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EDITORIAL

Anatomy and physiology in ischaemic heart disease: a second honeymoon?

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This editorial refers to 'Coronary plaque quantification and fractional flow reserve by coronary computed tomography angiography identify ischaemia-causing lesions'†, by S. Gaur *et al.* on page 1220.

The marriage between coronary anatomy and physiology was sealed four decades ago with the evidence that progressive decreases in coronary lumen diameter resulted in reduced myocardial blood flow. Since that time, coronary artery revascularization has been based on visual assessment of the severity of coronary lumen diameter reduction during invasive coronary angiography (ICA), assuming that this accurately reflects the physiological significance of the lesion.

However, this marriage was troubled by reports suggesting that more than two-thirds of acute myocardial infarctions may have non-obstructive coronary artery stenosis.[1] Moreover, the 'hard endpoint' benefit of coronary revascularization was challenged by the results of several trials showing no mortality benefit of angiography-based percutaneous coronary intervention (PCI) compared with medical therapy.[2,3] Furthermore, the relationship between stenosis severity and ischaemia was questioned by many studies, including a COURAGE substudy showing that among patients with coronary artery stenosis $\geq$70%, only 32% of patients had severe ischaemia and 40% had negligible ischaemia by myocardial perfusion.[2] Similarly, Tonino *et al.*[3] showed that 20% of lesions with $\geq$70% stenosis did not produce ischaemia and 17% of lesions with $<$50% stenosis caused ischaemia. Such mismatches between anatomy and physiology caused a severe rift in the relationship between anatomy and physiology in the management of coronary artery disease (CAD), and divorce papers have been served on more than one occasion.

To the rescue came fractional flow reserve (FFR) which provided a quantitative means of determining the haemodynamic significance of coronary artery lesions. Clinical validation was provided by prospective, randomized trial data demonstrating that FFR-guided treatment of ischaemia-causing lesions (FFR $\leq$0.80) provided improved long-term outcomes compared with medical therapy alone.[4] On the basis of such data, invasive FFR is now widely considered the gold standard for the functional assessment of coronary artery stenosis and is widely recommended in professional guidelines,[5] thus bringing physiology back to the side of anatomy.

At the same time, there is increasing evidence that certain atherosclerotic plaque characteristics make them unstable and vulnerable to rupture, resulting in adverse cardiac events.[6] Sannino *et al.*[6] highlighted the archetype vulnerable plaque as characterized by positive remodelling, a lipid-rich necrotic core, and a thin fibrous cap.

In this regard, coronary computed tomography angiography (CCTA) is uniquely well positioned to bring together key anatomical and functional elements needed for the diagnosis and treatment of CAD. First of all, CCTA provides excellent anatomical imaging of the coronary arteries and can reliably rule out the presence of significant CAD with high sensitivity and high negative predictive value. However, CCTA cannot determine the functional significance of coronary lesions, resulting in a high false-positive rate when compared with invasively measured FFR. This limitation has now been addressed with the availability of non-invasive FFR derived from CCTA images (FFR_{CT}) using computational fluid dynamics. FFR_{CT} provides significantly higher specificity and positive predictive value than CCTA, with a per-patient sensitivity and specificity of 86% and 79%, respectively, with a reduction of 68% of the number of false-positive cases due to calcified lesions even in patients with a high calcium score $>$400.[7] More recently, the PLATFORM trial has shown how the use of the FFR_{CT} diagnostic strategy as gatekeeper in patients undergoing ICA is a feasible and safe alternative to invasive evaluation and results in a reduction in ICA use of 61%[8] and a 32% avoidance of cost.[9]

However, missing from the CCTA/FFR_{CT} marriage is the element of the atherosclerotic plaque itself. CCTA is able to describe high-risk plaque (HRP) features such as positive remodelling, spotty calcifications, and low attenuation plaque that are related to acute coronary syndrome and can potentially serve as independent predictors of major adverse cardiac events (MACE).[10] Can plaque characteristics now be brought into the marriage of CCTA and FFR_{CT} to make the picture complete?

