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Prediction of improvement of ventricular function after revascularization

^{18}F-fluorodeoxyglucose single-photon emission computed tomography vs low-dose dobutamine echocardiography

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Aims To compare assessment of myocardial flow and glucose metabolism by single-photon emission computed tomography (SPECT) with low-dose dobutamine echocardiography in predicting improvement in regional and global left ventricular function after coronary artery bypass grafting.

Methods and results Thirty patients with regional wall motion abnormalities (mean ejection fraction 32 ± 19%) were studied with low-dose dobutamine echocardiography (5 and 10 μg . kg^{-1} . min^{-1}) and thallium-201/^{18}F-fluorodeoxyglucose(FDG) SPECT prior to surgery. For comparative analysis, a 13-segment model was used. Postoperative improvement was predicted if the echocardiogram showed that wall motion abnormalities were reversible during the dobutamine infusion and there was normal perfusion or relatively increased FDG uptake in perfusion defects (mismatch) in dyssynergic segments on SPECT. After surgery, ventricular function was reassessed. An echocardiogram was taken at the 3 month follow-up with the patient at rest. Regional wall motion had improved in 62/168 (37%) revascularized segments. In predicting functional outcome, low-dose dobutamine echocardiography reached a sensitivity of 89% and a specificity of 82%, with a positive predictive value of 74% and a negative predictive value of 93%, whereas for thallium-201/FDG SPECT these values were 84%, 86%, 78% and 90%, respectively. In patients with more than two viable segments on either technique, the wall motion score index, a surrogate of global ventricular function, improved significantly.

Conclusion For the optimal prediction of functional outcome, combined assessment of flow and FDG imaging is needed. Both thallium-201/FDG SPECT and low-dose dobutamine echocardiography appear comparable and similarly accurate in predicting improvement of left ventricular function after surgical revascularization.
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Key Words: ^{18}F-fluorodeoxyglucose SPECT, dobutamine echocardiography, myocardial viability.

Introduction

Assessment of myocardial viability is necessary for the optimal treatment of the rising number of patients with left ventricular dysfunction due to significant coronary artery disease. It has been demonstrated that in some patients coronary artery bypass grafting can improve left ventricular function, functional state and survival, even in the presence of severe left ventricular dysfunction[1–3]. The presence of residual viability in dyscontractile myocardial tissue has been used to explain improvement of left ventricular function after revascularization. However, it is likely that a 'critical mass' of viable tissue is necessary for functional recovery to occur.

Among the available techniques, positron emission tomography of myocardial perfusion and metabolism (using ^{18}F-fluorodeoxyglucose (FDG)) is considered the most accurate method for the identification of viable myocardium[4–15]. By detecting normal perfusion, perfusion–metabolism mismatches or matches, this technique is able to predict reversibility of

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regional as well as global left ventricular function[4–7]. However, this technique is of limited availability. To respond to the increasing demand for viability studies, other techniques have been proposed, including imaging myocardial FDG uptake with single-photon emission computed tomography (SPECT) using special 511 keV collimators[16–22], and low-dose dobutamine echocardiography[23–29]. These techniques are attractive from a clinical point of view, but they elucidate different cellular mechanisms of viability. The present study was designed to compare thallium-201/FDG SPECT and low dose dobutamine echocardiography in predicting improvement of regional and global left ventricular function after uncomplicated coronary artery bypass grafting.

Methods

Patients and study protocol

Thirty patients with stable left ventricular dysfunction (ejection fraction ranging from 13% to 50%; in four patients >45%) were prospectively enrolled in the present study prior to scheduled coronary artery bypass grafting. They fulfilled the following criteria: (1) history of myocardial infarction; (2) regional dyssynergy on resting echocardiogram; (3) no recent episodes of unstable angina; (4) no significant valvular disease. All had undergone coronary arteriography and contrast ventriculography. The decision to revascularize was based on clinical criteria and was taken before study entry. The results of the SPECT and low dose dobutamine echocardiography studies were withheld from the physicians managing the patients. Adequate revascularization of a dyssynergic segment was considered achieved if upon review of the operative report and the pre-operative coronary arteriogram, bypass grafts were placed to the major branches supplying the dyssynergic segments. Each patient gave informed consent to the study protocol that was approved by the ethical committees of the participating hospitals.

