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EDITORIAL COMMENTARY

Estimation of coronary flow reserve by SPECT: myth or reality?

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Quantification of myocardial blood flow (MBF) has been an unresolved challenge since the earliest days of nuclear cardiology. Positron emission tomography (PET) is the only non-invasive method for absolute measurement of coronary blood flow, and experimental results with PET correlate well with flow measurements obtained using intracoronary microsphere techniques. Nevertheless, the methodology used for absolute quantification of regional blood flow is complex, requiring the development of specific calculation algorithms for each tracer and each type of equipment, and it has in fact never become widely applied in medical practice [1–3].

Clinical implications

Authors who perform MBF studies using PET have demonstrated the importance of knowing myocardial perfusion in a number of clinical situations in which baseline MBF and, in particular, its response to vasodilating stimuli must be monitored [4]. The ratio between baseline flow and flow at maximum vasodilation is known as coronary flow reserve (CFR). Early compromise of CFR is seen in diseases of the coronary wall. Primary or secondary endothelial dysfunctions initially appear in the form of an impaired vasodilation response. Even before the atheroma plaque produces a consistent reduction in coronary flow, the affected coronary segments show a reduced capacity to vasodilate when stimulated pharmacologically—for example, with adenosine. Furthermore, before the arterial disease manifests as visible changes on coronary angiography, or multidetector computed tomography detects the presence of soft or calcium plaques, apparently healthy anatomical regions can already show functional alterations that are not picked up by anatomical imaging techniques [5, 6].

Most studies on the effects of diet or drugs require imaging to evaluate the effect of a reduction of coronary risk factors on myocardial perfusion. In actual fact, assessing the efficacy of risk factors modification, the reduction of morbidity and mortality in large population is a long-term effort that might be undertaken using surrogate markers such as improvement in CFR. Such studies have been performed with PET methodology using the flow tracers ^{15}O-water or ^{13}N-ammonia [7–11], and have mainly focussed on the evaluation of microvascular abnormalities in patients with diabetes mellitus or hypercholesterolaemia while monitoring response to interventional strategies [12–16].

In the era of fibrinolytic therapy and primary angioplasty, the amount of salvaged myocardium after myocardial infarction has increased. More accurate evaluation of ventricular function and myocardial perfusion is required to determine appropriate management after acute coronary syndromes. Selective revascularisation by angioplasty is the most widely used procedure to restore coronary flow, but the rationale for therapeutic strategies should not be solely anatomical. Many studies have called for mandatory functional evaluation of myocardium at risk to permit a more targeted use of therapeutic coronary angiography [17–22].

In fact, two clinical situations can be used to exemplify the interest in detecting MBF modifications and CFR impairment:

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1. Although not a common pattern, diffuse coronary atherosclerosis can produce a homogeneous reduction in CFR that does not induce the appearance of focal perfusion defects on post-stress tomographic acquisitions. Under such circumstances, when MBF is severely compromised there are sufficiently indicative signs thereof: unmistakable electrographic changes indicative of ischaemia, clinical signs of low output, typical chest pain or changes on myocardial imaging such as increased pulmonary uptake, post-stress ventricular dilatation or a fall in the ejection fraction on post-stress gated SPECT [23–25]. In the case of less severe coronary disease, however, an insufficient global vasodilation response may occur that neither manifests clinically nor produces an alteration in left ventricular function, particularly when stress ECG is of no assistance, as in cases of abnormal baseline repolarisation or intraventricular conduction disorders.
2. Another disease that can lead to misinterpretation on myocardial perfusion imaging is dilated cardiomyopathy. Patients presenting left ventricle dysfunction and cavity dilatation constitute a diagnostic dilemma for non-invasive testing. Many patients present with myocardial perfusion defects and partial reversibility in antero-apical and infero-basal regions with apparent left ventricle cavity dilatation and myocardial wall thinning. No clear scintigraphic semiology seems to distinguish ischaemic and non-ischaemic patients with sufficient accuracy [26]. Demonstration of reduced coronary reserve in these patients might help in selecting candidates for coronary angiography with a view to diagnostic confirmation, and ultimately, selective revascularisation [27].

Technical considerations

For many years, quantification of myocardial perfusion imaging has been based on bull's eye or, more recently, 3D rendered presentation of myocardial activity normalised to maximal myocardial counts. Simple (visual) or more sophisticated methods have been used to assess differences between stress and rest images. In the 1980s, Cedars-Sinai and Emory methods used ^{201}Tl washout analysis as an indirect index of coronary reserve, a particularly useful approach in patients with balanced myocardial ischaemia [28–32]. Unfortunately, many factors concur in modulating the pharmacokinetics of ^{201}Tl, and vasodilatory capability of the coronary tree is not the only factor responsible for ^{201}Tl washout abnormalities.

With the introduction of technetium agents such as sestamibi and tetrofosmin, the quality of images improved, and use of gated SPECT became more widespread. At present these tracers are widely used in the assessment of myocardial perfusion, although they do not permit semi-quantitative analyses of tracer washout. The absence of significant redistribution of these tracers means that two injections, during stress and at rest, are required for testing. Consequently, only changes in the percentage of regional myocardial uptake with respect to the maximum can be used in comparing basal perfusion versus stress.