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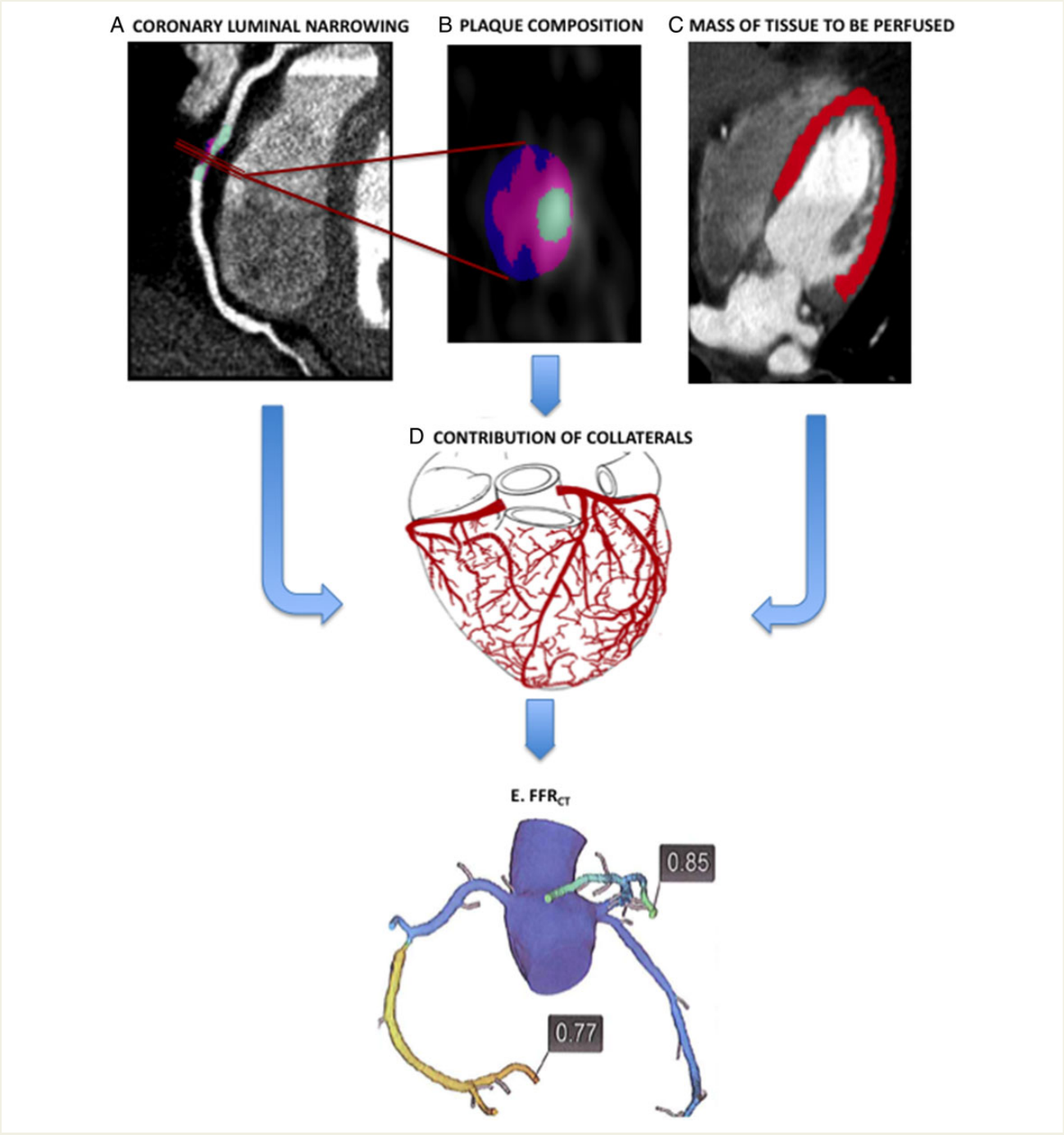

Figure 1 Potential mechanism responsible for computed tomography-derived fractional flow reserve (FFRCT): (1) Linear reduction of blood flow (green colour) related to the degree of coronary stenoses (*A*); (2) Plaque morphology characterized by a high plaque volume with positive remodelling and large low attenuation core (purple colour) that could produce oxidative stress and local inflammation leading to clinically relevant 'functional stenoses' (*B*); (3) Myocardial mass to be perfused (red colour) according to the principle that larger it is, lower FFR for a given stenosis will be detected (*C*). All these three determinants have to be balanced on the contribution of collateral vessels for both stenoses supplied by collaterals but also for stenosed arteries providing collaterals to another more critically diseased vessel (*D*). These four determinants are responsible for a pathological FFR_{CT} (yellow colour) as detected by CCTA in the middle-distal right coronary artery (*E*). CCTA could be uniquely suited to provide the best platform for defining the relationships between these key determinants of coronary artery disease.

