Editorial

Cardiovascular Research Spotlight on Microvascular Disease

Title: Microvascular disease – the next frontier for cardiovascular research

Authors: Colin Berry[1,2] MD/PhD, FRCP, FESC, FACC, Dirk J. Duncker[3,4] MD/PhD FESC

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; [3]Division of Experimental Cardiology, Department of Cardiology, Thoraxcenter, Cardiovascular Research School, COEUR, Erasmus MC, University Medical Center Rotterdam, Rotterdam, The Netherlands; [4]Netherlands Heart Institute, Utrecht, The Netherlands.

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: text 1636, references 1157

Acknowledgements: None

Sources of funding: Dr Berry has research funding from the British Heart Foundation (FS/17/26/32744; RE/18/6134217) and 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 ischaemic heart disease. The companies include Abbott Vascular, AstraZeneca, Boehringer Ingelheim, GSK, HeartFlow, Menarini, Novartis, and Siemens Healthcare. These companies had no involvement in this manuscript.

Key words

Angina; ischemia; microvascular; translational research

Introduction

Ischemic heart disease (IHD) persists as a leading cause of premature death and disability worldwide [1]. IHD may present as acute myocardial infarction (MI) or manifest as a chronic coronary syndrome [2]. IHD is increasingly recognized as a concomitant problem in systemic health problems, such as rheumatoid arthritis. Coronary atherosclerosis is a major cause of IHD and the historical primacy of coronary artery disease (CAD) leads some clinicians to view coronary heart disease (CHD) and IHD as synonymous, interchangeable terms. Emerging clinical evidence indicates this is far from being the case and a major reappraisal is warranted [3].

Under-recognition of coronary microvascular disease: time for a reappraisal

Coronary microvascular dysfunction (CMD) has, historically, been under recognized, not least since the microvessels are invisible. This simple issue has underpinned key misconceptions about IHD and major knowledge gaps relating to CMD [3]. Atherosclerosis is the major cause of CAD and the pathogenesis, prognosis and treatment of these problems are well established [2]. In recent years, new insights into the causes and consequences of IHD have called into question the CAD stenosis-centred/CHD paradigm. Most recently, the ISCHEMIA trial results were reported at the Scientific Sessions of the American Heart Association (November 16, 2019) [5, 6]. The central hypothesis of the ISCHEMIA trial was that in patients with angina and moderate-severe myocardial ischaemia, compared with initial non-invasive, medical management, a routine invasive strategy with cardiac catheterisation followed by coronary revascularisation plus optimal medical therapy, would improve prognosis. After 3.3 years follow-up, there was no difference in the primary endpoint between the randomized groups [6]. This trial did have limitations. Under-recruitment and a

lower than expected event rate reduced the statistical power for analysis of the primary outcome that ultimately led to a belated, yet prespecified change in the primary composite outcome. Longer term follow-up with accrual of more events may provide new insights. Nonetheless, ISCHEMIA is the largest study of its kind, and the results call into question the benefits of coronary revascularization in patients with myocardial ischaemia.

Clinical relevance of coronary microvascular dysfunction

Coronary microvascular dysfunction is increasingly implicated as a relevant cause of IHD [6]. Angina secondary to myocardial ischaemia may occur in patients with no obstructive CAD (INOCA). In fact, around 1 in 5 patients presenting with known or suspected angina have obstructive CAD, as revealed by anatomical imaging with CT coronary angiography (CTCA) [7] (Figure 1). In the clinic, the cause of the angina is uncertain in the majority of affected patients, most of whom are women [7,8]. This becomes all the more relevant given that CTCA-guided management leads to worse angina and quality of life overall, contrary to what might be anticipated [9]. The Coronary Microvascular Function and CT Coronary Angiogram (CorCTCA) study is currently examining the prevalence and clinical significance of CMD in patients with angina but no obstructive CAD, as defined by CTCA [10]. The recent Coronary Microvascular Angina (CorMicA trial) served evidence that undertaking tests of coronary vascular function during clinically-indicated coronary angiography identifies relevant endotypes (microvascular angina, vasospastic angina, non-cardiac chest pain) and targeted therapy was associated with improvements in angina and quality of life at 6- [11] and 12-months [12] (Figure 2). Considering acute myocardial infarction, about 1 in 10 patients presenting with MI have no obstructive coronary arteries (MINOCA) [13]. Microvascular and vasospastic disease are also implicated. Considering the natural history, INOCA and MINOCA may underlie the development of heart failure with preserved ejection

