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EDITORIAL
Interventional cardiology

Lessons from coronary physiology: *primum non nocere*

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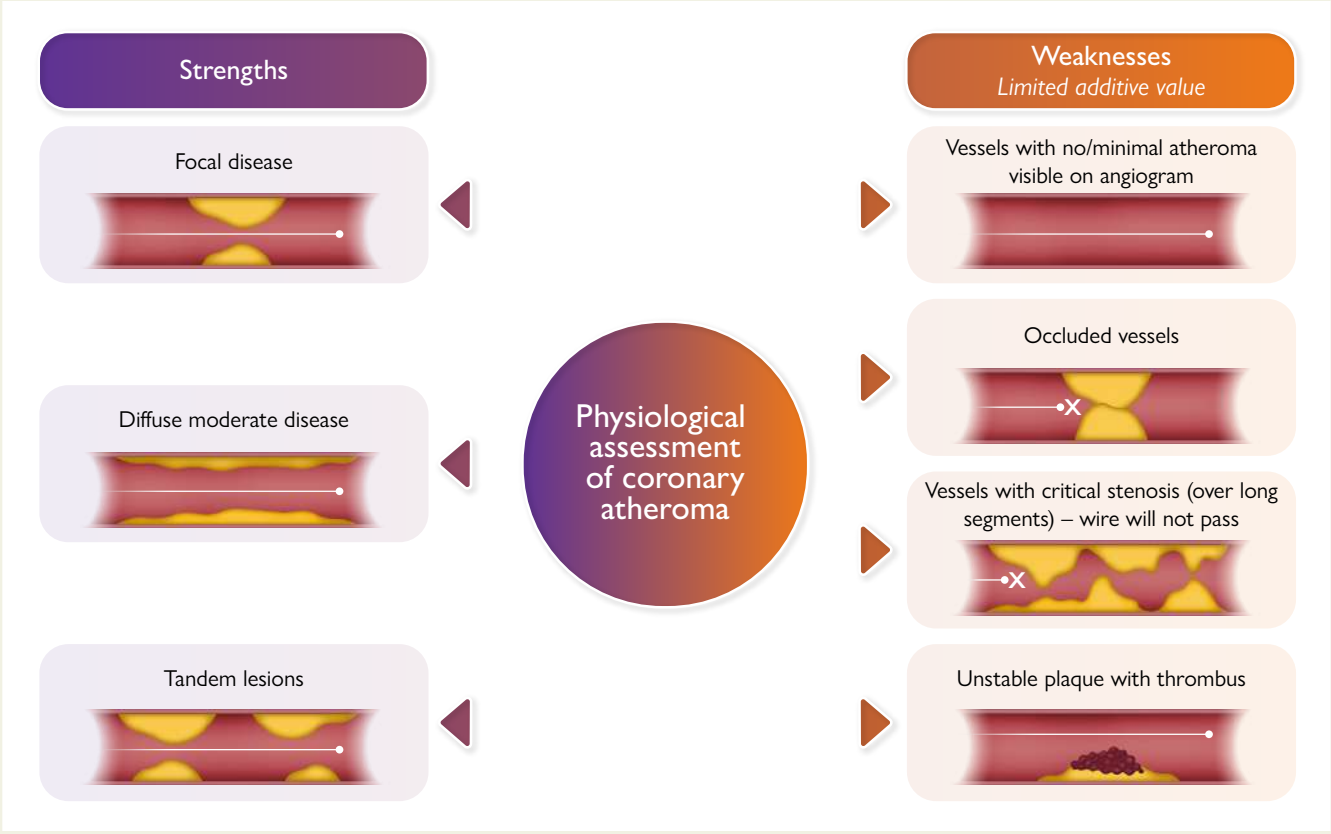
This editorial refers to 'Fractional flow reserve vs angiography to guide percutaneous coronary intervention: an individual patient data meta-analysis', by F. Mangiacapra *et al.*, https://doi.org/10.1093/eurheartj/ehaf504.

Graphical Abstract



The scenarios where coronary physiological measurement has strengths and weaknesses in the assessment of coronary atheroma.

It is quite easy to forget and underestimate the groundbreaking insights that measurement of intracoronary physiology revealed to the interventional cardiology community. The availability of an intracoronary guide wire which could decide whether it is likely to be beneficial to treat a lesion in a coronary artery of ambiguous severity was a fundamental developmental step in the evolution of contemporary percutaneous coronary intervention.[1] Before physiological measurement, decisions to treat a stenosis were based on a 2-dimensional angiographic appraisal and, in retrospect,

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this technique biased decisions to treat focal discrete stenosis and to perhaps ignore more diffuse longer segments of disease.

Previous rapid, technological development had made the process of implanting coronary stents much easier, and there was a perception that perhaps 'placing more stents was likely to mean more benefit'. Recognizing that many areas of focal atheroma can safely be treated medically improved interventional decision-making, by focusing the interventional procedure on areas of atheromatous disease causing ischaemia.[2] Using physiology led to a reduction in the number of implanted stents and consequently a fall in the incidence of both peri-procedural myocardial infarction and subsequent restenosis with the need for subsequent repeat revascularization.

