The parallel tales of microvascular angina and heart failure with preserved ejection fraction: a paradigm shift

Filippo Crea1*, C. Noel Bairey Merz2, John F. Beltrame3, Juan Carlos Kaski4, Hisao Ogawa5, Peter Ong6, Udo Sechtem6, Hiroaki Shimokawa7 and Paolo G. Camici8 On behalf of the Coronary Vasomotion Disorders International Study Group (COVADIS)

An increasing number of studies clearly demonstrate that coronary microvascular dysfunction (CMD) plays a pivotal role in several cardiovascular diseases. In particular, emerging evidence suggests that CMD is the main contributor to myocardial ischaemia in a large subset of patients with chronic stable angina. Indeed, non-obstructive coronary atherosclerosis is observed in up to 50% of patients with angina and positive stress test results undergoing diagnostic coronary angiography. Thus, the prevalence of microvascular angina (MVA) is higher than previously thought and associated with worse clinical outcomes than those observed in asymptomatic subjects with similar risk factor burden. The diagnosis of MVA is based on the following criteria: (i) symptoms of myocardial ischaemia; (ii) absence of obstructive epicardial coronary artery disease; (iii) evidence of myocardial ischaemia on non-invasive stress testing; and (iv) evidence of impaired coronary microvascular function. The clinical relevance of MVA has historically been overlooked since the diagnostic tools required for the evaluation of the coronary microcirculation are infrequently utilized.

A parallel ‘tale’ could be proposed for heart failure (HF) with preserved ejection fraction (HfP EF). Indeed, HfP EF is observed in about 50% of patients presenting with HF symptoms and is characterized by the absence of a relevant reduction of left ventricular ejection fraction (LVEF). As with MVA, patients with HfP EF have poorer clinical outcomes compared with asymptomatic subjects exhibiting a similar burden of risk factors. The diagnosis of HfP EF is based on the following: (i) symptoms with or without signs of HF; (ii) normal or only mildly reduced LVEF; (iii) elevated levels of natriuretic peptides; (iv) relevant structural heart disease (i.e. left ventricular hypertrophy, left atrial enlargement) and/or diastolic dysfunction. In both MVA and HfP EF, no therapeutic intervention has hitherto been proven to improve patient outcome; similarly, symptomatic treatment is largely empirical. A key shared characteristic of both conditions is the high prevalence of post-menopausal women. This is widely held to be related to sex hormones such as oestrogen, although the molecular effects of oestrogen on endothelial cells, smooth muscle cells and myocytes are incompletely understood. Nevertheless, experimental studies and post-mortem and observational clinical studies suggest the presence of important differences in myocardial remodelling between females and males in response to different types of injuries including aging, pressure and volume overload, and myocardial infarction.

The common soil hypothesis

Based on the above considerations, the question arises as to whether these parallel ‘tales’ of MVA and HfP EF represent two extreme clinical presentations of a disease continuum (Figure 1). This tantalizing question is justified by the results of recent studies showing that CMD can be demonstrated not only in MVA but also in HfP EF. The hypothesis of a common soil for these two conditions appears to be endorsed by the clinical observation that dyspnoea is present in a large proportion of patients with MVA and, vice versa, angina-like symptoms are reported in about 50% of those with HfP EF. Several factors have been reported to predispose to CMD, including traditional risk factors such as smoking, hypertension, and diabetes as well

The opinions expressed in this article are not necessarily those of the Editors of the European Heart Journal or of the European Society of Cardiology.