fraction (HFPEF) [14], which is an increasingly recognized, prevalent cause of heart failure.

Coronary microvascular disease may be part of a systemic continuum of microvascular disease, with multiple affected organ beds [15]. Small vessel disease in the heart and brain links INOCA with vascular dementia [15]. The deleterious effects of vascular risk factors, such as hypertension, obesity, smoking and diabetes are relevant, and genetic associations [4], notably leading to increased exposure to endothelin-1 [16], are also implicated. CMD is causally implicated in multiple systemic conditions including the cardiotoxicity of chemotherapy, systemic inflammatory conditions, such as rheumatoid arthritis, heart failure and pregnancy [17]. Sex associations are also relevant [18]. Obstructive CAD typically associates with male sex whereas small vessel disease associates with female sex [7,8,10,11]. Since anatomical imaging with CTCA is diagnostically most useful for identifying and excluding CAD and compared with ischaemia testing, least useful for the diagnosis of CMD, an all-comers strategy based on CTCA introduces a sex bias [3]. Under-recognition and under-treatment of heart disease in women is a hot topic [17,18], and more research seems warranted.

Some of the persisting, clinically-relevant questions are: 1) In INOCA and MINOCA, is myocardial ischaemia the consequence and/or cause of microvascular dysfunction? Is chronic myocardial ischaemia therapeutically modifiable? Is microvascular dysfunction a common problem after successful revascularization? If so, what are the mechanisms underlying microvascular dysfunction, what treatments might be disease-modifying and beneficial to patients? Is CMD other systemic conditions are modifiable target? What is the natural history of CMD? The clinical relevance of microvascular dysfunction in patients with flow-limiting CAD is being investigated in the DEFINE-FLOW study [19], due to be reported in 2020. The Changes in Ischemia and Angina Over 1 Year Among ISCHEMIA Trial Screen Failures With no Obstructive CAD on Coronary CT Angiography (CIAO) substudy will also be

100 informative [20].

101 Accordingly, CMD has generated substantial interest in the clinical and basic science
102 communities in recent years. This Spotlight Issue brings together internationally leading
103 thought-leaders, researchers and their trainees. The authors have a broad range of
104 backgrounds including basic science, translational research and clinical studies. Their remit is
105 to focus on 'hot topics' in CMD and give perspectives on the science.

106 The Spotlight Issue begins with a Position Paper, "*Coronary Microvascular*
107 *Dysfunction in Cardiovascular Disease*", from the European Society of Cardiology (ESC)
108 Working Group on Coronary Pathophysiology and the Microcirculation [21]. The Position
109 Paper by Drs. Padro, Badimon and coauthors highlights, firstly, updated evidence on the
110 pathophysiological consequences of microvascular dysfunction in the heart. Secondly, they
111 focus on the relevance of cardiovascular risk factors and co-morbid conditions for
112 microcirculatory dysfunction. Thirdly, they highlight the clinical consequences of CMD,
113 which is not a benign problem. They conclude that clinical strategies should prioritise
114 detection of CMD which in turn will help in the stratification of cardiovascular in support of
115 precision medicine.

