Myocardial blood flow (MBF) must respond to changes in metabolic conditions and oxygen requests to meet the needs of myocytes and autoregulation plays a major role in the control of coronary circulation [1-3]. It has been demonstrated that as coronary artery was progressively narrowed, resting flow did not change at first, but maximal flow (achieved by injecting a vasodilator) decreased progressively [4, 5]. Coronary flow reserve (CFR) is the term used to describe the amount of additional blood flow that can be supplied to the heart over baseline blood flow. The absence of CFR implies maximal vasodilatation of the resistance vessels at rest and an inability to further increase MBF. Nevertheless, this approach has not been applied to routine studies because of its high cost and complexity. Recently, attempts to estimate CFR with single-photon emission computed tomography (SPECT) tracers have been made in order to obtain, with noninvasive methods, data for quantitative functional assessment of CAD. This review analyzes the relative merit and limitations of CFR measurements by cardiac imaging techniques and describes the potential clinical applications.

Keywords: coronary artery disease, coronary flow reserve, cardiovascular imaging.

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blood velocity is proportional to flow for a constant vessel area, CFVR may be calculated from the hyperemic flow divided by resting blood velocity in a vessel [22, 23]. In humans, a cut-off value of <2.0 was found to define a significant stenosis [24]. CFVR reflects the combined impact of epicardial and microvascular resistance on limiting hyperemic flow. Conditions affecting myocardial or microvascular properties such as age, left ventricular (LV) hypertrophy, diabetes mellitus, or myocardial infarction will affect the CFVR value, independent on epicardial coronary artery disease (CAD) [18]. Limitations of Doppler-tipped guide wire assessment of CFVR include the technical difficulty in obtaining reliable Doppler ultrasound scanning envelopes, variability in measurement with hemodynamic changes, and significant overlap between normal and abnormal measurements [25, 26].

**Pressure-derived method**

With this method flow reserve can be evaluated by using pressure-tipped catheters that are small enough to pass coronary lesions. The use of side-hole catheters is possible, but only if intravenous rather than intracoronary vasodilators are used [14, 27]. Two types of flow reserve, namely coronary FFR and myocardial FFR, can be estimated. Myocardial FFR is defined as the maximal flow in the myocardium supplied by the stenotic artery, divided by the theoretical normal maximal flow in the same region distribution in the absence of stenosis. Coronary FFR is defined as the maximal flow through the stenosis divided by the maximal flow in the same artery without stenosis, excluding collateral blood flow. The difference between myocardial FFR and coronary FFR yields collateral FFR, the fractional collateral flow [28]. In the attempt to overcome the intrinsic limitations of coronary reserve assessment by invasive techniques, technical developments have produced a guide wire equipped with both a pressure and Doppler velocity sensor that allows simultaneous assessment of both stenosis and microvascular hemodynamic [29].

**Echocardiographic based techniques**

Recently CFR has entered the echocardiography laboratory, with the combination of coronary flow assessment by Doppler and vasodilator stress. With transesophageal (TEE) (sampling proximal tract) or transthoracic (TTE) echocardiography (exploring mid-distal tract), the coronary blood flow velocity profile recorded with pulsed wave Doppler is consistent with the pathophysiological premises. Accordingly, coronary flow velocity by Doppler assessment appears to be biphasic, with a lower peak during systole and a higher peak during diastole. Myocardial extravascular resistance is higher in systole and lower in diastole due to the effect of myocardial contraction. The flow velocity variations are proportional to the total blood flow if the vessel lumen is kept constant, a reasonable assumption with the administration of drugs such as dipyridamole or adenosine. The coronary flow velocity variation between the baseline and peak effect of a coronary vasodila-
tion. Estimates of global and regional myocardial perfusion reserve are calculated dividing the perfusion values for the stress studies by the corresponding values for the rest studies [33-36]. Low resolution-related factors, such as scatter, attenuation and partial volume effect, hamper the absolute quantitation of both arterial and tissue counts, but they may be canceled out by computing the ratio of tissue and arterial counts. A good correlation between CFR values estimated by SPECT imaging and those measured by intravascular Doppler ultrasound in patients undergoing percutaneous coronary intervention has been demonstrated [35]. SPECT imaging has also shown good reproducibility for both global and regional CFR assessment [35]. These findings support the concept that SPECT may compete with other modalities for CFR estimation. This technique has been also previously validated by comparison with PET imaging. In particular, CFR measured by SPECT was well correlated with PET data, despite some underestimation at higher flow rate [36]. The reasons for this underestimation could be due, in large part, to the limited extraction of SPECT traces at high blood flow. This limitation is characteristic of any extractable flow tracer in that the amount of tracer extracted is limited by flow only at low flow rates and plateaus at high flow rates, at which the extraction of the tracer becomes limited by membrane transport [39].