In this issue of the journal, Gaur *et al.*[11] present an intriguing post-hoc analysis of the NXT trial[7] evaluating coronary plaque characteristics, coronary artery stenosis severity, non-invasive FFR_{CT}, and their relationship to invasive FFR, and report an inverse relationship between coronary plaque volumes and lesion-specific ischaemia. More specifically, they found that non-calcified plaque volume,

plaque length, and mainly low-density non-calcified plaque consistently predict ischaemia beyond the degree of stenosis, providing additional value to FFRCT identification of ischaemia-causing lesions. This apparently surprising association between coronary artery anatomy and physiopathology could be explained by the evidence that oxidative stress and local inflammation, as determined by low-density plaque, may negatively influence the balance between vasodilators and vasoconstrictors, leading to clinically relevant 'functional stenoses'. Similar results have been found by Park *et al.*[12] who showed that positive remodelling of coronary plaque is associated with ischaemia-causing lesions independent of stenosis severity. Accordingly, the study by Gaur *et al.*[11] is a crucial piece of evidence regarding the potential missing link between atherosclerotic burden and ischaemia that could have several implications. First, in patients with pathological FFR, two different scenarios may be present. Some patients may have a mild to moderate stenosis with strong thrombogenic stimuli while others may have a severe stenosis with associated high shear stress. Secondly, early identification of high-risk plaque could become pivotal in the management of patients with suspected CAD, and CCTA images based on segmented lumen borders for plaque characterization, calculation of computation fluid dynamics to estimate longitudinal shear stress and axial plaque stress, and measurement of coronary artery stenosis may have a relevant impact to enable strategies to limit cardiac morbidity and mortality. Thirdly, therapeutic implications could be derived from the findings of this study. There is robust evidence of clinical benefit of statin-mediated LDL-cholesterol-lowering therapy.[13] However, Puri *et al.*[14] showed that baseline coronary atheroma volume remained strongly associated with subsequent MACE despite statin treatment. Moreover, patients with a higher baseline coronary atheroma volume experienced more pronounced disease regression,[14] confirming the powerful prognostic capacity of disease burden above and beyond traditional cardiovascular risk factors and significant LDL-cholesterol lowering. High-dose statin therapy limits the progression, regresses coronary atherosclerosis, and lowers clinical event rates by a possible procalcific effects.[14] Accordingly, the most recent US guidelines advocate high-intensity statin therapy in all individuals with known atherosclerosis, regardless of baseline lipoprotein levels,[13] highlighting the role of coronary imaging in this regard. This scenario could open up the option to reserve invasive diagnostic and revascularization procedures for those patients with positive FFR or FFR_{CT} in the setting of obstructive disease, and to target high-intensity statin therapy towards patients with positive FFR in the setting of non-obstructive high-risk plaque with the aim to reach plaque stabilization and consequently FFR normalization.

Despite this study opening up such intriguing scenarios, some limitations require discussion. Accurate segmentation of lumen borders by CCTA is at the core of both plaque characterization and FFR_{CT} calculation. However, this step is sometimes problematic due to limited spatial and temporal resolution. Moreover, the plaque characterization process could be realistically proposed in clinical practice only if it is performed with a fully automated approach such as in this study. Of note, in contrast to previous studies,[12] this report takes a much more rigorous and clinically applicable approach because it provides optimal thresholds for quantifying plaque characteristics, and examines all plaques in coronary arteries $\geq$2.0 mm in diameter, rather than artificially restricting analysis to plaques upstream of an invasive FFR sensor. However, a further and larger validation study of this automated analysis in the real clinical world would be desirable. Finally, conflicting data still exist regarding the agreement between CCTA and intravascular ultrasound (IVUS) in plaque characterization, showing alternatively a underestimation or overestimation of plaque burden with coronary CTA when compared with IVUS.

Considering its capability to evaluate plaque characteristics and lumen stenosis and to be used for FFR calculation, CCTA is uniquely suited to provide the best platform for defining the relationships among the key determinants of CAD and future cardiac events. CCTA-derived information may enhance the options to optimize medical therapy based on a combination of anatomy, physiology, and plaque characteristics, in addition to systemic atherosclerotic risk factors, thus consummating the 'perfect marriage'. Prospective clinical trials focusing on a combination of all these data and consequent interventions are needed to shift the question from 'does it improve risk prediction' to 'should the practitioner do something differently because of the evidence?'[15]

The study of Gaur *et al.*[11] is an important step forward in this direction, opening up the era of a CCTA-based second 'honeymoon' between anatomy and physiology in the diagnosis and treatment of ischaemic heart disease.

Conflict of interest: none declared.

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