EDITORIAL

Title: The Human Microcirculation in Ischemic Heart Disease

Authors: Novalia Sidik BMedSci MRCP[1,2], Andrew Morrow BSc MRCP[1,2], Colin Berry BSc, PhD, FRCP[1,2].

Affiliations: [1]British Heart Foundation Glasgow Cardiovascular Research Centre, Institute of Cardiovascular and Medical Sciences, University of Glasgow, Glasgow, UK; [2]Golden Jubilee National Hospital, Clydebank, United Kingdom.

Correspondence: Professor Colin Berry, BHF Glasgow Cardiovascular Research Centre, Institute of Cardiovascular and Medical Sciences, 126 University Place, University of Glasgow, Glasgow, G12 8TA, Scotland, UK. Telephone: +44 (0) 141 330 3325 or +44 (0) 141 951 5000. Fax +44 (0) 141 330 6794; Email: colin.berry@glasgow.ac.uk

Word count: 1283 – text; 2267 (including text, references and figure legend)

Acknowledgements: None

Sources of funding: Drs Berry and Sidik have research funding from the British Heart Foundation (both, FS/17/26/32744; and to CB; RE/18/6134217). Drs Berry and Morrow have research funding from the Medical Research Council (MR/S018905/1).

Disclosure: Dr. Berry is employed by the University of Glasgow which holds consultancy and research agreements with companies that have commercial interests in the diagnosis and treatment of angina. The companies include Abbott Vascular, AstraZeneca, Boehringer Ingelheim, GSK, HeartFlow, Novartis, and Siemens Healthcare. These companies had no involvement in this manuscript.

Key words

Angina; microvascular; fractional flow reserve; remodeling; percutaneous coronary intervention.

Abbreviations

CAD	Coronary artery disease
FFR	Fractional flow reserve

Introduction

Ischemic heart disease persists as a leading cause of premature death and disability worldwide [1]. In patients with angina, the standard of care is coronary angiography performed invasively during cardiac catheterization or non-invasively by computed tomography coronary angiography [2]. These anatomical imaging tests for coronary anatomy and disease inform the diagnosis and treatment of coronary heart disease, this being a subset (endotype) of ischemic heart disease. Around 10 million coronary angiograms are performed in clinical practice worldwide each year.

During the past 5 decades, research has provided pivotal new insights in the field of medicine. Key concepts have emerged from basic research in coronary physiology, unexpected outcomes from randomized controlled trials, and epidemiology studies. Whilst a comprehensive review is beyond the scope of this editorial, some pivotal developments are noteworthy. In 1974, Lance Gould and colleagues described the physiological basis of a flow-limiting coronary artery stenosis. In an experimental model of coronary artery disease (CAD), he demonstrated that the hyperemic flow response (coronary flow reserve) was markedly impaired as stenosis severity increased beyond 60 - 70% of the reference vessel diameter in contrast to flow at rest which had a narrower range and was less affected. Coronary flow reserve, expressed as hyperemic flow / resting flow, may be measured invasively or non-invasively [2]. Relatedly, another key concept is that coronary flow reserve may be impaired in the absence of a coronary artery stenosis. This paradox is typically explained by microvascular disease, independent of stenosis severity, which becomes clinically relevant for patients given that coronary flow reserve has prognostic importance [4,5] and, potentially, may be a modifiable therapeutic target. Another key concept is myocardial fractional flow reserve (FFR), first introduced by De Bruyne and Pijls [6,7]. FFR is a pressure-derived index that is measured invasively under hyperemic conditions; when coronary resistance is minimized, the pressure-flow relationship becomes

approximately linear [6]. FFR is defined as the fraction of myocardial blood flow in a diseased coronary artery indexed to myocardial blood flow were the artery normal [6,7]. Clinical studies using FFR to assess the functional significance of 'lesion-level' CAD highlighted discordance between the anatomical severity of CAD, as revealed by invasive angiography [8,9] or computed tomography coronary angiography [10]. FFR-guided percutaneous coronary intervention (PCI) reduces the risk of myocardial infarction compared to patients undergoing angiography-guided management [11,12]. Accordingly, FFR and, relatedly, non-hyperemic pressure ratios, are now recommended by practice guidelines notably to guide decisions for revascularization (or not) in patients with coronary lesions of intermediate severity [2], and FFR-CT is an emerging option in the clinic [13].