All patients underwent thallium-201/FDG SPECT and low dose dobutamine echocardiography within 1 week without intervening cardiac events. Beta-blockers were withdrawn 36 h before low dose dobutamine echocardiography; all other cardiac medication (e.g. calcium antagonists, nitrates, ACE inhibitors) were continued during both tests. To assess recovery of function, resting echocardiograms were obtained before and 3 months after coronary artery bypass grafting.

Thallium-201/FDG SPECT

First, myocardial perfusion was delineated using an early resting thallium-201 SPECT, as described previously[30]. A single dose of 111 MBq thallium-201 chloride was administered intravenously and imaging was performed 10 min after injection. Delayed thallium-201 images were not acquired. The FDG SPECT study was performed on the same day during hyperinsulinaemic euglycaemic clamping to standardize metabolic conditions[31], and guarantee good image quality even in patients with diabetes mellitus[32]. FDG (185 MBq) was injected after 60 min of clamping; another 45 min was allowed to obtain optimal myocardial FDG uptake[33]. Data acquisition was performed with a large-field-of-view rotating dual head gamma camera (ADAC Laboratories, Milpitas CA), equipped with a low-energy high-resolution collimator for the thallium-201 study and equipped with 511 keV collimators (van Mullekom, Nuclear Fields, Boxmeer, The Netherlands) for the FDG study. The specific details of these collimators have been described previously[34]. The dual head gamma camera system was rotated over 180° around the patient. From the raw scintigraphic data, 6 mm-thick (1 pixel) transaxial slices were reconstructed by filtered back projection using a Hanning filter (fc=0·63 cycle . cm^{-1}). Slices were not corrected for attenuation. Further reconstruction yielded long- and short-axis projections perpendicular to the heart axis.

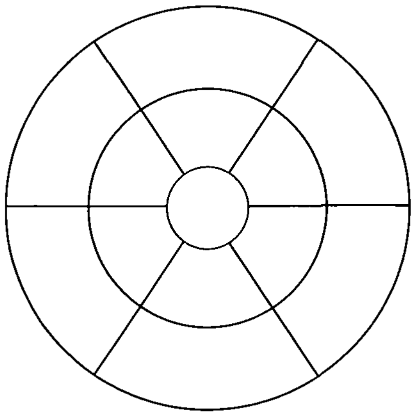

Figure 1 **The 13-segment model used for analysis of both the SPECT and echocardiographic studies. The myocardium is divided into one apical segment, six distal and six basal segments (anterior, anterolateral, posterolateral, inferior, inferoseptal and anteroseptal).**

SPECT analysis

Semi-quantitative analysis was performed as described previously[20]. Circumferential count profiles (60 radii, highest pixel/radius) from thallium-201 and FDG short-axis slices were generated and displayed in a polar map. The polar maps were divided into 13 segments, dividing the myocardium into one apical, six distal and six basal segments (Fig. 1). The segment with the highest thallium-201 uptake was considered as normal. The mean activity of this segment was adjusted to a normal database[17,20], and all other segments were adjusted correspondingly. For FDG SPECT, the same adjustment procedure as for thallium-201 was followed, except that a separate normal database for FDG was used[17,20].

A perfusion defect was considered present if the segmental thallium-201 activity was below 2 SD of normal. In the segments with a perfusion defect, the mean FDG and thallium-201 activities were compared. Dyssynergic segments with either normal perfusion or a 7% increased FDG uptake in perfusion defects (perfusion–metabolism mismatch) were considered myocardial regions with a high probability of functional improvement after revascularization. In contrast, dyssynergic segments with a thallium-201 perfusion defect without increased FDG uptake (perfusion–metabolism match) were classified as having a low probability of functional recovery. The 7% cutoff value was defined previously using receiver operating characteristic analysis in a different group of patients undergoing revascularization[31]. For analysis on a patient basis, patients were considered to have the ability to recover functionally ('recoverable') if ≥2 adjacent dyssynergic segments showed normal perfusion or a mismatch pattern on SPECT.

