Mini-Symposium

Advances in Coronary Microvascular Dysfunction

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Considerable focus has been directed towards coronary arterial disease in the management of coronary heart disease, however the coronary microcirculation plays a major role in the regulation of coronary blood flow. Thus while we have multiple medical and revascularisation therapies to treat large vessel coronary artery disease, therapies directed towards the microcirculation are very limited.

This review paper summarises important aspects of coronary microvascular dysfunction including (a) methods of assessment, (b) clinical classification of associated disorders, (c) possible pathophysiological mechanisms, and (d) potential therapies. Hence this will provide important background to advancing our understanding and management of coronary heart disease by targeting the coronary microcirculation.

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Coronary heart disease (CHD) is the most common form of heart disease in Australia, with a self-reported prevalence of 1.9% [1]. It is the single largest cause of death in Australians and is predicted to become the single leading health problem for the world by 2020. In addition to the alarming mortality associated with CHD, there is considerable morbidity with 2.5% of all hospitalisations attributable to this disorder [1].

Considering the prevalence and impact of CHD on the community, substantial research and clinical efforts have been directed towards the diagnosis and management of this condition. The advent of selective coronary arteriography has provided significant insights into this disorder and is the cornerstone of coronary revascularisation therapies. Its predominance in the management of CHD has prompted a focus on epicardial coronary artery disease with little attention to the coronary microcirculation. While revascularisation therapies directed at obstructed epicardial vessels have been very effective in alleviating CHD associated symptoms, a recent Australian survey demonstrated that almost a third experience persistent angina regardless of contemporary anti-anginal therapies [2].

Although the clinical focus has been on the large coronary arterial system, it is noteworthy that these epicardial vessels normally contribute <10% of the coronary vascular resistance and only become of haemodynamic significance when >70% of the arterial lumen is obstructed [3]. In contrast, the coronary microvasculature is responsible for more than 70% of the coronary resistance under physiological circumstances [4]. Thus, further advances in the management of CHD will be dependent upon improving our understanding and developing therapeutic strategies for the treatment of coronary microvascular dysfunction. Hence the purpose of this Cardiac Society of Australia and New Zealand Annual Scientific Meeting session was to examine the role of coronary microvascular dysfunction in cardiac disease with a particular focus on its clinical manifestations, underlying pathophysiology mechanisms and therapeutic strategies.

Before embarking on a discussion concerning coronary microvascular dysfunction, it is important to understand the methods employed in evaluating the coronary microcirculation and the physiological concepts that have been derived from such investigations. These are addressed below.

Understanding the Coronary Microvasculature

There are several unique aspects to the coronary circulation that are a consequence of the contractile myocardium it supplies. These include being responsible for its own perfusion pressure, blood flow occurring predominantly in diastole rather than systole, and having a reversal of flow in the subendocardial layers during systole. Hence

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Table 1. *Clinical Techniques Frequently Utilised to Evaluate Functional Abnormalities in the Human Coronary Microvasculature.*

Assessment of myocardial ischaemia
Electrocardiograph (stress ECG test)
Positron emission tomography (metabolic tracers)
Magnetic resonance spectroscopy
Transmyocardial metabolic studies
Myocardial perfusion techniques
Myocardial scintigraphy
Positron emission tomography (blood flow tracers)
Magnetic resonance imaging
Contrast echocardiography
Angiographic myocardial blush
Coronary blood flow techniques
Coronary sinus thermodilution
Intracoronary Doppler flowire
Angiographic frame count
Doppler echocardiography

this circulation warrants special consideration, yet is very difficult to evaluate considering these properties.

Assessing the Coronary Microvasculature

The current coronary imaging technologies that are clinically available are unable to image vessels that are less than 0.5 mm in diameter and thus the human coronary microvasculature cannot be imaged *in vivo*. Consequently, sophisticated imaging techniques in anaesthetised animal studies have provided important fundamental insights into the coronary microcirculation. However, these studies are limited by their invasive nature, species differences and inability to adequately examine coronary disease states.