Most affected patients do not have obstructive CAD, a fact that is under-recognized by clinicians, patients and other stakeholders e.g. healthcare providers and research funders. Clinical trials involving coronary artery imaging in relatively unselected patient populations, such as Scottish Computed Tomography of the HEART (SCOT-HEART) [14,15] and the Prospective Multicenter Imaging Study for Evaluation of Chest Pain (PROMISE) trials [16], have informed this gap. SCOT-HEART was a clinical trial of computed tomography coronary angiography vs. standard care in 4,146 patients referred to Chest Pain Clinics in the National Health Service in Scotland. Of 1778 (44% women) patients with known or suspected angina, only 1 in 4 had obstructive CAD, and this was 3-fold more common in men than in women (347 (29.9%) of 1162 men vs. 105 (11.5%) of 911 women; $p<0.001$). The cause of angina in the patients with no obstructive CAD (mostly female) was not determined, however, computed tomography coronary angiography-guided management was associated with worse angina and quality of life during follow-up [15]. Examining this conundrum further, the CorMicA study [17] determined that half of patients referred for invasive coronary angiography do not have obstructive CAD and 3 in 4 of these patients have microvascular angina and/or vasospastic

angina, most of whom are female. These findings support the case for a major reappraisal of ischemic heart disease [18]. Small vessel disease may be the most common cause of ischemic heart disease and the availability and validity of relevant tests in the clinic becomes more relevant. Clearly, anatomical and functional tests have essential, complementary value in the clinic.

With these points in mind, the validity of physiological measurements *in vivo* has crucial importance. However, in vivo validation presents a methodological challenge. Experimental models of the coronary circulation inevitably have limitations. Theoretical concepts may be proven experimentally, but is their translation to multimorbid patients routinely valid? On the other hand, clinical physiology studies in patients necessarily require carefully considered research protocols, written informed consent and assurance of patient safety especially in relation to instrumentation of the coronary arteries. A further gap relates to correlation between clinical physiology measurements in vivo and pathological validation. With these points in mind, the research by de Waard *et al* [19] is a welcome addition to the literature.

Van Royen's group identify a gap in the literature relating to remodeling of the coronary microcirculation in patients with CAD. There is some controversy around whether or not microvascular remodeling occurs, such that theoretical concepts relating to minimization of coronary resistance that underpins FFR have been questioned, notably in relation to microvascular dysfunction secondary to CAD. De Waard et al [19] investigated whether microcirculatory remodeling occurs downstream of CAD in the human coronary circulation. The data were gathered from clinically-indicated post-mortem examinations in the VU University Medical Center in Amsterdam. Pathology examinations were performed using cardiac tissue from 36 deceased patients who had undergone invasive coronary angiography on clinical grounds within two years prior to death. Using formalin-fixed, paraffin embedded tissue, anti-CD31 immunostaining was performed for quantification of capillary density,

smooth muscle actin alpha staining was performed for quantification of arteriolar dimensions and density, and hematoxylin & eosin staining was used for the assessment of myocardial disease. Regions of interest were identified in the epicardium and endocardium of myocardial sections. The analyses of the microvessels (vessel counts, morphology) were undertaken manually using digital microscopy and computer-based analysis.

In this study, 115 coronary arteries from 55 deceased patients who had undergone coronary angiography were assessed. Of these, 29 (53%) patients had no angiographic evidence of CAD, 19 (35%) had single- or two-vessel CAD and 7 (13%) had three-vessel CAD. Therefore, 53 disease-free coronary arteries from 29 negative control subjects was included. Patients with percutaneous coronary intervention or coronary artery bypass graft surgery performed between the angiogram and the post-mortem examination were excluded. In the main analysis of within-subject comparisons of arteries with or without atherosclerosis, 32 pairs of an unobstructed coronary artery and a coronary artery with a stenosis within the same patient (n=55) were formed. No statistically significant differences between any of the microcirculatory parameters (microvessel density or morphology) were found. The statistics included generalized estimating equations to take account for multiple testing within the same subject. In an analysis of unpaired data including 115 coronary arteries with microvascular pathology data, again, no correlations were observed between stenosis severity, microvascular parameters and arteriogenesis.

De Waard *et al* concluded that the human coronary microcirculation distal to non-critical stenoses does not undergo structural remodeling [19]. This conclusion supports the notion that measurements of coronary resistance in vivo, and relatedly, FFR, are not confounded by microvascular remodeling. Limitations of this study include lack of in vivo data on coronary vascular function, the sample size, retrospective design, and patient selection. The lack of perfusion fixation is an inherent limitation to pathology studies of humans. In this regard, the

work of William Fulton using stereo-arteriography to delineate the microcirculation and innate collateral connections is particularly revealing (Figure 1).

In conclusion, de Waard *et al* [20] provide histopathological evidence on the human coronary microcirculation, that supports the adoption of invasive and non-invasive tests of coronary vascular function in the clinic.

References

1. Roth GA, Abate D, Hassen Abate K, et al. Global, regional, and national age-sex-specific mortality for 282 causes of death in 195 countries and territories, 1980-2017: a systematic analysis for the Global Burden of Disease Study 2017 GBD 2017 Causes of Death Collaborators. Lancet. 2018;392:1736–1788.
2. Knuuti J, Wijns W, Saraste A, et al; ESC Scientific Document Group. 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes. Eur Heart J. 2019. pii: ehz425. doi: 10.1093/eurheartj/ehz425.
3. Gould KL, Lipscomb K, Hamilton GW. Physiologic basis for assessing critical coronary stenosis. Instantaneous flow response and regional distribution during coronary hyperemia as measures of coronary flow reserve. Am J Cardiol. 1974;33:87-94.
4. Taqueti VR, Hachamovitch R, Murthy VL, Naya M, Foster CR, Hainer J, Dorbala S, Blankstein R, Di Carli MF. Global coronary flow reserve is associated with adverse cardiovascular events independently of luminal angiographic severity and modifies the effect of early revascularization. Circulation. 2015;131:19-27.
5. Gupta A, Taqueti VR, van de Hoef TP, et al. Integrated Noninvasive Physiological Assessment of Coronary Circulatory Function and Impact on Cardiovascular

Mortality in Patients With Stable Coronary Artery Disease. Circulation. 2017;136:2325-2336.

