How important is microcirculation in clinical practice?

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KEYWORDS: Coronary disease; Coronary spasm; Microvascular coronary dysfunction; Myocardial ischaemia; Angina pectoris

Patient with chronic angina have an increased risk of adverse cardiovascular events. These patients also have an increased risk of complications with consequent higher healthcare expenditure. Furthermore, angina symptoms can considerably limit daily activities, quality of life, and often cause early retirement.

Angina pectoris is caused by myocardial ischaemia, and for more than two centuries epicardial atherosclerotic coronary artery disease (CAD) has been recognized as its main cause. The clinical manifestations of chronic CAD are secondary to the progressive decrease in tissue perfusion due to the growth of plaques inside the vessel lumen and the consequent reduction of the coronary flow reserve (CFR), that is, the ratio between blood flow during maximal coronary vasodilation and resting flow. The clinical demonstration of the CFR reduction is ischaemia from increased oxygen demand and effort angina.

The non-invasive tests for inducible ischaemia, such as nuclear perfusion imaging or stress echocardiography, could demonstrate reversible regional perfusion abnormalities or impaired myocardial contractility usually confirmed by ST-segment depression on the electrocardiogram (ECG). Coronary angiogram usually demonstrates one or more stenoses in the epicardial coronary arteries with more than 70% lumen reduction.

Some patients, however, do not manifest the classical angina symptoms. Angina can occur at rest, rather than with effort, during night-time, in bouts, and the stress test could be normal. The ECG during the angina episode could reveal an elevation of the ST-segment when the focal stimulus is >90%, determining trans-mural ischaemia. When the stimulus is not focal, but still >90%, and affects one or more segments of the vessel, it determines subendocardial ischaemia, and the ST-segment on the ECG is depressed. In a good number of these patients, CAD could coexist (Prinzmetal variant angina). Ong et al. studied a large cohort of consecutive patients (921) undergoing coronary angiogram for suspected myocardial ischaemia, but without evidence of obstructive CAD. All patients underwent acetylcholine provocative test, and the documented overall frequency of epicardial coronary arteries spasm was 33.4%. Furthermore, 24.2% of the patients had evidence of microvascular spasm (angina and ECG ischaemic changes without epicardial coronary arteries spasm after acetylcholine infusion).

A significant fraction of patients undergoing coronary angiogram for angina has normal coronary arteries or non-obstructive CAD (stenosis <50%). A study by Cannon and Epstein, demonstrated that patients with chest pain and normal coronary arteries at angiogram, as compared to a group of asymptomatic controls, had an enhanced sensitivity to coronary microcirculation vasoconstrictive stimuli, and a limited microcirculatory vasodilatation response during pacing-induced atrial tachycardia; the condition was defined microvascular angina.

In its entirety, the coronary arterial system comprises three functional components, albeit not clearly distinct anatomically. The proximal component includes the large epicardial coronary arteries with a diameter between 2–5 mm and 500 μm; they function as capacitance vessels and offer little resistance to the blood flow. During systole, the epicardial coronary arteries increase their blood volume up to 25%, storing in this way elastic energy which is converted in kinetic energy at the beginning of diastole, thus contributing to the re-opening of the intra-myocardial vessels, compressed during systole. The intermediate component is represented by the pre-arterioles, with a diameter between 500 μm and 100 μm, and is characterized by pressure loss throughout its course. These vessels are not subject to the vaso-motor control by the myocardial metabolites due to their extra-myocardial localization and the thickness of their wall. Their specific function is the maintenance of pressure at the origin of the arterioles within a narrow range when the pressure or the coronary flow change. The proximal pre-arterioles react more readily to changes in flow, whether the distal pre-arterioles are...
more responsive to changes in pressure. The most distal compartment is represented by the intramural arterioles, with a diameter less than 100 μm, and is characterized by significant pressure drop throughout its course. At rest microvascular tone is elevated, allowing, during increase myocardial oxygen consumption, a rapid increase of blood flow through quick changes in the small vessels diameter, a mechanism known as functional hyperaemia. The drop of the arteriolar resistance spawns a series of vascular adjustments involving both pre-arterioles and small arteries. The initial arteriolar response is due to the close interaction between these vessels and the cardiomyocytes, representing the basis for the metabolic vasodilation.
The function of coronary microcirculation could indirectly be assessed with various techniques, both invasive and non-invasive, allowing measurements of various parameters, such as myocardial blood flow and CFR, which in normal circumstances are function of microcirculation integrity.

Clinically, the integrated use of non-invasive imaging with anatomical and functional invasive techniques provides for a detailed functional characterization and clinical definition of coronary microcirculatory dysfunction7 (Figure 1).

The term coronary microvascular dysfunction (CMD) offers a general definition, common to various clinical situations in which a reduced CFR along with evidence of myocardial ischaemia are not secondary to epicardial coronary artery stenoses9 (Figure 2).

Camici and Crea9 proposed a clinical classification of CMD into four main categories: Type 1—CMD without CAD or myocardial disease; Type 2—CMD in patients with evidence of myocardial disease; Type 3—CMD in patients with obstructive coronary disease; and Type 4—CMD after coronary revascularization, either surgical (coronary artery bypass graft), or percutaneous (percutaneous coronary intervention). This situation is also called iatrogenic (Table 1).

**Conflict of interest:** none declared.

### Table 1  Classification of coronary microvascular dysfunction

| Type       | Description                              | Risk factors                                                                 | Endothelial dysfunction               |
|------------|------------------------------------------|-------------------------------------------------------------------------------|---------------------------------------|
| Type 1     | No myocardial disease or obstructive CAD | Risk factors, Microvascular angina                                           | Endothelial dysfunction               |
| Type 2     | Myocardial diseases                      | Hypertrophic cardiomyopathy, Dilatative cardiomyopathy, Anderson-Fabry, Myocarditis, Aortic stenosis, Connective tissue disease | Vascular remodelling, SMC dysfunction, Vascular remodelling SMC dysfunction, Extramural compression, Lumen obstruction |
| Type 3     | Obstructive CAD                          | Stable angina, Acute coronary syndrome, PCI                                  | Vascular remodelling SMC dysfunction, Lumen obstruction, Lumen obstruction autonomic dysfunction |
| Type 4     | Iatrogenic                               |                                                                                 |                                       |

CABG, coronary artery bypass graft; CAD, coronary artery disease; PCI, percutaneous coronary intervention; SMC, smooth muscle cell.

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