Low-dose dobutamine echocardiography

A two-dimensional transthoracic echocardiogram in standard apical and parasternal views and a 12-lead ECG were recorded at rest. Dobutamine was infused by a volumetric pump through an antecubital vein at doses of 5 and 10 $\mu g \cdot kg^{-1} \cdot min^{-1}$, for 5 min at each dose. Continuous monitoring of the echocardiogram was obtained during the test, and the last minute of both stages were recorded on video tape. The echo images were also digitized (Prevue-III, Nova-Microsonics or Vingmed CFM 800) and displayed in quad-screen format to facilitate the comparison of rest and dobutamine images. A 3-lead ECG was continuously monitored. Blood pressure was measured by sphygmomanometer at each stage.

Analysis of echocardiograms

The interpretation of echocardiograms was performed by two experienced observers, blinded to the clinical data and SPECT results. In case of disagreement, a third observer reviewed the study and a majority decision was achieved. The stress and postoperative resting echocardiograms were interpreted within 1 week after acquisition. Postoperative resting echocardiograms were analysed without knowledge of the low dose dobutamine echocardiography results. For analysis of echocardiograms we used a 13-segment model to allow comparison with SPECT images[20]. Wall motion, including wall thickening, of every segment was scored with a 4-point scoring system (0=normal, 1=mildly hypokinetic, 2=severely hypokinetic, 3=akinetic or dyskinetic). We defined a segment as severely hypokinetic in the presence of minimal wall thickening (<2 mm) with a limited inward motion; as akinetic in the absence of systolic wall thickening; as dyskinetic in the presence of systolic outward motion with thinning. Wall thickening was primarily utilized for the classification of wall motion, preempting the problem of postoperative paradoxical septal motion. Additionally, in order to reduce the confounding effect of tethering, segmental wall thickening was analysed frame by frame during the first half of systole.

Dyscontractile regions were considered to have a high probability of postoperative functional improvement when wall motion improved by at least one point during the infusion of dobutamine. Functional recovery was considered a low probability when there was a lack of improvement or direct worsening in wall motion. For analysis on a patient basis, patients were considered to have the ability to recover functionally ('recoverable') if ≥2 adjacent dyssynergic segments showed improved wall motion during dobutamine infusion. Follow-up echocardiograms were compared with the corresponding pre-operative resting images, without knowledge of the dobutamine studies. For each segment, recovery of function was defined as an improvement of one or more grades. We previously reported a low level of inter- and intra-observer variability in the classification of resting wall motion (agreement 84% and 87%) and the response to low-dose dobutamine (agreement 92% and 94%) in a different but comparable patient group[23]. For individual patients, functional recovery was defined as an improvement in segmental wall motion score after revascularization in ≥2 adjacent segments. Finally, a wall motion score index was calculated from the pre-operative and postoperative resting echocardiograms to evaluate change in global left ventricular function. Wall motion score index was defined as the sum of the scores of each segment divided by the total number of segments analysed.

Statistics

Continuous data are expressed as mean ± SD. A paired or unpaired Student's t-test was used when appropriate. Univariate analysis for categorical variables was performed using the chi-square test with Yates' correction. Sensitivity, specificity, positive and negative predictive values were based upon their standard definitions. McNemar's test was used to compare the sensitivity and specificity of SPECT and low dose dobutamine echocardiography in the prediction of functional recovery. Differences were considered significant if the null hypothesis could be rejected at the 0·05 probability level.

Results

Characteristics of the study group

The study group comprised 30 patients (25 men, five women) with stable coronary artery disease and regional left ventricular dysfunction who underwent an uncomplicated coronary artery bypass grafting procedure.

