What is the role of cardiac PET in patients with ischaemic heart disease and significant left ventricular dysfunction?

Numerous prospective studies have demonstrated the clinical value of PET metabolic imaging in selecting those patients who would most likely benefit from a revascularization procedure. Within this population, PET studies are particularly useful in defining the subgroup who have viable segments in the setting of severe left ventricular dysfunction as these patients benefit most from a modest (>5%) increase in global ejection fraction following revascularization[1–4]. In this clinical setting, the accuracy of patient selection is critical as the overall risk of revascularization (PTCA or CABG) is high and unnecessary procedures should be avoided.

Since the relief of heart failure symptoms and the improvement in survival rates in patients with heart failure following successful revascularization mainly result from an improvement in global left ventricular function, the development of imaging techniques which can accurately predict functional recovery is important.

Most prior cardiac PET studies have based their prediction of viability on post-revascularization improvement (or non-improvement) in regional (as opposed to global) left ventricular function. This index has been used as the clinical gold standard to calculate sensitivity and specificity values. However, in the multicentre cardiac PET study reported in this issue by Gerber et al.[5], the authors measured changes in global cardiac function as the clinical gold standard for outcome. When comparing changes in global ejection fraction to regional myocardial glucose uptake as a marker of metabolic viability, a high overall accuracy for the prediction of viability was observed. The highest sensitivity (79%) and specificity (55%) values for predicting improvement in postoperative ejection fraction were found when three or more dysfunctional segments had a relative FDG uptake >45% of that of remote non-ischaemic myocardium. One of the explanations given by the authors for their rather disappointing specificity is that failure to improve function after revascularization may occur when the endocardium is necrosed and the epicardial rim of viable myocardium (causing the FDG uptake) is tethered by the subendocardial scar. In this context, the combined use of flow and metabolic measurements could have increased the specificity of their PET results. If a flow/metabolism PET scan had revealed either decreased flow and relatively preserved metabolism (mismatch pattern) or normal flow and normal metabolism, a recovery of function could have been expected. However, if a combined decrease of flow and metabolism (a PET match pattern, which may be due either to a chronic transmural or non-transmural infarction) was observed, no improvement in left ventricular contractility would have been expected after revascularization. In contrast, the situation encountered after an acute myocardial infarction would have been completely different. Functional recovery of viable subepicardial regions is an established mechanism of late improvement in both regional and global ejection fraction after an acute non-transmural infarction. This has recently been demonstrated in a study in which MRI tagging was used to quantify regional fibre strains, wall thickening, and ejection fraction 1 week and 3 months after an acute infarction. In this study, functional recovery occurred in PET match areas[6].

As in many other viability studies, the study by Gerber et al.[5] evaluated the recovery of left ventricular function for a time window restricted to between 2 and 6 months after revascularization. Sampling only this time frame may be inappropriate as it has been shown that both regional and global recovery of function after successful revascularization is progressive and follows a mono-exponential time course which is dependent on the extent of the established structural changes in the cardiomyocytes. Furthermore, studies in patients with chronic ischaemic heart disease which correlated PET findings with changes in myocardial ultrastructure have demonstrated the presence of viable myocardial cells with a variable loss of contractile material (sarcomere loss) in PET...
mismatch areas. It has been postulated that this loss of contractile apparatus is a consequence of the de-differentiation of the cardiac myocytes rather than a degenerative process\cite{7,8}. However, the loss of the contractile apparatus is more probably a reversible and protective response of the cardiac myocyte to the ischaemia. This then raises the question about the length of time required to reconstitute the normal cardiac contractile apparatus after return of normal tissue perfusion. Variations in the time course of recovery could be considerable and be responsible for the wide difference in recovery time differences noted in viability studies. In fact, it may be that follow-up periods of 1 year or even longer are necessary to allow the accurate evaluation of recovery of both regional and global left ventricular function after a revascularization procedure.