*Corresponding author. Tel: +39/06/3051166, Fax: +39/06/3055535, Email: filippo.crea@unicatt.it
Published on behalf of the European Society of Cardiology. All rights reserved © The Author 2016. For Permissions, please email: journals.permissions@oup.com.
as chronic inflammatory diseases, such as chronic obstructive pulmonary disease, chronic kidney disease, and auto-immune conditions.\textsuperscript{1} CMD is well documented in MVA and responsible for the reduced coronary flow reserve (CFR) frequently observed in this condition.\textsuperscript{1} Recent studies suggest that CMD might play a key role also in HFpEF. Indeed, endothelial activation/dysfunction reduces nitric oxide (NO) bioavailability, cyclic guanosine monophosphate content, and protein kinase G in adjacent cardiomyocytes.\textsuperscript{11} These changes are known to favour hypertrophy and fibrosis contributing to diastolic dysfunction. The importance of inflammation for the induction of cardiac fibrosis and vascular rarefaction has been convincingly demonstrated.\textsuperscript{12} In particular, transforming growth factor (TGF)-\(\beta\) is likely to play a major role in this setting, as suggested by the observation that disruption of TGF-signalling attenuates pressure overload-induced interstitial fibrosis in the heart.\textsuperscript{13} Furthermore, endothelial dysfunction contributes to cardiac fibrosis via the reduced bioavailability of NO, known to exert direct anti-fibrotic effects involving the cyclic guanosine monophosphate pathway.\textsuperscript{14} Finally, NO deprivation favours endothelial cell conversion to a mesenchymal cell type that can give rise to fibroblasts.\textsuperscript{15} Thus, a cross-talk between the endothelium and the surrounding vascular tissue as well as the myocardium seems to play a key role in the pathogenesis of HFpEF. Obviously, hypertrophy and fibrosis not only can cause dyspnoea but they also contribute to angina as they are extravascular mechanisms of ischaemia.\textsuperscript{1}

\begin{figure}
\centering
\includegraphics[width=\textwidth]{figure1.png}
\caption{The figure summarizes the common soil hypothesis for microvascular angina (MVA) and heart failure with preserved ejection fraction (HFpEF). The common soil is represented by coronary microvascular dysfunction, which can be caused by traditional risk factors, chronic inflammation and aging while female sex is a predisposing factor. Coronary microvascular dysfunction is determined by a variable combination of endothelial dysfunction, vascular smooth muscle cell hyperreactivity, vascular remodelling, vascular fibrosis, vascular rarefaction, and increased extravascular pressure. Possible modulating factors have been suggested (see text), which may determine an effect in the direction of MVA (mainly characterized by angina and effort-induced ischemia) or, at the other extreme, of HFpEF (characterized by dyspnoea and echocardiographic alterations). Of note, microinfarcts per se can promote myocardial fibrosis leading to HFpEF. Legend: VSMCs = smooth muscle cells. Sterearteriogram created by Dr William F.M. Fulton, M.D. Thesis (1960), University of Glasgow and provided with permission from Professor Colin Berry, University of Glasgow.}
\end{figure}

\textbf{Modulating factors}

A critical question is why angina prevails at one end of the spectrum of clinical presentations while dyspnoea prevails at the other end in the presence of a ‘common soil’ nurturing the development of MVA and HFpEF or, by the same token, a continuum of disease. A first response to this intriguing question comes from a large body of evidence suggesting that patients with MVA have two important additional alterations contributing to their angina symptoms: (i) hyperreactivity of smooth muscle cells to constrictor stimuli in coronary microvessels; (ii) enhanced perception of cardiac algogenic stimuli.\textsuperscript{16} Indeed, a large percentage of patients with MVA exhibit coronary microvascular spasm, angina and ST-segment depression following the intracoronary administration of acetylcholine (ACh).\textsuperscript{17} Of note, recent clinical evidence indicates that coronary microvascular spasm in patients with CMD can cause subtle contractile abnormalities, and can be associated with mild elevations of high-sensitivity cTn.\textsuperscript{18} Although still a working hypothesis at present, it is tempting to speculate that coronary ‘microvascular’ and ‘epicardial’ spasm have a similar origin. Indeed, we have convincing experimental and clinical evidence that enhanced Rho-kinase activity in vascular smooth muscle cells—not in endothelial cells—plays a major pathogenic role in this setting.\textsuperscript{18} In MVA, the presence of microvascular spasm helps explaining why a sizeable proportion of patients report predominantly angina at rest, or a combination of rest and effort-related angina.
The importance of enhanced pain perception was initially proposed in 1988 by Shapiro et al. and subsequently confirmed by other investigators. Using positron emission tomography to measure changes in regional cerebral blood flow as an index of neuronal activity, Rosen et al. provided evidence that altered central neural handling of afferent signals may contribute to the abnormal pain perception in patients with MVA. More recently, Valeriani et al. demonstrated abnormal cortical pain processing in patients with MVA. This was characterized by inadequate habituation to pain which might be the main cause of enhanced cardiac pain perception and also account for the symptomatic improvement observed in these patients using tricyclics and adenosine antagonists like theophylline.19 It is worth noting that in MVA, reduced CFR, hyper-reactivity to constrictor stimuli, and enhanced pain perception, may combine differently in different patients thus accounting for the disappointing results of standard angina treatments in many of these patients.20