Table 1 **Baseline characteristics of the study population**

	n=30
Gender (M/F)	25/5
Age (years) mean ± SD	61 ± 11
Diabetes mellitus (n)	4
Previous CABG/PTCA (n)	5/1
Previous myocardial infarction (n)	30
<1 month	1
>1 month	19
Q/non-Q wave	20/10
Anterior/Inferior	13/7
Effort angina (n (%))	24 (80)
Effort dyspnoea (n (%))	16 (53)
Coronary arteriography (n)	30
1 vessel disease (n (%))	7 (23)
2 vessel disease (n (%))	6 (20)
3 vessel disease (n (%))	17 (57)
LVEF (%)	
Mean ± SD	35 ± 10

CABG=coronary artery bypass grafting; LVEF=left ventricular angiographic ejection fraction; PTCA=percutaneous transluminal coronary angioplasty.

The demographic, clinical and angiographic data are summarized in Table 1. Of the 390 segments, 388 were visualized by resting echocardiography. Of these segments 212 (55%) had normal wall motion and 176 (45%) abnormal wall motion at rest. The mean number of abnormal segments per patient was 5·6 ± 3·5. Eight dyssynergic segments were excluded from postoperative evaluation due to inadequate revascularization. Thus, 168 segments were available for serial analysis. Sixty-six (39%) dyssynergic segments were classified as mildly hypokinetic and 102 (61%) as severely dyssynergic (33 severely hypokinetic and 69 a/dyskinetic).

Postoperative results

At 3 months follow-up, 62 (37%) of the 168 dyssynergic segments showed an improvement in wall thickening and motion. The improvement was observed in 35 (53%) of the 66 mildly hypokinetic segments and in 27 (26%) of the 102 severely dyssynergic segments (in 16 severely hypokinetic and 11 a-/dyskinetic segments). Thus, segments showing mild hypokinesia recovered more frequently (P<0·01). The mean wall motion score index decreased significantly from 0·90 ± 0·48 to 0·72 ± 0·44 (P<0·05). Patient-by-patient analysis revealed improvement of wall motion in ≥2 adjacent segments in 15 of the 30 patients. None of the patients complained of residual angina pectoris at follow-up.

SPECT

Thallium-201/FDG SPECT identified a high probability of recovery in 52 of the 62 (84%) segments showing improved wall motion after revascularization. A mismatch pattern was present in 24 of these 52 segments and 28 had normal perfusion. An example of a perfusion–metabolism mismatch at SPECT is shown in Fig. 2. In contrast, SPECT identified 91 of the 106 (86%) segments failing to improve as a low recovery probability. These results yielded a sensitivity of 84% and a specificity of 86%, with a positive predictive value of 78% and a negative predictive value of 90% for thallium-201/FDG SPECT to predict functional recovery (Fig. 3). Thallium-201 activity (%) was significantly higher in segments showing functional recovery (78·4 ± 18·7 vs 64·7 ± 12·6; P<0·05).

When analysed patient-by-patient, thallium-201/FDG SPECT correctly identified 14 of the 15 (93%)

