distal to the stenosis creating the pressure drop. Over a wide range of percentage diameter stenosis, but—again—short of complete occlusion, they documented a gradual increase in resting trans-stenotic coronary pressure gradients from 5 to 45 mmHg, i.e. a perfusion pressure drop with a constant flow velocity of ~20 cm/s, which is close to the above definition of autoregulation. The finding is short of that definition, because the study was not designed to test the physiological law in the low pressure range (< 40 mmHg; with a direct relationship between pressure and flow), i.e. during coronary (balloon) occlusion, or in the upper perfusion pressure range (myogenic response).

The (f)utility of myocardial hyperaemia for stenosis assessment

The more relevant finding than the confirmation of human coronary autoregulation is that assessing the relevance of functional stenosis may not need myocardial hyperaemia. Nijjer et al. specified that even structurally mild stenoses with a reduction of ≤50% in diameter manifested with a resting pressure gradient as obtained during the so-called wave-free period, but less so during the entire cardiac cycle. Hyperaemic pressure gradients for the same categories of stenosis severity were consistently higher, and thus more sensitive, than resting gradients, but FFR values varied widely for a given, quantitatively determined stenosis severity. In this context, the question arises of which of the two instruments for gauging stenosis, FFR or coronary angiography, is ‘at fault’ for the mentioned noise between the two. FFR repeatedly underwent clinical testing, the proponents argue. In the original of those studies, patients being treated by PCI according to FFR reached the endpoint of death, non-fatal infarct, or revascularization within 1 year less frequently (13.2%) than those in the angiography group (18.3%; P = 0.02). This result appears to favour most convincingly the diagnostic test of FFR.

Figure 1 (A) Schematic drawing of the different anatomical components of the coronary circulation as adapted from Prinzmetal et al. (B) Simultaneous recordings of phasic and mean aortic pressure (Pao, red), distal coronary occlusive pressure (Poccl, black), central venous pressure (CVP, blue), and an intracoronary ECG (V1) with (left side) and without (right side) balloon occlusion of the distal left internal mammary artery (LIMA) with two 1-min proximal balloon occlusions of the left anterior descending artery (LAD). Poccl is higher and ECG ST elevations smaller with vs. without LIMA occlusion. (C) Right coronary (RCA) angiography with complete retrograde contrast filling of the proximally occluded LAD via a large apical branch collateral artery (arrow). Reprinted with kind permission from Seiler (Collateral Circulation of the Heart, Springer 2009).
because its application was beneficial for patient outcome. However, the mentioned study did not—as would have happened in real life—compare FFR vs. visual estimation of coronary stenosis for deciding on PCI, but it evaluated FFR against the pre-selected, and thus non-representative, group of patients who had already been angiographically identified to require PCI. In other words, the angiography group was put at a disadvantage by study design, and the real comparison between functional and structural coronary stenosis assessment was not performed.

‘Apart from such methodological issues in evaluating FFR, a number of practical consequences of erroneous assumptions for the theoretical basis of FFR\(^\text{14}\) have to be considered. They concern induction of myocardial hyperaemia, the essential action during FFR measurement. The purpose of generating hyperaemia is briefly to paralyse microvascular vasomotion, and thus autoregulation, thereby allowing the technically much more robust measurement of coronary pressure for flow. This appealing concept is described by Ohm’s law, which states that the coronary perfusion pressure drop in unabstructed arteries (\(\Delta P\), occurring mostly in the microcirculation) is equal to the product of coronary flow (\(Q\)) and vascular resistance (\(R\)) against flow. \(\Delta P = Q \times R\). In humans, coronary flow rate is awkward and P is easy and dependable to measure; Q changes linearly with P under the assumption of a constant and minimal coronary resistance. In this context, the authors of a recent study on the utility of FFR define a value of \(\leq 0.80\) as ‘a drop in maximal blood flow of 20% or more caused by stenosis.’\(^\text{13}\) However, the cited definition is—except for the words ‘drop’ and ‘20%’—entirely challengeable.

First, and as outlined, coronary pressure and not flow is obtained. Secondly, ‘flow’ is not diminished in comparison with ‘maximal blood flow’, because it is unlikely that coronary resistance is constant or minimal. It has been shown that the coronary microcirculation is distensible, i.e. coronary resistance is inversely dependent on coronary pressure.\(^\text{9}\) Therefore, and according to Ohm’s law, pressure can no longer be taken for flow. Thirdly, pressure drop is not just ‘caused by stenosis’, i.e. FFR is a myocardium- and not stenosis-specific parameter. Myocardium- and stenosis-specific FFR would only be equal in the absence of microvascular coronary disease, and in the absence of the stenosis-mitigating effect of the coronary collateral circulation.

The utility of coronary occlusion for stenosis assessment

The contribution of the collateral circulation to FFR can be easily determined by obtaining coronary occlusive pressure. The real stenosis-specific FFR is equal to the difference between conventional FFR and the ratio between coronary occlusive and aortic pressure. In other words, coronary occlusive pressure tends to normalize conventional FFR or alleviate stenosis-specific myocardial ischaemia. As a consequence, inducing hyperaemia by adenosine (140 \(\mu\)g/kg/min) or by a 1-min coronary occlusion results in widely varying FFR values depending on collateral function (post-occlusive FFR lower than adenosine-induced FFR with poor collateral function).

Based on these considerations and on the important finding of the IDEAL report that even a mild coronary stenosis can be detected by a diastolic pressure gradient at rest, pharmacological myocardial hyperaemia induction might be replaced by a 1-min diagnostic proximal coronary balloon occlusion at low inflation pressure. In addition to detecting a relevant stenosis at rest by the wave-free distal-to-proximal pressure ratio, the reportedly safe procedure of proximal diagnostic occlusion\(^\text{15}\) would yield the post-occlusive, hyperaemic myocardial FFR and coronary collateral function, the two necessary variables for calculating the true stenosis-specific FFR.

Conflict of interest: none declared.

References