What about HFpEF? Which mechanisms in addition to endothelial dysfunction might explain a phenotype characterized by dyspnoea rather than chest pain? It is conceivable that circulating factors might modulate the effects of CMD favouring the production of fibrosis and development of LHV. In this setting, fibrocytes, circulating monocyte-derived cells with the tissue remodelling properties of fibroblasts, might play a modulatory role.21 Interestingly, in a murine model of cardiac remodelling in which fibrocytes are recruited to chronically injured myocardium, treatment of these animals with serum amyloid P decreased fibrocyte accumulation and the development of fibrosis.22 Albeit one of the main functions attributed to fibrocytes is extra-cellular matrix production, these cells may have other actions that are more typically associated with both macrophages and fibroblasts. Atrial natriuretic peptide (ANP) may be another modulatory factor. Indeed, recent findings suggest that ANP signalling results in phosphorylation of Smad proteins, thus blocking their nuclear translocation and binding to TGF-Smad responsive elements in the promoter regions of extra-cellular matrix genes.23 An additional potential mechanism, as suggested by Pepine et al., involves recurrent cycles of ischaemia-reperfusion that impair myocyte relaxation thereby producing diastolic dysfunction and HFpEF.24–26 In turn, the latter can trigger myocardial ischaemia by increasing intra-myocardial tension, an important determinant of myocardial oxygen consumption. This vicious circle may explain why dyspnoea is a frequent symptom in MVA while on the other hand, angina is frequent in HFpEF. It may also explain why cTn is occasionally elevated in asymptomatic patients who will later go on to develop HFpEF, thus suggesting that subclinical ischaemia can directly contribute to the pathogenesis of HFpEF.27 This is confirmed by a very recent study showing a substantial reduction of CFR in patients with HFpEF.28 Interestingly, Rho-kinase inhibition, known to prevent epicardial and microvascular coronary spasm, ameliorates diastolic function in hypertensive rats.29 Attesting to the gradual and progressive nature of these mechanisms, patients exhibiting HFpEF tend to be older than those presenting with MVA.

**A paradigm shift**

If the common soil hypothesis of MVA and HFpEF is correct, then a paradigm shift is required to incorporate CMD as both a common diagnostic and therapeutic target for these entities. These two conditions, MVA and HFpEF, have been identified and accepted by the scientific community only recently and rather reluctantly. This may be because they do not exhibit the classic anatomic features of ischaemic heart disease and HF, namely obstructive coronary stenoses and reduced LVEF, respectively, which are the targets of current therapeutic guidelines. It is nevertheless increasingly acknowledged by the medical community that MVA and HFpEF represent a substantial public health burden given their high prevalence and guarded prognosis.

Thus, a first important challenge facing the scientific community is to devise strategies for the early diagnosis of CMD. The latter can be helped by the non-invasive assessment of CFR using transthoracic Doppler echocardiography, cardiac magnetic resonance or positron emission tomography. Furthermore, the demonstration of coronary microvascular spasm by intracoronary ACh, as well as the measurement of coronary blood flow and microvascular resistance during hyperaemia at the time of coronary angiography, may provide additional diagnostic information.

A second challenge is the standardization of the diagnostic criteria for MVA and HFpEF. Efforts should be directed towards an accurate definition of these two conditions and this should be reflected in international guidelines.

A third challenge is the identification of new biomarkers for the diagnosis and risk stratification of MVA and HFpEF. Recent studies suggest that among patients with MVA, a lower CFR is associated with worse clinical outcomes, and suitable biomarkers are needed for prospective studies in larger cohorts of patients.30 In patients with HFpEF, serum levels of certain biomarkers, in particular natriuretic peptides and soluble ST2, appear to correlate with diastolic load and growing evidence suggests that such biomarkers may provide relevant diagnostic and prognostic information.31,32 Analogous considerations apply to recent techniques developed for the identification of interstitial myocardial fibrosis by cardiac magnetic resonance imaging.

**Therapeutic implications**

The identification of effective evidence-based treatments for these conditions is yet another challenge confronting contemporary cardiology. Current pharmacological agents used in angina pectoris and HF have largely been developed for the management of obstructive epicardial coronary artery disease and reduced left ventricular function, respectively. They are, however, generally ineffective in controlling symptoms in patients with MVA and HFpEF, and have little if any impact on prognosis.

