Coronary atherosclerosis: extending to the microcirculation?

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Online publish-ahead-of-print 18 February 2010

This editorial refers to ‘Coronary microcirculatory vasodilator function in relation to risk factors among patients without obstructive coronary disease and low to intermediate Framingham risk score’†, by R. Rubinshtein et al. on page 936

The coronary circulation, responsible for the delivery of oxygen and other nutrients to the myocardium, is a complex system of conductance and resistance vessels. Each has its own mechanisms of dynamic regulation of its calibre through changes in the contractile state of the underlying smooth muscle. In addition, each plays a different role in determining myocardial perfusion in health and disease.

The larger epicardial coronary arteries normally offer no significant resistance to blood flow and thus contribute little to the adaptive response of the coronary circulation to the physiological changes in myocardial oxygen demands that occur, for example, during exercise. However, they are the site for the development of coronary atherosclerosis, the best known and most dreaded form of ischaemic heart disease. That atherosclerotic obstructions of the epicardial coronary arterial lumen contribute to the occurrence of myocardial ischaemia and necrosis is easily demonstrable and well accepted. In fact, the diagnosis of ‘coronary artery disease’ is conventionally applied only to patients who are shown to have significant narrowing of one or more major epicardial coronary artery. Although controversies persist regarding their optimal utilization, there is a large armamentarium of therapies available to treat patients with severely narrowed epicardial coronary arteries. These include multiple medications, and percutaneous and surgical revascularization, in many instances supported by the results of randomized clinical trials demonstrating their relative efficacy.

The smaller coronary arteries (i.e. too small in calibre to be visualized by angiography) constitute the coronary microcirculation and are those that normally offer significant vascular resistance. Consequently, it is the changes in the calibre of these smaller vessels that determine coronary blood flow and thereby the appropriate matching of myocardial oxygen demands with myocardial perfusion. Within the coronary microcirculation, it is important to recognize the difference between the pre-arterioles (ranging from 100 to 500 μm in diameter) and the microarterioles (<100 μm). The former (similar to the epicardial vessels) are under endothelial vasomotor control1,2 and, since they are extramyocardial, are not regulated by local metabolites. Unlike the epicardial vessels, the coronary pre-arterioles normally contribute to vascular resistance and therefore changes in their calibre participate—to some degree—in the regulation of myocardial blood flow. The smaller microarterioles are those that normally provide most of the vascular resistance and thus are most important for changes in coronary blood flow. The microarterioles are probably not under endothelial vasomotor regulation and largely respond to the local concentration of metabolites produced in varying amounts by the surrounding myocytes according to their energy expenditure.3 This mechanism allows for finely tuned autonomic regulation that becomes critical when myocardial perfusion is threatened by selective narrowing of an epicardial coronary artery. For a more detailed discussion of the coronary microcirculation in different disease states, the reader is referred to the excellent article by Camici and Crea.4

In contrast to the syndrome of coronary insufficiency due to significant atherosclerotic narrowing of the epicardial coronary arteries, the role of abnormalities of the microcirculation as a cause of heart disease is less well established, except in the primary or secondary forms of cardiomyopathy, and perhaps as the mechanism to explain the ‘no-reflow’ phenomenon in acute coronary syndrome. Indeed, it has been traditionally accepted that the microcirculation is not affected by the atherosclerotic process. The term ‘syndrome X’ has been applied to the occurrence of chest pain and exercise-induced ST-segment depression in the absence of significant luminal narrowing of the epicardial coronary arteries.5 Later, the term microvascular angina was coined to impute the occurrence of chest pain and certain findings, such as increased lactate production, to presumed abnormalities of the coronary microcirculation.6 However, consistent evidence of myocardial ischaemia in the large group of patients presenting

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† doi:10.1093/eurheartj/ehp459

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with chest pain but no significant stenoses on the coronary angiogram remains elusive. Further, certain findings are difficult to reconcile with an ischaemic aetiology of the chest pain syndrome, including the lack of contraction abnormalities even during pain provocation, the observation that similar symptoms can be elicited by electrical stimulation of the right ventricular endocardium, and the observation that at least some of these patients have abnormal central pain perception. However, whether abnormal function of the coronary microcirculation leading to myocardial ischaemia is the phenomenon that explains the presence of chest pain in all patients without epicardial coronary stenoses is far from conclusively demonstrated. Largely as a consequence of this, there is no universally accepted therapy for the treatment of these patients.

An important element in our current understanding of coronary physiology and pathophysiology is the role played by endothelial cells in the regulation of coronary vascular biology. The endothelium not only modulates vascular tone through the release of a variety of molecules known as endothelium-derived factors, but is also central in other key processes, such as leucocyte adhesion and migration, lipid oxidation, and platelet aggregation, that are critical to the development of atherosclerosis. All of the conditions associated with the premature development of atherosclerosis, such as hypercholesterolaemia, hypertension, smoking, and diabetes, have been associated with endothelial dysfunction, a term broadly applied to the demonstration of an abnormality in one or more of the variables that reflect the role of the endothelium in vascular biology. Impaired vasodilation in response to endothelium-dependent agents has been previously demonstrated at the level of the epicardial coronary arteries (measured using quantitative coronary angiography) and at the level of the microcirculation (assessed indirectly as the coronary blood flow response to endothelium-dependent agents). These abnormalities have been reported in patients with coronary atherosclerosis and in those with risk factors, even in the absence of narrowing of the epicardial coronary arteries. Thus, an impairment of endothelial function could have two important untoward consequences in the coronary circulation: first, as the mechanism preceding and leading to the development of atherosclerosis of the epicardial vessels, and secondly, as a mechanism responsible for vasocostriction—or reduced vasodilation—of the segment of the coronary microvasculature under endothelial control (i.e. the pre-arterioles).