116 The first article focuses on experimental models of CMD. Duncker *et al.* discuss the
117 benefits and pitfalls of existing small and large animal models of CMD, with a specific focus
118 on metabolic disturbances which may be experimentally induced or spontaneous [22]. They
119 provide a comprehensive description of relevant experimental research involving a range of
120 species. They also highlight the value of experimental models for identifying novel
121 therapeutic targets and for the subsequent development and testing of novel therapeutic
122 interventions.

123 The next article focuses on “Diagnosis of coronary microvascular dysfunction in the clinic”.
124 Ong *et al*. [23] cover the diagnosis of CMD in an article that discusses the invasive and non-
125 invasive methods for the assessment of CMD in humans. They highlight an integrative
126 approach for assessing coronary vascular function using a diagnostic guidewire initially and
127 then pharmacological reactivity testing using intracoronary administration of acetylcholine
128 (ACh). They highlight the IDP developed by Berry and Ford [11] as the current gold standard
129 for assessing coronary vascular function. A review from Bairey Merz *et al.* [24] on
130 ‘Treatment of CMD’, provides a comprehensive overview of pharmacotherapies with
131 potential efficacy in alleviating CMD. The article highlights pivotal clinical trials in CMD,
132 such as CorMicA [11] and WARRIOR (ClinicalTrials.gov Identifier: NCT03417388). In
133 addition, they highlight novel therapeutics, including gene and cell-based therapies.

134 The Spotlight also includes articles on CMD in different cardiovascular disease
135 settings. Sechtem *et al.* [25] focus on CMD in stable IHD, including INOCA and obstructive
136 CAD. They focus on challenging concepts including CMD in the absence of atherosclerosis,
137 CMD detection, microvascular spasm, collateral connections, and the prognostic importance
138 of global coronary flow reserve. Konijnenberg, van Royen *et al.* [26] focus on the
139 pathophysiology and diagnosis of CMD in acute myocardial infarction. The authors state that
140 the current standard of care, primary percutaneous coronary intervention (PCI), successfully
141 restores coronary blood flow in the vast majority of patients yet most also have evidence of
142 failed myocardial perfusion, revealed as microvascular obstruction (MVO) using magnetic
143 resonance imaging. MVO confers an adverse prognosis and in spite of multiple therapeutic
144 trials, MVO has no evidence-based treatment and has an unmet therapeutic need. The
145 manuscript also discusses pre-clinical models. Camici *et al.* [27] discuss the mechanisms by
146 which CMD is a contributing factor to the transition from left ventricular hypertrophy heart
147 failure with either a reduced or preserved ejection fraction. Relevant mechanisms are

discussed. CMD in genetic cardiomyopathy is also described. Maas and colleagues [28] describe the pathogenic role of CMD in the setting of other cardiac or systemic conditions. They highlight diabetes mellitus, obesity and vascular inflammation as relevant causes of CMD.

A further disease modifier of CMD pathology is sex [17,18]. Women who are under investigation for myocardial ischemia are more likely to have non-obstructive CAD on coronary angiography and CMD is relevant. Meta *et al.* [29] explore sex-associations of INOCA, MINOCA, symptoms, risk factors and, intriguingly, sex-specific factors such as inflammation, mental stress, autonomic and neuro-endocrine dysfunction that may cause women to be more likely to develop CMD relative to men. Sex differences have major implications for both diagnosis and treatment of cardiovascular disease.

We recognize and thank experts from the COVADIS (Coronary Vasomotor Disorders International Study Group) and ESC Working Group on Coronary Pathophysiology and Microcirculation for their collaboration. The Editors hope that by bringing this collection of articles together, the Spotlight will enhance interest for research in CMD. This problem pervades human disease, mechanisms are poorly understood and specific treatments are lacking. CMD presents an exciting field for discovery and translation to reduce the unmet therapeutic need.