Non-invasive functional imaging techniques continue to play an important role in the evaluation of myocardial viability in everyday clinical practice. In medically treated patients who have severe global left ventricular dysfunction early after an acute myocardial infarction, the inference of regional myocardial viability, (as judged by increased thickening in the ‘at risk’ zone during a low-dose dobutamine infusion) is associated with a higher probability of survival. The higher the number of segments showing an increase in thickening following an inotropic infusion, the better the impact on survival. The presence of inducible ischaemia in this set of patients is also the best predictor of cardiac death\cite{9,10}. Pre-discharge low-dose dobutamine echocardiography has been shown to be an accurate method of detecting viable myocardium and predicting late segmental recovery after a myocardial infarction\cite{11}. The positive and negative predictive value of early low-dose dobutamine echocardiography in predicting functional recovery has been reported to be 76% and 92%, respectively\cite{11,12}.

Low dose dobutamine echocardiographic studies remain the most commonly used clinical methods for defining segmental viability in clinical practice. They are frequently applied in patients with ischaemic heart disease who have impaired left ventricular dysfunction. However, Szilárd et al., studying regional function in an experimental animal model of prolonged global LV ischaemia, found that in the setting of severe chronic global ischaemia, the left ventricular myocardium did not respond to a low dose dobutamine challenge\cite{13}. Yet this myocardium was consistently shown to be viable at post mortem study. Szilárd et al.’s findings, if validated in clinical practice, would suggest that functional studies may not be the optimal approach for defining segmental viability in ventricles with severe global dysfunction. In such ventricles, metabolic PET studies may be the only method of defining regional viability. Whether this caveat would also apply to chronically ischaemic segments in non-dilated ventricles, in which the contractile force induced in the ischaemic segment by a dobutamine infusion is unable to overcome the abnormally elevated wall stress is not known. If it were so, in ventricles with chronic severe regional ischaemia, inotropic provocation might also not predict segment viability and metabolic imaging may be the only method of predicting the possibility of functional recovery. A recent article by Pace et al.\cite{14} would appear to add weight to this argument as the authors confirmed a reduced accuracy for dobutamine echocardiography in patients with severely reduced global ventricular function.

In cases where ultrasound image quality is poor or where additional depiction of left ventricular anatomy and function at rest and during low-dose dobutamine stress is required, MRI studies offer an alternative imaging approach. Such studies may be especially useful in detecting viable segments in patients with severely impaired left ventricular function\cite{15}. Using dobutamine cine-MRI to study patients with severe ischaemic left ventricular dysfunction, Sechtem et al. found they could predict non-viable segments with a sensitivity of 79% and a specificity of 93%. In their study, postoperative changes in wall thickening were used as the gold standard. First-pass analysis increased these values to 97% and 96%; analysis of late enhancement with T1-weighted imaging, to 62% and 98%\cite{16}. Referring again to the discussion above, the loss of contractile material (sarcomere loss) in the cardiomyocytes of such patients with severe ischaemic left ventricular function may be responsible for any under-estimation of the amount of viable cells by either stress echocardiography or stress MRI.

In conclusion, in patients with severe ischaemic left ventricular dysfunction, the use of inotrope-based functional testing may not be the optimal approach for defining segment viability. In such patients, a metabolic tracer study may be necessary to correctly evaluate the myocardial viability. Moreover, it may also be necessary to continue the follow-up of regional left ventricular function over substantially longer periods of time to determine the exact time course and potential for functional recovery after successful revascularization.

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Conducting large-scale clinical trials of fibrinolytic therapy in ST-segment elevation acute myocardial infarction has become an international, global endeavour. It started 15 years ago with the Gruppo Italiano per lo Studio della Streptochinasi nell’Infarto Miocardico (GISSI)-1 trial, published in 1986. This trial recruited 11,806 patients in 17 months, of whom only a few patients were recruited outside Italy[11]. In the International Study of Infarct Survival (ISIS)-2 trial[13], co-ordinated in Oxford and published 2 years later, 10,974 (64%) of the 17,184 patients came from 14 countries outside the United Kingdom including North-America, Western Europe and Australia/New Zealand. More or less the same countries participated in ISIS-3[3]. In the GISSI-2/International trial[4], two new regions (countries) appeared on the scene: Israel and Argentina. In the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO)-I trial[5], for the first time, an Eastern-European country participated: Poland. In more recent trials, the relative contribution of Eastern Europe and South America increased significantly and new countries like South Africa, the United Arab Emirates and Turkey came on board.

References