Traditional and Novel Biomarkers for Coronary Microvascular Dysfunction

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Coronary microvascular dysfunction (CMD) is related to a broad variety of clinical scenarios in which cardiac microvasculature is morphologically and functionally affected, and it is associated with impaired responses to vasoactive stimuli. Although the prevalence of CMD involves about half of all patients with chronic coronary syndromes and more than 20% of those with acute coronary syndrome, the diagnosis of CMD is often missed, leading to the underestimation of its clinical importance. The established and validated techniques for the measurement of coronary microvascular function are invasive and expensive. An ideal method to assess endothelial dysfunction should be accurate, non-invasive, cost-effective and accessible. There are varieties of biomarkers available, potentially involved in microvascular disease, but none have been extensively validated in this heterogeneous clinical population. The investigation of potential biomarkers linked to microvascular dysfunction might improve the assessment of the diagnosis, risk stratification, disease progression and therapy response.

Keywords: coronary microvascular dysfunction ; endothelial dysfunction ; biomarkers

1. Definition and Pathophysiology

Coronary microcirculation is constituted by the vascular compartment of vessels with less than 500 μm diameter (pre-arterioles, arterioles and capillaries), which has a key role in the physiological modulation of cardiac perfusion. The endothelial monolayer can administer the exchange of fluids and metabolites and, furthermore, can manage vascular hemostasis. In case of a raised myocardial metabolic request, the coronary microvasculature modulates the peripheral vascular resistance and administrates the blood flow distribution that can reach a fivefold increase in healthy subjects [1].

Coronary microvascular dysfunction (CMD) relates to a broad range of clinical settings in which cardiac microvasculature is morphologically and functionally affected and it is associated with an impaired response to vasoactive stimuli [2].

Camici and Crea proposed a clinical–pathogenetic classification of CMD in four principal categories: (1) CMD in the absence of myocardial diseases and obstructive coronary artery disease (CAD), (2) CMD in myocardial diseases, (3) CMD in obstructive epicardial CAD and (4) iatrogenic CMD [2].

It is known that a wide spectrum of agents and cardiovascular risk factors such as chronic illness [3], diabetes, metabolic syndrome, smoking [4] and hemodynamic forces [5][6][7] can disturb the homeostasis of endothelial cells and thus determine CMD [8].

The endothelial dysfunction relies on four principal effectors: inflammation, platelet activation, hemodynamic forces and autonomic dysfunction.

Inflammation is inevitably connected with both microvascular endothelial dysfunction and atherosclerosis pathogenesis. CMD seems to be triggered by the low-grade inflammatory state such as epicardial coronary artery disease [9][10].

The endothelial cell activation, triggered by inflammation, increases the production of reactive oxygen species (ROS), enhances the expression of adhesion molecules promoting platelet and leukocyte adhesion and activation and leaks the endothelial barrier [11].

Platelet activation, microvascular thrombosis and distal embolization can affect endothelial microcirculation function, enhancing vasoconstriction and inflammation [12]. In this context, the interplay between platelet CD40L and endothelial CD40-receptor is a relevant trigger for inflammation and thrombosis [13].

Arterial hypertension can help elicit the atherosclerotic process both in epicardial arteries and in coronary microcirculation [14]. Shear stress and hemodynamic forces activate molecular pathways in the endothelium that can influence its structural and functional phenotype, resulting in microvascular dysfunction and injury [14].

The imbalance between the sympathetic and parasympathetic tone enhances vasoconstriction and endothelial damage of coronary microcirculation [15]. In general, adrenergic-derived vasoconstriction is relevant in clinical situations in which normal non-neural vasodilator mechanisms are impaired, such as dyslipidemia and diabetes, also involved in CMD pathogenesis [15].

2. The Current State of the Art for the Diagnosis of CMD

The gold standard for the diagnosis of CMD consists of invasive coronary functional tests [16].