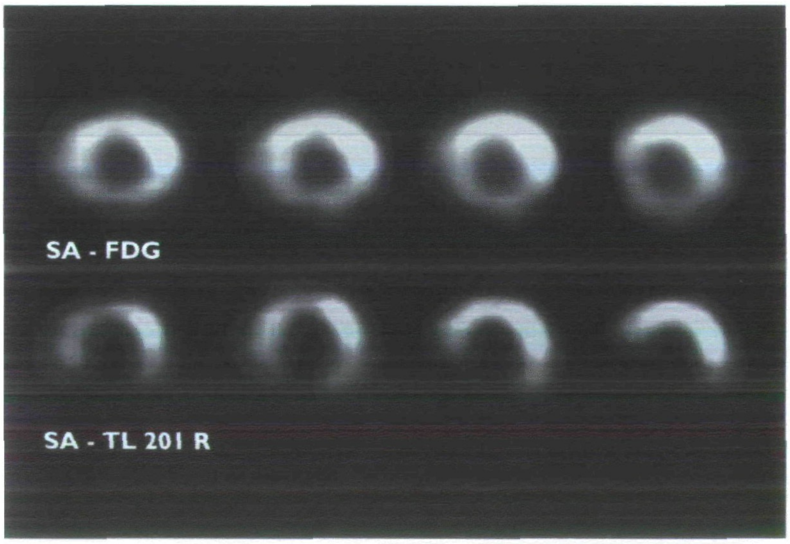

Figure 2 **Corresponding series of short axis FDG (top) and thallium-201 (bottom) slices demonstrating a perfusion–metabolism mismatch in the infero-septal region.**

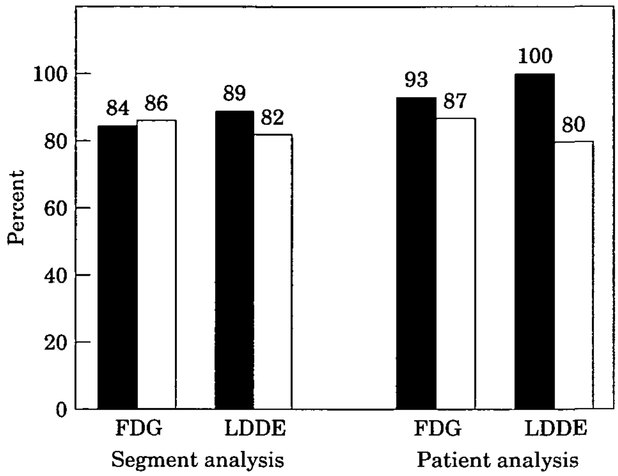

Figure 3 **Bar graph showing the sensitivity (■) and specificity (□) of thallium-201/FDG SPECT and low dose dobutamine echocardiography (LDDE) for recovery of contractile function after coronary artery bypass grafting, both on a segmental and on a patient basis.**

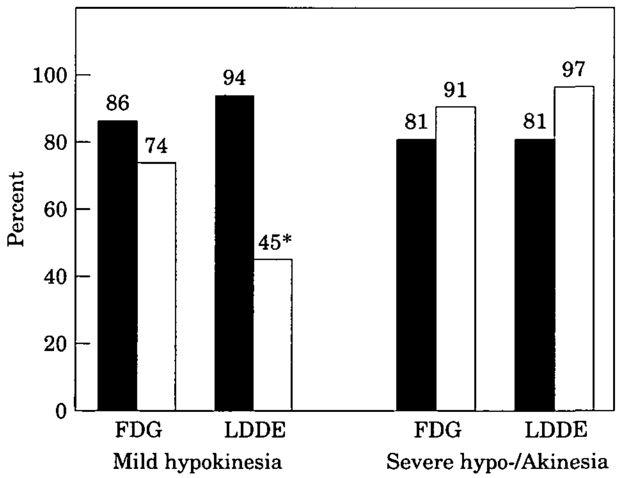

Figure 4 **Bar graph showing the sensitivity (■) and specificity (□) of thallium-201/FDG SPECT and low dose dobutamine echocardiography (LDDE) for recovery of contractile function after coronary artery bypass grafting, in segments with mild hypokinesia vs severe dyskinesia. *P<0·05 vs FDG.**

patients who recovered postoperatively and 13 of the 15 (87%) who did not recover postoperatively (Fig. 3). In patients with ≥2 viable segments with a high recovery probability on SPECT, the wall motion score index decreased significantly from 0·92 ± 0·54 before to 0·64 ± 0·46 after coronary artery bypass grafting (P<0·01). In patients with ≤1 viable segment, the wall motion score index remained unchanged (0·87 ± 0·39 vs 0·81 ± 0·39, ns).