Rubinstein et al. have reported an independent association between the Framingham risk score (FRS) and the vasodilator function of the coronary microvasculature. Briefly, the authors found that patients without significant epicardial coronary stenoses and lower coronary blood flow response to the endothelium-dependent vasodilator agent acetylcholine had a tendency to have a higher FRS ($P = 0.076$). In addition, patients with reduced coronary flow reserve in response to adenosine, generally regarded as an endothelium-independent agent that probably tests the behaviour of the microarterioles, had a higher FRS, an association that was statistically significant in multivariable analysis ($P < 0.001$). As indicated above, previous studies had reported the finding of impaired coronary microvascular function in patients with risk factors. The present study extends those observations using the commonly applied FRS to a large population of patients ($>1000$) with low to intermediate risk (i.e. FRS $<20$%). Given the large number of patients included and the meticulous measurements performed by an experienced group of investigators, this study is important in confirming the presence of functional abnormalities at the level of the microvasculature in patients at risk for atherosclerosis. Although no control group of subjects was included to ascertain what values should be considered ‘normal’, the association described above supports the concept of ‘abnormal’ function in patients with higher FRS. More difficult to understand is the relevance of these findings with regard to the patients’ clinical presentation. The authors do not provide information regarding the presence or absence of angina-like symptoms. One could assume that all these patients had chest pain (otherwise a coronary angiogram would not have been performed); however, only one-third had previously used nitrates. Further, the association between use of nitrates (presumably a marker of symptom severity) and coronary vasodilator function was not reported. Hence, these findings could not be used to support a microvascular abnormality as the cause of chest pain in patients without epicardial stenoses.

Imbedded in the authors’ methodology is the performance of an invasive study to assess coronary endothelial function. This, however, is not an accepted clinical indication and should be reserved for the context of experimental studies performed as part of approved research protocols. Although impaired endothelium-dependent coronary vasodilation of the epicardial and microvasculature has been associated with adverse risk, there is no demonstration that any form of therapy should be initiated or titrated based on the results of endothelial function studies. It is clear that intensive risk factor modification should be pursued in all appropriate patients, but there is no evidence to lend support to the concept that, for example, the blood pressure or lipid level targets should be any different according to the vasodilator response of the coronary microvasculature to endothelium-dependent or—indeed—agents. Hence, a dedicated assessment of endothelial function (particularly if invasive) to guide therapy is, in my opinion, not yet ready for prime time in the clinical arena.

A potential implication of the findings reported by Rubinstein et al. is that the impaired vasodilator response is an indication of early atherosclerosis not yet apparent in the epicardial vessels. However, how can we rule out that the epicardial coronary arteries of their patients were indeed free of atherosclerosis? Would we derive the same conclusion if the FRS in these patients correlated with the vasodilator response of the epicardial coronary arteries to acetylcholine? In fact, many previous studies would suggest that this is indeed the case. Further, results from the Women’s Ischemia Syndrome Evaluation (WISE) study showed that, when studied in the same patients, the prognostic value of impaired epicardial endothelium-dependent vasodilation is greater than that of reduced microvascular responses. Thus, rather than representing early atherosclerosis, it is more likely that these functional abnormalities of the coronary microvasculature signify an epiphenomenon of the atherosclerotic process.
that extends beyond the traditional and well known localization in the epicardial vessels. This unifying hypothesis would support the concept of diffuse involvement of the coronary vasculature in atherosclerosis and incorporate the findings of impaired vasodilator function as part of the spectrum of vascular abnormalities associated with this condition.

In summary, the coronary microcirculation is a complex array of vessels that play a critical role in the physiological regulation of myocardial perfusion. However, its causative contribution to myocardial ischaemia in non-cardiomyopathic disease states is not so well established. Reduced vasodilation of the coronary microvessels has been reported in several previous studies of patients with risk factors with or without luminal narrowing of the epicardial arteries, including the report by Rubinshtein et al.16 These observations suggest that the microcirculation is part and parcel of the process of coronary atherosclerosis. Nevertheless, focusing on the coronary microcirculation is still a disappointing task for the clinician as the independent value of that information and how to use it to improve quality of life or prognosis remain a matter of uncertainty. Therefore, continued investigation is needed to unravel the precise mechanisms that explain the abnormalities of the coronary microvasculature, to understand their role in different ischaemic syndromes, to reach consensus about definitions, and ultimately to discover therapies that modify the disease process specific to the microcirculation.

Conflict of interest: none declared.

References