First, a correct invasive assessment of coronary microcirculation is based on the examination of the endothelium-independent microvascular vasodilatation, estimated by both the coronary flow reserve (CFR) and the index of microvascular resistance (IMR). Second, the endothelium-dependent dysfunction can be evaluated by the response to intracoronary acetylcholine provocation test (ACh-test) [16][17][18][19][20][21].

The first mechanism is tested through intracoronary vasodilator injection (i.e., adenosine). CFR is measured as the ratio between the maximal coronary flow, after vasodilator-induced hyperemia, and the resting state. CFR reflects both epicardial and microvascular response [22].

IMR is the result of the multiplication of the distal coronary pressure with the mean transit time of saline flush at ambient temperature, in the context of adenosine-triggered hyperemia. IMR is specific for the assessment of the microcirculation, and it is not affected by resting hemodynamic state [23].

CMD is characterized by CFR values below 2.0–2.5 or elevated IMR, generally >25, and/or evident vasoconstriction in response to the ACh-test [16][17].

In addition, patients with CMD could exhibit a slow contrast flow on coronary angiogram, defined as the “coronary slow flow phenomenon”, because of an increased coronary microvascular resistance.

The Coronary Vasomotion Disorders International Study Group (COVADIS) established the international standardized diagnostic criteria of CMD based on clinical presentation, absence of obstructive epicardial coronary artery disease, evidence of myocardial ischemia through non-invasive testing and invasive assessment of impaired coronary microvascular function [16][17].

However, standard techniques to measure microvascular function (i.e., CFR, IMR and ACh-test) are invasive, laborious and costly [24]. Moreover, the functional assessment of CMD requires additional specific equipment and devices, not always available on routine coronary angiographies on a large scale.

Therefore, CMD is still an infrequent and often missed diagnosis, leading to the underestimation of its clinical importance. The prevalence of CMD seems to be on the rise, affecting about 50% of patients with chronic coronary syndromes and more than 20% of those with acute coronary syndrome (ACS) [1]. A post hoc analysis of a large cohort highlighted the unfavorable prognosis of patients with ACS without obstructive CAD: the incidence of adverse event rates at one-year follow-up was 15.5%, including 3.3% of death and acute myocardial infarction (AMI) [24].

In recent years, numerous non-invasive tests (e.g., transthoracic Doppler-echocardiography evaluating the coronary flow velocity reserve (CFVR), cardiac magnetic resonance (CMR), computed tomography coronary angiography (CTCA), positron emission tomography (PET)) have been indicated for the assessment of CMD [16]. However, most of them have some limitations (**Table 1**).

Table 1. Characteristics of non-invasive methods for coronary microvascular dysfunction assessment.

Modality	Agent	Pros	Cons
Transthoracic Doppler echocardiography	**Adenosine/Dipyridamole**	**Easily accessible. No radiation exposure.**	**Need previous rule-out of obstructive CAD. Operator-dependent.**

Modality	Agent	Pros	Cons
Myocardial contrast echocardiography	Echocardiographic contrast substance	No radiation exposure. Assessment of global perfusion.	Lacking availability of standardized commercial software. Operator-dependent.
Positron emission tomography (PET)	Adenosine tracer (15O-H2O, 13 Nammonia, 82 R(b)	Reference standard of non-invasive methods. Assessment of global perfusion at the same time.	Difficult availability. Expensive. Radiation exposure. Need previous rule-out of obstructive CAD.
Cardiac Magnetic Resonance (CMR)	Adenosine/Regadenoson Gadolinium-based substances	No radiation exposure. Assessment of global perfusion. Used in the setting of obstructive CAD and structural heart disease.	Difficult availability. Expensive. Nonlinear relationship of tissue contrast concentration and MR signal intensity. Need of specific protocol.
Computed Tomography (CT)	Adenosine/Regadenoson Iodine-based contrast agent	Assessment of global perfusion at the same time. Used in the setting of obstructive CAD.	Need of further validation. Radiation exposure.