The diagnostic accuracy of SPECT was also determined according to the severity of the wall motion abnormalities at baseline (Fig. 4). In mildly hypokinetic segments, the sensitivity and specificity were 86% and 74%, whereas in severely dyssynergic segments they were 81% and 91%.

Dobutamine echocardiography

No complications occurred during the tests. Heart rate increased from 73 ± 15 beats . min^{-1} at rest to 86 ± 14 beats . min^{-1} during the test (P<0·01). Low dose dobutamine echocardiography revealed contractile reserve in 55 of the 62 (89%) segments showing improved wall motion after surgery, and in 87 of 106 (82%) segments failing to improve. Consequently, low dose dobutamine echocardiography had a sensitivity of 89% and a specificity of 82%, with a positive predictive value of 74% and a negative predictive value of 93% to predict functional recovery (Fig. 3).

In individual patients, low dose dobutamine echocardiography had a sensitivity of 100% (15/15) and a specificity of 80% (12/15) to predict postoperative functional improvement (Fig. 3). In patients with ≥2 viable segments on low dose dobutamine echocardiography, the wall motion score index decreased significantly from 1·00 ± 0·54 before to 0·70 ± 0·50 after coronary artery bypass grafting (P<0·01). Conversely, in patients with ≤1 viable segment, the wall motion score index remained unchanged (0·75 ± 0·31 vs 0·74 ± 0·31, ns).

Similar to SPECT, the diagnostic accuracy of low dose dobutamine echocardiography was determined according to the severity of wall motion abnormalities prior to surgery (Fig. 4). In mildly hypokinetic segments, sensitivity and specificity were 94% and 45%, whereas in severely dyssynergic segments they were 81% and 97%.

Comparison between SPECT and dobutamine echocardiography

The agreement between SPECT and low dose dobutamine echocardiography on a segmental basis was 83%. Both techniques identified 56 segments as having a high recovery probability (recoverable) and 83 segments as having a low recovery probability. Discordance was noted in 11 severely dyssynergic (four false-positives) and 18 mildly hypokinetic segments (13 false-positives of which 11 on low dose dobutamine echocardiography). In severely dyssynergic segments, the sensitivity and specificity to predict postoperative functional outcome were comparable for SPECT and low dose dobutamine echocardiography (Fig. 4). However, in mildly hypokinetic segments the specificity of low dose dobutamine echocardiography was significantly less in comparison with SPECT (45% vs 74%, P<0·05).

Discussion

To select the most appropriate treatment for patients with advanced left ventricular dysfunction, a correct identification of the amount of potentially reversible (viable) dysfunctional myocardium is important for the prediction of improvement of global ventricular function after coronary revascularization. The present study is a direct comparison of two recently developed techniques set up to identify myocardial segments with a low or high probability of postoperative recovery, thallium-201/FDG SPECT and low dose dobutamine echocardiography. The main findings are as follows:

SPECT and low dose dobutamine echocardiography are equally accurate in predicting postoperative improvement of regional left ventricular function, particularly in severely dyssynergic segments. In mildly hypokinetic segments, the specificity of both techniques is less. Low dose dobutamine echocardiography, in particular, overestimates the probability of functional recovery in mildly hypokinetic segments. On a patient basis, both SPECT and low dose dobutamine echocardiography provide 90% correct information regarding functional outcome. It should be stressed that these results may not be applicable to patients with more severe left ventricular dysfunction leading to dilatation and/or cellular dedifferentiation. Further studies are needed to answer this question.

It is important to distinguish the concept of metabolically viable myocardium from the ability to recover its mechanical ventricular function. Although mildly hypoperfused dyssynergic myocardium with a matched reduction in FDG uptake represents residual viablility (viable match), it is less likely to recover functionally after adequate revascularization[5]. By differentiating between perfusion–metabolism match or mismatch, positron emission tomography has demonstrated adequate prediction of recovery of regional and global left ventricular function after revascularization[4,8–15]. This underscores the need for combined assessment of myocardial flow and FDG uptake.