What is more, the relationship between myocardial uptake and the range of myocardial flow is non-linear. At high flow rates in particular, myocardial uptake ceases to be proportional to the rise in flow, and persists at a maximum, invariable level. Glover and Okada have experimentally determined that the distribution of technetium agents is linearly related to flow up to approximately 2.0 ml min^{-1} g^{-1} [33–35]. Yet perfusion agents underestimate flow impairment and the area of ischaemic regions, indicating a non-linear relationship between flow and myocardial uptake at low flow rates.

From the perspective of image acquisition systems, the limitations of SPECT in obtaining absolute measurements of tissue uptake are well known. Factors related to low resolution, such as radiation attenuation, scatter and partial volume effect, have limited the use of quantitative methods to assess physiological parameters in nuclear medicine. In fact, the majority of so-called quantitative methods are based on the ratios between target tissues and reference ones.

Storto et al. [36] analysed myocardial flow reserve in patients with chest pain and a normal angiogram using a new methodology proposed by Sugihara et al. [37], and later validated by Storto et al. [38] in a comparative study with the intracoronary Doppler technique. This method is based on the ratio between myocardial counts, obtained in short axis slices, and time integral first-pass tracer counts for the pulmonary artery as an estimation of MBF. Coronary flow reserve is expressed as the ratio of stress MBF to rest MBF. With this approach the aim is to obviate attenuation and scatter factors by comparing the same myocardial regions of the same patient under stress and at rest, assuming the same SPECT artefacts in the two acquisitions. The ratio of myocardial counts to first-pass activity in the pulmonary artery corrects for modifications of myocardial uptake induced by changes in cardiac output due to vasodilatory drugs such as dipyridamole or adenosine.

From a practical point of view, this new method permits a comparison of myocardial uptake at rest and at stress by normalising myocardial activity, adjusted for administered dose (activity at the pulmonary artery) and rate pressure (heart rate x systolic blood pressure). Although in reality MBF is not actually quantified, the difference in activity in the myocardium adequately represents CFR, just as the ejection fraction is obtained from end-systolic and end-diastolic counts in radionuclide ventriculography, irrespective of absolute ventricular volumes.

First-pass studies, however, have intrinsic difficulties. Bolus integrity is mandatory to obtain best-fit gamma function. Ten to twenty percent of Qp/Qs (pulmonary-to-systemic flow ratio) and ejection fraction studies are non-optimal owing to technical factors relating to injection or the characteristics of great vessel anatomy in the adult population. Leaving aside these difficulties, there are a number of methods for comparing flows, adjusting gamma functions to the first-pass curve in a vascular compartment. But up until now the activity under the curve ratios compared have always been from the same first-pass recording. The innovation proposed by this new method consists in comparing quantitative data from first-pass and from SPECT reconstructed images.

Although it might initially seem surprising to compare measurements of activity obtained using such different methods as a planar dynamic study and an image obtained by 3D reconstruction algorithms, the authors defend its validity inasmuch as the variables that could affect this ratio remain stable in both the baseline and the stress study. Probably aspects such as type of reconstruction (iterative, backprojection), pre- and post-processing filters and attenuation or scatter correction have an important influence on the accurate measurement of true myocardial counts. The real impact of these factors on the technique should be analysed in the future.

Method feasibility

In an earlier article, Storto et al. [38] proved the correlation of CFR measurement with this method and with the intracoronary Doppler technique (r=0.85, p<0.001). As expected, the limited extraction of ^{99m}Tc-labelled agents produced a myocardial retention plateau at high flow rates. In any event, the more relevant implications of CFR impairment in preclinical coronary disease or in diffuse coronary atherosclerosis are, in theory, confirmed by this method.

A number of questions still remain to be resolved, however; notably, the capacity to determine CFR in the coronary territories, use of this method to measure regional differences in flow reserve, and the ability to evaluate patients with previous myocardial infarction. Storto et al. analysed 14 patients with coronary artery disease, seven of whom had two- or three-vessel disease. Owing to the limitations of intracoronary Doppler technique, only one vessel was selected to compare intravascular velocities with ^{99m}Tc-sestamibi CFR estimation. No data on differences in CFR between normal or myocardial regions depending on coronary stenotic vessels were analysed, despite six regions being defined on the short axis slices. In a recent study [36], the same authors measured sestamibi myocardial uptake in two global ROIs at mediobasal and medio-apical levels. In consequence, CFR estimations represent modifications of the total myocardial mass, with average myocardial uptake changes in left ventricular segments.

The interesting findings obtained with this method warrant further study in other groups of patients in whom CFR assessment could be beneficial, such as those with multivessel disease, dilated cardiomyopathies, preclinical coronary atheromatosis or, of course, angina without significant stenosis. Confirmation of the effectiveness of this method in these populations could change the current strategy for workups of this kind in these patient groups, in whom exercise testing would be replaced by vasodilating drugs and a first-pass study with intravenous administration of a radiolabelled compound.

In any case, the introduction of methods to evaluate CFR offers a new perspective in the analysis of MBF by SPECT using ^{99m}Tc-labelled agents. Although measuring myocardial flow in absolute terms will be reserved for PET studies, the possibility of using myocardial perfusion imaging for CFR analysis could offer solutions to as yet unresolved issues in nuclear cardiology.

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