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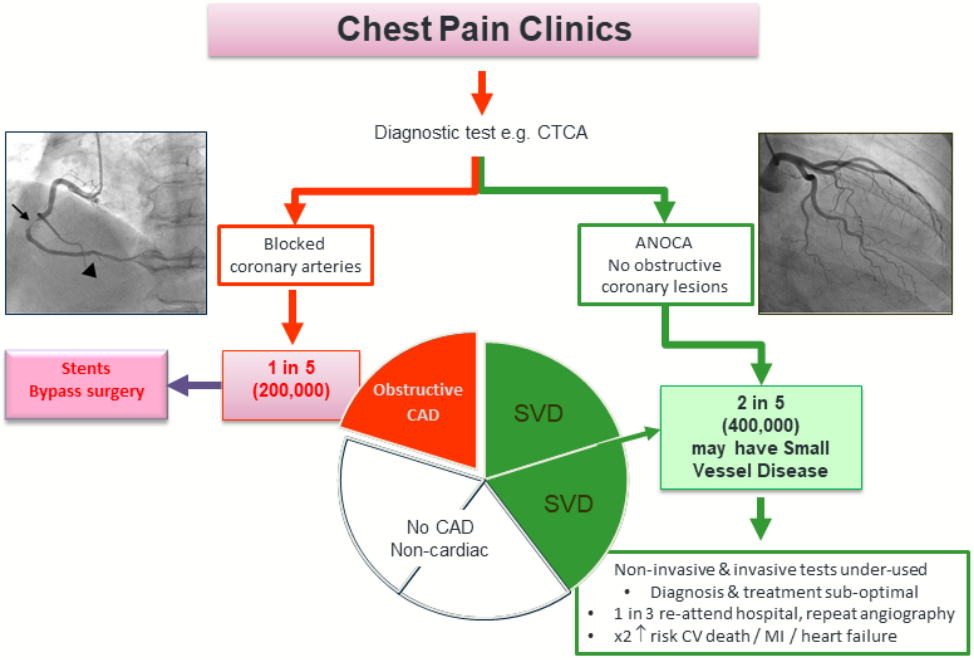
285 **Figure 1.**



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287 Legend: ANOCA – angina with no obstructive coronary arteries; CAD – coronary artery
288 disease; CTCA – Computed tomography coronary angiography; CV – cardiovascular; MI –
289 myocardial infarction.

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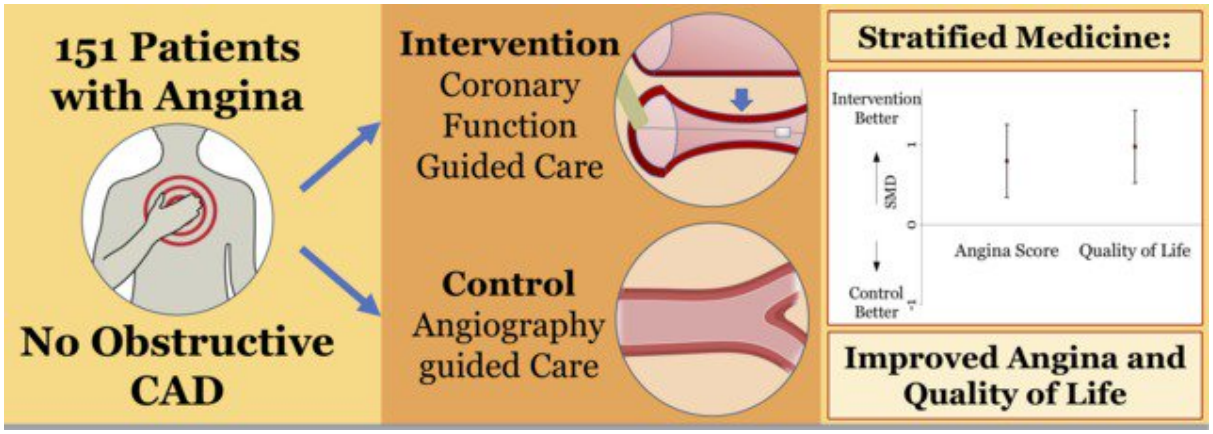
291 **Figure 2.**



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