We herewith propose that CMD should be the main therapeutic target in both MVA and HFpEF. Given that the mechanisms of CMD are multiple, it is unlikely that one single treatment will be of benefit in all patients. This multiplicity of pathogenic mechanisms may explain why currently available pharmacological agents have hitherto failed to improve symptoms and outcomes in patients with either the MVA or HFpEF. In particular, angiotensin converting enzyme inhibitors, angiotensin receptor blockers and digoxin were not effective in reducing mortality in HFpEF. Similarly, β-blockers have not shown benefits, therapy with spironolactone showed improvement in diastolic function and hypertrophy but not clinical outcomes, sildenafil...
showed no improvement in exercise capacity, quality of life, or clinical status. Interestingly, the Prospective Comparison of Angiotensin Receptor Neprilysin Inhibitor with Angiotensin Receptor Blockers on Management of HFpEF (PARAMOUNT) trial showed favourable effects of angiotensin receptor neprilysin inhibitor on natriuretic peptides and left atrial volumes, and a phase III trial with this agent is ongoing.34

Indeed, previous trials have targeted the phenotype rather than the underlying mechanism of CMD, which can be different in different patient subsets exhibiting the same phenotype. Strategically, it may perhaps be more effective to target those specific mechanisms causing CMD and test these interventions in homogeneous subsets of patients. We may need to develop therapeutic strategies to tackle both the functional and structural abnormalities underlying CMD.

If the prevailing mechanism is smooth muscle cell hyper-reactivity, then old and new vasodilators (e.g. Rho-kinase inhibitors) might reduce the ischemic burden. In the patient subset in which the prevailing mechanism is vascular remodelling, ACE-inhibitors have been proved to be effective, particularly in hypertensive patients. In those cases where the prevailing mechanism is myocardial fibrosis, aldosterone antagonists and phosphodiesterase-5 inhibitors may be of help, and in the patients in whom the prevailing mechanism is advanced coronary microvascular rarefaction, cell therapy might have to be considered. Undoubtedly, and despite all the necessary future developments outlined above, to address coronary risk factors both the functional and structural abnormalities underlying CMD.

In conclusion, we advocate action to develop appropriate diagnostic and therapeutic strategies for tackling these ‘new’ disease epidemics in the years to come.

Conflict of interest: none declared.

References

Successful transvenous cardiac resynchronisation therapy in a case of coronary sinus ostial atresia

David Wilson*, Nauman Ahmed, Phoebe Sun, and Ihab Diab

Bristol Heart Institute, Bristol Royal Infirmary, Upper Maudlin St, Bristol BS2 8HW, UK
* Corresponding author: Tel: +0117 346567, Fax: +0117 3425926, Email: David.wilson45@nhs.net

A 42-year-old male with non-ischaemic dilated cardiomyopathy, sinus rhythm, LBBB morphology (QRS duration 150ms), New York Heart Association class III heart failure symptoms and recurrent syncope with non-sustained ventricular tachycardia was referred for cardiac resynchronisation therapy with defibrillator (CRT-D) implantation. Implantation of the LV lead proved difficult due to inability to cannulate the coronary sinus (CS) ostium despite the use of multiple catheters and delayed acquisition coronary angiography (Supplementary material online, Videos S1 and S2). Computed tomography revealed a severe ostial stenosis (Panel A, arrow) and no evidence of a persistent left superior vena cava. Eventually, during a second procedure, an anomalous branch of the CS which drained into the high RA was cannulated with a Boston Scientific diagnostic fixed Josephson curve quadripolar catheter (Boston Scientific, San Jose, California, USA). Occlusive venography demonstrated a suitable lateral vein with extensive collateralization of the venous drainage into the RA but no drainage into the RA via the CS ostium which appeared as a blind pouch. (Panel B; Supplementary material online, Videos 3 and 4). A St Jude Medical QuickFlex™ Micro 125BT-86 IS-1 bipolar lead was delivered over the wire to a lateral target vessel. All electrical parameters were within normal limits, R wave 6.6mV, impedance 1500Ω and capture threshold 0.4V at 0.5ms. An LV lead was implanted via this collateral branch into a suitable lateral branch (Panels C, D, and E) allowing successful delivery of CRT (Panel F).

This is to the best of our knowledge the first reported case of successful delivery of an LV lead via right atrial accessory venous collateral in a case of CS ostial atresia.

Supplementary material is available at European Heart Journal online.

Published on behalf of the European Society of Cardiology. All rights reserved. © The Author 2016. For Permissions, please email: journals.permissions@oup.com.