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REVIEW

Imaging techniques for assessment of coronary flow reserve

Metodiche di imaging per la valutazione della riserva di flusso coronarico

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ABSTRACT: ***Imaging techniques for assessment of coronary flow reserve. M. Petretta, W. Acampa, E. Zampella, R. Assante, M.P. Petretta, R. Cuocolo, I. Fabiani, G.L. Della Ratta, P. Perrone-Filardi, A. Cuocolo.***

The assessment of coronary flow reserve (CFR) may be useful for the functional evaluation of coronary artery disease (CAD). Invasive techniques, such as intracoronary Doppler ultrasound and pressure-derived method, directly assess CFR velocity and fractional flow reserve. Positron emission tomography (PET) has emerged as an accurate noninvasive technique to quantify CFR. 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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Myocardial blood flow (MBF) must respond to changes in metabolic conditions and oxygen requests to meet the needs of myocytes and *autoregulation* plays a mayor 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. Different terms are used to describe CFR [6, 7]. *Absolute flow reserve* is the ratio of blood flow during maximal hyperemia in a stenotic artery to blood flow in the same artery under resting conditions [8, 9]. The invasive, Doppler-based technique that measures coronary blood velocity at rest and during hyperemia and positron emission tomography (PET), that measures absolute MBF at rest and during hyperemia, are good examples of absolute CFR measurements. *Relative flow reserve* is the ratio of hyperemic flow in a stenotic artery to hyperemic flow in a normal artery [10, 11]. Myocardial perfusion imaging by single-photon emission computed tomography (SPECT) is based on this concept to demonstrate ischemia and identify significant coronary artery stenosis. *Fractional flow reserve* (FFR) is a term used to describe the ratio of the maximum achievable flow in the presence of a stenosis to the theoretic maximum flow in the same artery if the artery were normal [12, 13]. This is the basis of the pressure-derived method that is the invasive method of choice to determine the significance of a stenosis of moderate severity [14]. It must be considered that several factors influences CFR measurement, such as the ability to achieve maximal coronary vasodilatation, heart rate and myocardial contractility, right atrial pressure, serial coronary stenosis, coronary resistance, coronary collateral circulation [15-21]. Each of these factors has different impact according to the method used for CFR evaluation.

Intracoronary Doppler ultrasound

Doppler guide wires make it possible to calculate coronary flow velocity reserve (CFVR), which is the ratio between intracoronary mean velocity under baseline conditions and after pharmacological induction of maximum hyperemia.(6) Because

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 recoded 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 vasodilator allows a coronary flow reserve index in the left anterior descending artery territory to be derived. Peak diastolic flow is the simplest parameter to be measured and the most easily obtained, in addition to being the most reproducible and the one with the closest correlation with coronary perfusion reserve measured by positron emission tomography. The coronary flow signal on left anterior descending coronary (LAD) was first made possible by TEE with excellent diagnostic results [30], but more recently there has been an increase in clinical interest due to the development of the TTE method [31, 32]. Technological factors allow the non-invasive TTE imaging of mid-distal LAD: second harmonic imaging, with better definition of smaller structures, such as LAD; high frequency transducers (up to 8 MHz in second harmonic), leading to improved resolution imaging of near-field structures. The availability of contrast agents also improved the signal-to-noise ratio, thereby increasing the feasibility of TTE imaging of LAD above the threshold of potential clinical impact, although it is true that after a training period its use may not be necessary. The Doppler assessment of CFR has some limitations. The assessment of absolute blood velocity can be limited in some patients by the large incident angle between the Doppler beam and blood flow. However, calculation of the flow reserve allows assessment of flow patterns without the need for absolute values. More importantly, the velocity ratio is used as a surrogate of flow reserve: flow within the coronary artery is not calculated because cross-sectional visualization of the vessel does not allow an accurate measurement of the diameter of the vessel. The estimated flow reserve can be accurate if the coronary functions only as a conduit, without changing in diameter during drug infusion. This assumption is reasonable with dipyridamole and less valid with dobutamine: this is an additional reason to stress coronary flow reserve with vasodilators.

Cardiac SPECT imaging

Recently, attempts to estimate CFR with SPECT tracers have been made in order to obtain, with simple noninvasive methods, data for quantitative functional assessment of CAD [33-36]. A distinctive attribute of these studies is that SPECT myocardial perfusion imaging, a technique used in daily practice to assess relative myocardial perfusion, is used to obtain quantitative measurements of myocardial perfusion and perfusion reserve. The method used in these investigations is potentially open to implementation in most nuclear cardiology laboratories, and it could be adapted for general application [37, 38]. The procedure utilized for the estimation of CFR by radionuclide imaging is based on the microsphere method, considering that Tc-99m labeled tracers are taken up by myocardium according to blood flow. After intravenous administration of the tracer, anterior planar list-mode images of the heart are obtained and counts from a right pulmonary artery region of interest are used to estimate the arterial input function of the tracer. A quantitative estimate of tissue perfusion is derived dividing myocardial counts on the SPECT perfusion images by the integrated arterial input func-

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 a 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 P*et al*lows 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. Semiquantitative 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]. Pellegrino *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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