### Cardiac PET

PET with oxygen-15 water is the noninvasive gold standard for obtaining quantitative regional blood flows; absolute regional CFR is computed by the stress-rest ratio of flows calculated by quantitative, compartment analysis [40-43]. The measurement of CFR has also been performed by means of PET with other tracers, using either generator produced Rb-82 or cyclotron-produced N-13 ammonia. This approach acquires data in list mode over 2 min after intravenous injection. From these data, a single image of myocardial uptake and a single image of arterial input function are reconstructed. It therefore has the advantage of simplicity for routine application compared to compartmental analysis using multiple serial PET images. Because of its ability to provide non-invasive regional absolute quantification of MBF, PET has been widely used to assess CFR in healthy volunteers [44, 45], in asymptomatic subjects with cardiovascular risk factors [46, 48], in patients with CAD [49], and other cardiac diseases [50-52]. The ability to make quantitative measurements of MBF with PET allows determination of the functional significance of epicardial coronary lesions. In patients with single-vessel CAD, chronic stable angina, and no previous history of myocardial infarction, CFR in response to a standard dose of dipyridamole was found to be markedly reduced in the myocardial regions supplied by the stenosed coronary artery compared with those regions supplied by angiographically normal vessels [53]. Other studies with PET evaluated the relationship between stenosis severity, measured by quantitative coronary angiography, and regional MBF and CFR [54]. Different from the canine model [55], one study showed that in humans resting MBF was preserved up to 95% diameter stenosis.(49) Similar to the studies in dogs, the hyperemic response to dipyridamole and adenosine became attenuated at >40% diameter stenosis and was abolished at >80% stenosis [49, 54]. Although the inverse relation between stenosis severity and CFR was highly significant, a certain degree of variability was observed mainly at stenoses of intermediate severity. Variability was significantly less when minimal coronary resistance was plotted against stenosis severity, indicating the importance of accounting for inter-individual differences in perfusion pressure [49].

### Cardiac magnetic resonance imaging

Previous studies have shown the usefulness of qualitative assessment of cardiac magnetic resonance imaging (MRI) perfusion for the diagnosis of CAD [56]. Semiquantitative methods to analyze MRI perfusion data have been developed in an attempt to provide a more objective imaging interpretation. Semi-quantitative parameters include maximum up-slope or the peak-intensity. Up-slope index yields a high diagnostic accuracy for detection of CAD using semi-quantitative parameters. The value of up-slope index to evaluate severe hemodynamically significant CAD defined by angiography and FFR has been demonstrated [57]. However, the standard method to quantify myocardial perfusion with MRI has not been established. A quantitative approach, which defines myocardial perfusion reserve, using a deconvolution technique, has recently been validated and utilized in clinical research protocols [58]. Constrained deconvolution analysis using a Fermi function was applied to the first pass curves and provided an adjusted or absolute MBF measurement. The initial amplitude of the Fermi function has been shown to correspond to absolute MBF. Perfusion reserve is calculated as the ratio of MBF at maximal hyperemia divided by the MBF at rest [58]. The reproducibility of quantitative MRI first pass imaging has also been reported and showed a good intra- and interobserver agreements [59]. One should expect that the threshold to differentiate normal from abnormal perfusion in a given coronary territory should take into account the population being tested. It is possible that different cutoff values should be applied to different patient subsets such as diabetics and multivessel disease. MRI perfusion indexes rely on adenosine as the pharmacological stimulation and may also be affected by endothelial dysfunction and the microcirculation status. The benefit of a non-invasive highly sensitive diagnostic approach to detect CAD, which does not require ionized radiation or contrast agents and, therefore, can be repeated over time with minimal risk for patients, is unquestionable. However, maturation of medical technologies takes time and further studies are needed to further establish the value of MRI to screen, detect and localize hemodynamically significant CAD, and define the prognostic implications of MRI findings.

### Potential clinical applications of CFR evaluation

One potential clinical use for quantitative measures of MBF and CFR is to determine the adequacy...
of the hyperemia achieved during pharmacologic stress perfusion imaging with adenosine or dipyridamole. In addition, quantitative measurements of CFR could serve to enhance the detection of coronary stenoses in patients with balanced multivessel CAD. Conversely, in patients without balanced disease, quantitative estimates of CFR might improve the sensitivity for determining the extent of CAD. Among patients with cardiac risk factors who do not have significant stenoses on angiography, those with reversible SPECT perfusion defects are more likely to have endothelial dysfunction, as evidenced by diminished brachial artery reactivity, than those without stress-induced perfusion abnormalities [60]. Pellegro et al. [61] assessed the relationships between brachial artery flow-mediated dilation and CFR in patients with peripheral artery disease without cardiac symptoms and with normal stress SPECT imaging. Their results showed that the impairment of endothelium-dependent vasodilatation in coronary arteries can be demonstrated in patients with peripheral artery disease and that compromised CFR is related to the degree of peripheral artery dysfunction. In diabetic patients, coronary vasodilator capacity may be reduced even in the presence of normal coronary arteries [62, 63]. In these patients the impairment in hyperemic flows is multifactorial and reflects microvascular disease, endothelial dysfunction, abnormalities in regional sympathetic innervations, or the direct effects of glucose and insulin on coronary flow [64-68]. In patients with angina, coronary angiography may reveal normal or near normal epicardial coronary arteries [69-72]. Transient myocardial ischemia, in the course of spontaneous or provoked angina, accounts for cardiac-based pain in this subset of patients [73-75]. The evaluation of the human coronary microcirculation is only indirect and relies on assessing parameters, such as MBF and CFR, which reveal its functional status. Thus, in the absence of coronary artery stenosis, their measurement provides an index of microvascular function [76]. Also in patients with idiopathic dilated cardiomyopathy CFR can be impaired despite angiographically normal coronary arteries, which is attributable to coronary microvascular dysfunction [77, 78]. Finally, it has been recently demonstrated that noninvasive assessment of coronary vasodilator function with SPECT or PET is a powerful, independent predictor of cardiac events in patients with known or suspected CAD and provides incremental risk stratification over clinical and gated myocardial perfusion imaging variables [79, 80].

**ABBREVIATIONS LIST**

- CAD: coronary artery disease
- CFR: coronary flow reserve
- CFVR: coronary flow velocity reserve
- FFR: fractional flow reserve
- LV: left ventricular
- LAD: left anterior descending coronary
- MRI: magnetic resonance imaging
- MBF: myocardial blood flow
- PET: positron emission tomography
- SPECT: single-photon emission computed tomography
- TEE: transesophageal echocardiography
- TTE: transthoracic echocardiography

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