6. Pijls NH, van Son JA, Kirkeeide RL, De Bruyne B, Gould KL. Experimental basis of determining maximum coronary, myocardial, and collateral blood flow by pressure measurements for assessing functional stenosis severity before and after percutaneous transluminal coronary angioplasty. Circulation. 1993;87:1354-1367.

7. Pijls NH, De Bruyne B, Peels K, Van Der Voort PH, Bonnier HJ, Bartunek J Koolen JJ, Koolen JJ. Measurement of fractional flow reserve to assess the functional severity of coronary-artery stenoses. N Engl J Med. 1996;334:1703-1708.

8. Tonino PA, Fearon WF, De Bruyne B, Oldroyd KG, Leesar MA, Ver Lee PN, Maccarthy PA, Van't Veer M, Pijls NH. Angiographic versus functional severity of coronary artery stenoses in the FAME study fractional flow reserve versus angiography in multivessel evaluation. J Am Coll Cardiol. 2010;55:2816-2821.

9. Curzen N, Rana O, Nicholas Z, et al. Does routine pressure wire assessment influence management strategy at coronary angiography for diagnosis of chest pain?: the RIPCORD study. Circ Cardiovasc Interv. 2014;7:248-255..

10. Curzen NP, Nolan J, Zaman AG, Nørgaard BL, Rajani R. Does the Routine Availability of CT-Derived FFR Influence Management of Patients With Stable Chest Pain Compared to CT Angiography Alone?: The FFR(CT) RIPCORD Study. JACC Cardiovasc Imaging. 2016;9:1188-1194.

11. Xaplanteris P, Fournier S, Pijls NHJ, et al; FAME 2 Investigators. Five-Year Outcomes with PCI Guided by Fractional Flow Reserve. N Engl J Med. 2018;379:250-259.

12. Zimmermann FM, Omerovic E, Fournier S, et al. Fractional flow reserve-guided percutaneous coronary intervention vs. medical therapy for patients with stable coronary lesions: meta-analysis of individual patient data. Eur Heart J. 2019;40:180-186..

13. Fairbairn TA, Nieman K, Akasaka T, et al. Real-world clinical utility and impact on clinical decision-making of coronary computed tomography angiography-derived fractional flow reserve: lessons from the ADVANCE Registry. Eur Heart J. 2018;39:3701-3711.

14. SCOT-HEART investigators. CT coronary angiography in patients with suspected angina due to coronary heart disease (SCOT-HEART): an open-label, parallel-group, multicentre trial. Lancet. 2015;385:2383-2391.

15. Williams MC, Hunter A, Shah A, et al; Scottish COmputed Tomography of the HEART (SCOT-HEART) Trial Investigators. Symptoms and quality of life in patients with suspected angina undergoing CT coronary angiography: a randomised controlled trial. Heart. 2017;103:995-1001.

16. Douglas PS, Hoffmann U, Patel MR, et al; PROMISE Investigators. Outcomes of anatomical versus functional testing for coronary artery disease. N Engl J Med. 2015;372:1291-300.

17. Ford TJ, Stanley B, Good R, et al. Stratified Medical Therapy Using Invasive Coronary Function Testing in Angina: The CorMicA Trial. J Am Coll Cardiol. 2018;72:2841-2855.

18. Kaski JC, Crea F, Gersh BJ, Camici PG. Reappraisal of Ischemic Heart Disease. Circulation. 2018;138:1463-1480.

19. de Waard GA, Hollander M, Ruiter D, ten Bokkel Huinink T, Meer R, van der Hoeven NW, Meinsterc E, Beliën JAM, Niessen HW, van Royen N. The Downstream Influence of Coronary Stenoses on Microcirculatory Remodeling: A Histopathology Study. Arterioscler Thromb Vasc Biol. 2019; *in press*.

20. Fulton WF. The dynamic factor in enlargement of coronary arterial anastomoses, and paradoxical changes in the subendocardial plexus. Br Heart J. 1964.26:39-50.

Highlights

- Most patients with angina do not have obstructive coronary artery disease
- Coronary microvascular disease is more prevalent than macrovascular disease
- The microcirculation distal to non-obstructive atherosclerotic lesions does not undergo structural remodeling.
- The diagnostic evaluation of coronary artery disease and the microcirculation using invasive functional tests is useful for clinical and research purposes

Figure legend

A stereoarteriogram of the left and right coronary arteries from a deceased 50-year old man. The arteriogram reveals multiple non-obstructive plaques. The microcirculation is resolved revealing the sub-endocardial plexus and collateral connections.

214 **Figure 1.**