In the first instance, despite a high positive predictive value, the sensibility of these methods is partially hindered by the differential diagnosis of obstructive CAD that is mandatory to be ruled out with prior use of invasive coronary angiography or CTCA. Moreover, these non-invasive diagnostic tests contemplate the exclusive use of vasodilators (e.g., adenosine or dipyridamole), and can only establish the coronary vasodilator capacity, limiting the discrimination of all the different subtypes of CMD.

In this complex clinical setting, the measurement of traditional and novel biomarkers linked to endothelial dysfunction could improve the assessment of risk stratification, diagnosis, disease progression and therapy response.

Indeed, genetic and epigenetic differences contribute to modulating the endothelial function both in healthy subjects and in patients with cardiovascular diseases. In this landscape, noncoding RNAs represent attractive new biomarkers for their potential applications in personalized medicine.

3. Traditional Biomarkers: Troponin and Natriuretic Peptides

Cardiac troponin (Tn) represents an already well-validated biomarker of heart damage, crucial for the diagnosis of myocardial infarction and injury, but also in many different conditions and diseases [25].

The role of Tn as a biomarker in CMD is, however, less established [26][27]. Several studies, therefore, tried to investigate the possible role of Tn in CMD.

Research by Takashio et al. on 58 heart failure (HF) patients revealed that troponin T (TnT) plasma levels were increased in cases of CMD compared to healthy controls [28].

Fujii and collaborators demonstrated that patients undergoing elective percutaneous coronary angioplasty (PTCA) had higher post-PTCA values of IMR when abnormal troponin I (TnI) levels were detected, therefore suggesting a significant microvascular dysfunction [29]. These findings were also corroborated by another study that, similarly, found an analogous correlation between post-PTCA IMR values and plasma creatine kinase MB (CK-MB) [30]. A different study conducted on 55 patients treated with PTCA highlighted the same association between post-PTCA CFR value and Tn levels [31].

Interestingly, a more recent study conducted on 19 patients with stable angina did not find any correlations between Tn levels and the invasive assessment of CFR and found an only poor correlation with IMR [32]. Lastly, a larger study by Taqueti et al. conducted on patients with suspected CAD reported that higher Tn values were predictive of reduced CFR compared to patients without Tn increase. The association of low CFR and high Tn levels was related to an increased incidence of major adverse cardiovascular events (MACEs) [33]. The non-unique results of these studies underline, once again, how the role of Tn is yet to be fully understood in predicting CMD.

Natriuretic peptides (NPs) are well-known diagnostic and prognostic biomarkers of HF [34] and have proved to be useful in clinical decision making and risk stratification for hospital readmission of HF patients [35]. Indeed, only a few studies associate NPs and CMD.

The two primary NPs are the atrial natriuretic peptide (ANP), released when atrial wall stretching occurs, and the brain natriuretic peptide (BNP), secreted by ventricular myocytes in case of volume overload. Furthermore, the N-terminal prohormone of BNP (NT-proBNP) has an established role and clinical use as a biomarker. Both NPs control fluid homeostasis, natriuresis and express dose-dependent vasoactive effects.

ANP is essential for endothelial homeostasis through autocrine and paracrine secretion. In subjects with a high-salt diet, the vasoconstriction of the microvasculature of the skin in response to low-dose ANP infusion was observed, with decreased capillary density and increased renal vascular resistance [22]. When higher doses of ANP were administered, it conversely resulted in skin vessel dilatation and blood pressure reduction [36].

Moreover, patients presenting both CMD and left ventricle (LV) diastolic dysfunction showed increased levels of plasma NT-proBNP compared to healthy subjects [37].

In patients affected by symptomatic hypertrophic cardiomyopathy without CAD, Knaapen et al. observed a reduced myocardial blood flow reserve (MBFR) assessed by PET as an index of microvascular dysfunction. In these patients, NT-proBNP was inversely correlated with MBFR [38]. Using a different technique, Mitchell et al. assessed the MBFR by CMR in patients without overt CAD and, once again, they found an inverse association between NT-proBNP levels and MBFR [39]. Taken together, high NT-proBNP plasma levels might be related to CMD.

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