Functional and metabolic imaging reflect different physiological phenomena of myocardial viability. The adrenergic stimulus initiated by dobutamine leading to increased contractility represents the physiological rationale of low dose dobutamine echocardiography. By recruiting a critical mass of dormant but viable dyfunctional myocytes, echocardiography is capable of detecting viable myocardium with a high likelihood of functional recovery after adequate revascularization, especially in severe dysynergic regions. Myocardial FDG uptake, on the other hand, reflects metabolic activity, independent of contractility. Since glucose uptake is increased in ischaemically jeopardized but viable myocardium it is possible to detect myocardium with the potential to recover its contractile function[4–15].

In the present study, a surprisingly good agreement between the functional and metabolic imaging technique was found. This can be explained by the criteria used, since a viable match with SPECT was considered as having a low probability of functional recovery. Previous studies have reported the relationship between thallium uptake, contractile response to dobutamine and postoperative recovery[23,24,36]. Although thallium-201 SPECT detected myocardial viability (defined as >50% uptake) more frequently[36], it also seemed to overestimate functional recovery after coronary artery bypass grafting compared to low dose dobutamine echocardiography[23,24]. Our findings are also supported by a recent comparative study between low dose dobutamine echocardiography and positron emission tomography in similar patients[37]. The extent of dobutamine-induced contractile reserve appeared to compare less closely with the total extent of viable myocardium than with the extent of perfusion–metabolism mismatch.

Recently, the development of a special collimator made it possible to study myocardial FDG uptake with SPECT[16–22]. For clinical purposes, SPECT imaging is widely available for the detection of myocardial viability. In order to optimize and standardize metabolic conditions, we used the hyperinsulinaemic euglycemic clamping technique. These metabolic conditions allow sufficient exogenous glucose uptake for an optimal target-to-background ratio, resulting in good diagnostic image quality[31], and enhance more homogenous FDG uptake[38]. The more widespread alternative approach, employing oral glucose loading, may result in a more variable metabolic milieu and was therefore not chosen.

In comparison to the positron emission tomography literature, relying on comparable methodologies, similar sensitivities and specificities in patients undergoing revascularization were reached as compared to our FDG SPECT results. In the reported 194 patients derived from nine studies, positron emission tomography showed a mean sensitivity of 87% and a mean specificity of 77%[4,8–15].

In hypokinetic segments, both techniques, but especially low dose dobutamine echocardiography, seems to overestimate functional recovery after revascularization. These segments are likely to contain normal myocardium, subendocardial scar and/or viable but dysfunctional myocardium. If relatively little viable tissue is present, dobutamine challenge may stimulate normal myocardium to a hyperkinetic response simulating a positive test for viability. It is conceivable that combining low with high dose dobutamine infusion could have increased the specificity of stress echocardiography for predicting functional recovery[25]. Using the entire dose range, some segments might have exhibited a biphasic resonse (jeopardized but viable) with a high probability of recovery, whereas other segments might have showed continuous enhancement of wall thickening (non-jeopardized). However our patients only underwent a low-dose dobutamine infusion.

Limitations

Graft patency was not assessed after revascularization. Reocclusion may have accounted for the failure of some viable segments to recover in contractile function, particularly in the segments that were viable both on low dose dobutamine echocardiography and SPECT. In contrast to sophisticated SPECT analysis, the echocardiographic images were analysed visually. Inter-observer variability due to heterogeneity of contractile function of normal myocardium at rest and in response to dobutamine has been reported[39,40]. Our results are largely unaffected. Functional improvement was assessed arbitrarely 3 months after surgical revascularization. There is a possibility that additional functional improvement may occur later as suggested previously[41].

Conclusion

Both low dose dobutamine echocardiography and thallium-201/FDG SPECT imaging appear to be comparable and similarly accurate methods for the prediction of improvement of regional and global left ventricular function after coronary artery bypass grafting. Both methods are increasingly available and may be useful techniques for the routine detection of potentially reversible dysfunctional myocardium.

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