Conclusive data resulted in strong recommendations for application of intracoronary physiology in patients with chronic coronary syndromes, and using physiological assessment has been mandated serially by Guideline committees over the last 10–15 years.[3] More recent improvements in technology now allow physiological coronary stenosis assessment to be performed with a wire, but without the need for pharmacological infusions to generate hyperaemia,[2] for physiological measurement to be made using computers and the angiogram (by combing the silhouettes of the artery and relating it to the likely myocardial mass it subtends, thus preventing the requirement for passage of a guide wire),[4] and/or by using coronary computed tomography to make measurements of the likely physiological impact of atheroma detected using non-invasive imaging.[5] In light of all these advances, it is perhaps appropriate to consider why further data are being presented to justify the use of intracoronary physiology during interventional procedures in this issue of the *European Heart Journal*. What can these additional data possibly add to our extensive understanding?

The PRIME investigators[6] have performed a patient-level meta-analysis comparing intracoronary physiology with coronary angiography alone to guide an interventional approach. To generate the meta-analysis, 3463 manuscripts were initially identified and the inclusion criteria of 73 randomized trials were examined. However, eventually only five trials were considered for inclusion although this resulted in individual data being obtained and analysed from 2493 patients. Perhaps unsurprisingly, the conclusion of the investigators is that physiology is helpful and beneficial in preventing major adverse cardiac events compared with angiography alone. Using physiology, the number of patients needing stents is less (45% vs. 30% with physiology) and the number of stents implanted is less (2 vs 1.5 with physiology). These positive data for physiology contrast with findings from some recent individual trials using physiology and a study-level meta-analysis which concluded that physiology probably did not add much to angiographic assessment in the studied populations.[7]

Scientifically, a patient-level meta-analysis is recognized as a higher level of evidence than a trial-level meta-analysis, as it is designed to reduce the variability of a heterogeneous trial-level sample. However, this added data stringency usually also reduces the size of the observed sample.

In order to make sense of these discrepant findings derived from data from the same trials, it is necessary to drill down a little into the methods of the different analyses and accept some of the recognized limitations of coronary physiology. Firstly, some of the differences in the data interpretation reflect differences in the inclusion criteria used and the endpoint definitions which have been employed. By specifically selecting trials where physiology has only been used for intermediate stenosis assessment could be considered to be taking advantage of the 'sweet spot' of the technology. Physiology to decide whether to undertake intervention really has no role in vessels without some visible atheroma, or in vessels with a heavy atheromatous burden and multiple stenoses (if the myocardium is known to be viable) although, notably in vessels with diffuse severe disease, physiology can have a role in guiding the interventional approach.

The role of physiology in acute coronary syndromes is also potentially confusing. In patients with acute myocardial infarction, physiological measurements can be misleading in the culprit vessel and will change with time depending on the changes in myocardial oedema and necrosis.[8] Assessing non-culprit vessels with physiology during acute ST elevation myocardial infarction is an established approach and there is a strong evidence base to support intervention when physiology demonstrates significant ischaemia for these stenoses (*Graphical Abstract*).[9]

In patients with acute coronary syndromes but without ST elevation, physiology can reliably predict which stenoses will cause ischaemia, but it cannot necessarily predict which acute coronary lesions may progress quickly despite medical therapy and be a cause of recurrent chest pain or progress to occlusion with the risk of myocardial infarction and potentially arrhythmic death. Identification and classification of these very high-risk plaques is being, and will be, informed further by data from intracoronary imaging, probably used together with adjunctive molecular techniques.

Within these presented data, much of the observed benefit from adoption of physiology appears to relate to a reduction in the incidence of procedural myocardial infarction. Evaluation of the relevance and consequences of procedural myocardial infarction has been debated extensively in the fields of optimal lesion management but also in comparative trials of percutaneous coronary intervention vs. coronary artery bypass surgery in patients with multivessel coronary artery disease. Because of the higher than expected incidence of troponin elevation following routine coronary intervention, there was a perception that procedural myocardial infarction was probably not especially important or consequential. However, in contrast to those early opinions, it is now clear that elevated cardiac enzymes following a percutaneous coronary intervention procedure do reflect an element of myocardial necrosis.[10] Predictably, low levels of very sensitive cardiac enzymes such as troponin reflect essentially trivial myocardial necrosis and are unlikely to have prognostic consequence for a patient. Conversely, large enzyme elevations are directly related to significant areas of myocardial infarction, and unquestionably have a significant subsequent prognostic impact for the patient.[11] Therefore, it could be regarded as a reasonable principle that preventing any myocardial infarction for a patient is desirable. Consequently, the reduction of procedural myocardial infarction, which appears to be an important contributor to the observed combined primary endpoint benefit within the PRIME investigators' study, should not be trivialized.

For some individuals and industry, the limited penetration of the use of physiology in daily interventional practice has been a puzzle and frustration. Technical limitations regarding the handling properties of the wires, concerns about the side effects of infusions to induce hyperaemia, and limited catheter lab time are all cited as possible explanations. Reviewing and perhaps reappraising data collected over a period of time may have the benefit of reminding us about the validity of previous observations and perhaps serves to re-emphasize the message. Only time will tell whether these new collated data from the PRIME investigators will increase the penetration of physiology into interventional decision-making. But if it does, I would personally be both pleased and surprised. It is also notable that some of our patients might also be healthier as a consequence!

Declarations

Disclosure of Interest

The author declares no disclosure of interest for this contribution.

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