Endomyocardial biopsy studies allow visualisation of diseased and healthy vessels less than 0.2 mm but the slightly larger microvessels that play a major role in regulating coronary blood flow are not accessible via this endocardial approach. Furthermore, the selected biopsy areas may not be representative of the microvascular disorder particularly if the underlying pathology is patchy in nature. As morphological approaches to evaluate the microcirculation are extremely limited, functional methodologies must be employed and thus our understanding of the microcirculation is largely on a functional rather than anatomical basis.

Haemodynamically, the coronary microcirculation is the major site regulating myocardial blood flow and thus nutritive perfusion in the healthy human heart. Thus, myocardial blood flow may be utilised as a surrogate marker of microvascular function in the absence of obstructive epicardial coronary artery disease. Hence most clinical investigations of the coronary microvasculature must be confined to patients without significant epicardial coronary artery disease. Therefore, unfortunately, patients who have co-existing epicardial and microvascular disease cannot be fully evaluated utilising these techniques.

Table 1 summarises functional studies used to evaluate the human coronary microvasculature. They include techniques evaluating (a) the presence of myocardial ischaemia, (b) coronary blood flow and (c) myocardial perfusion, which all allude to coronary microvascular dysfunction in the absence of obstructive epicardial coronary artery disease. These techniques vary in complexity from simple non-invasive qualitative procedures to invasive quantitative measures requiring highly specialised equipment. They typically utilise the principle of an inappropriate response to standard provocative stimulus (exercise or pharmacological provocation) whether this be the induction of ischaemia, a perfusion defect or an inadequate coronary blood flow response. This later response is referred to as Coronary Flow Reserve (CFR) and is calculated as the ratio of maximal blood flow during near-maximal coronary vasodilatation with i.v. adenosine or dipyridamole divided by resting flow. A full discussion of the utility and limitations of the various techniques is beyond the scope of this review and has been extensively discussed by other authors [5].

Physiological Principles of the Coronary Circulation

Traditionally, the coronary circulation is considered as having two functional components, namely conduit epicardial coronary arteries (0.5–5 mm in calibre) which provide little resistance to flow, and the resistance microvessels (0.01–0.5 mm in calibre) which supply the single-layered capillaries (0.01 mm in calibre) where gas and nutrient exchange occurs. This traditional 2-compartment model has been superseded by a 3-compartment model following the appreciation that there are two types of resistance vessels [6].

The resistance microvessels are responsible for 60% of the total coronary resistance and include small arteries (or pre-arterioles) and arterioles. The arterioles are typically 0.01–0.1 mm in calibre and influenced by the surrounding metabolic milieu. Thus, in response to accumulated waste products, arteriolar vasodilatation will occur thereby increasing local blood flow. Besides this metabolic vasodilatory response, other important regulatory mechanisms in these microvessels include (a) autoregulation which maintains constant flow to the capillary bed despite proximal changes in perfusion pressure (K_{ATP} channels are believed to be pivotal in this process), and (b) myogenic control where increases in intraluminal pressure are detected by vascular wall stretch receptors and result in arteriolar dilation.

The pre-arteriolar vessels (typically 0.1–0.5 mm in calibre) also play a major role in coronary resistance but are influenced by different regulatory mechanisms to those described above. Unlike arterioles, the pre-arterioles are not exposed the local metabolic environment and thus the metabolic vasodilatory response is not evident in these microvessels. In contrast, the pre-arterioles are influenced by similar mechanisms regulating the large epicardial vessels including (a) sympathetic innervation and (b) endothelium-dependent shear stress responses. The sympathetic nerve responses in the pre-arterioles are mediated not only via alpha-1 adrenoceptors (as in the epicardial vessels) but also via alpha-2 adrenoceptors [7]; thus providing a potentially novel pharmacological target for these vessels.