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Prediction of Left Ventricular Functional Recovery by Dobutamine Echocardiography, F-18 Deoxyglucose or ^{99m}Tc Sestamibi Nuclear Imaging in Patients with Chronic Myocardial Infarction

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Key Words
Chronic myocardial dysfunction · Dobutamine echocardiography · F-18 deoxyglucose · Positron emission tomography · Receiver-operating characteristic curve analysis · Single photon emission computed tomography · ^{99m}Tc sestamibi · Viability testing

Abstract

Background: Currently, several modalities are available to predict viability, however, studies comparing various modalities validated by functional recovery after revascularization are scarce. This study analyzed the relative merits of low-dose dobutamine echocardiography, F-18 deoxyglucose (FDG) positron emission tomography (PET) and ^{99m}Tc sestamibi single-photon emission computed tomography to predict functional recovery after revascularization in patients with chronic myocardial infarction. ***Methods:*** Patients with chronic coronary occlusion (duration: 3.1 ± 4.8 years) and impaired left ventricular function (ejection fraction: 42 ± 13%) underwent low-dose dobutamine echocardiography (20 μg/kg/min), FDG-PET and ^{99m}Tc sestamibi imaging before revascularization. Revascularization was performed irrespective of any viability data. Follow-up angiography was obtained 4.8 ± 2.5 months after revascularization. ***Results:*** Viability analysis was performed in 34 patients with patent target vessel at follow-up, of whom 9 (27%) exhibited functional recovery on left ventricular angiography. For dobutamine echocardiography, improvement of ≥2 adjacent akinetic segments resulted in improved sensitivity of 89% and specificity of 80% to predict functional recovery. For glucose metabolism, FDG uptake >55% was an optimal threshold yielding a sensitivity of 89% and a specificity of 68%. With respect to perfusion, ^{99m}Tc sestamibi uptake >60% was the best cutoff resulting in a sensitivity and a specificity of 56 and 88%, respectively. A concordant match of FDG >55% and of ^{99m}Tc sestamibi >50% resulted in optimized sensitivity (78%) and specificity (80%) with dual imaging. ***Conclusions:*** Recovery of chronically dysfunctional myocardium can be predicted with high accuracy by stimulation of contractile reserve or by concordant match of preserved glucose metabolism and residual perfusion.

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Introduction

It is currently accepted that viable myocardium can be identified by stimulation of the contractile reserve using low-dose dobutamine echocardiography [1] and by nuclear imaging techniques of myocardial metabolism and perfusion [2]. Chronically dysfunctional myocardium with reduced perfusion, but preserved F-18 deoxyglucose (FDG) uptake frequently shows functional improvement after revascularization [3, 4]. However, recent studies using quantitative positron emission tomography (PET) have challenged the concept that dysfunctional but viable myocardium is due to a misbalance between myocardial perfusion and glucose metabolism [5–7]. Vanoverschelde et al. [5] were the first who demonstrated that dysfunctional but noninfarcted collateral-dependent myocardium had normal myocardial blood flow as compared to remote myocardium. More recent studies in patients with chronic infarction confirmed that dyskinetic myocardium which recovered after revascularization had normal perfusion at rest [6, 7].

Recent studies revealed that ^{99m}Tc sestamibi single photon emission computed tomography (SPECT) can be used to measure myocardial perfusion in patients with chronic left ventricular dysfunction [8, 9]. Maes et al. [8] found good correlation and agreement for imaging of perfusion comparing ^{99m}Tc sestamibi-SPECT and ^{13}N-ammonia-PET. Furthermore, both nuclear tracers were accurate to predict functional recovery after revascularization, supporting the concept that preserved perfusion may be used as an indicator of viable myocardium [8].

The purpose of this study was to analyze and to compare head-to-head the accuracy of contractile response by low-dose dobutamine echocardiography, preserved glucose metabolism by FDG-PET and sustained perfusion by ^{99m}Tc sestamibi-SPECT to predict functional recovery in patients with chronic coronary occlusion. Receiver-operating characteristic curve analysis was used to optimize the performance of each modality. All viability tests were validated by improved contractile function at follow-up.

Methods

Study Design

We prospectively analyzed 49 patients with chronic myocardial infarction (>3 months since the ischemic event) who were referred to the University Hospital Eppendorf, Hamburg, Germany for this study. Only patients with severe regional left ventricular dysfunction were included with proximal occlusion of the infarct-related coronary artery (target vessel). Exclusion criteria were severe post-infarction angina or unstable coronary syndrome at rest, significant valvular disease, insulin-dependent diabetes mellitus, sustained ventricular arrhythmia or an implantable defibrillator. Baseline data were obtained from angiography, low-dose dobutamine echocardiography, FDG-PET, and ^{99m}Tc sestamibi-SPECT prior to revascularization. The target vessel was subsequently revascularized irrespective of any viability data. All viability data were analyzed on a regional basis to predict functional recovery of the target perfusion territory. Follow-up angiography was obtained >3 months after revascularization to document patency of the revascularized artery and improvement of left ventricular function. Only patients with a patent target vessel at follow-up were included into the viability test analysis. The study was approved by the Institutional Review Board and a written informed consent was obtained from each patient.

Coronary Angiography

Multiplane coronary angiography and biplane ventriculography was performed in identical angulation both at baseline and follow-up. Ventriculograms were analyzed in random order by an investigator blinded to all viability data using the centerline method [10]. Chord motion was expressed in units of standard deviation (SD) of the normal mean. Data of normal chord motion were supplied by Florence H. Sheehan (University of Washington, Seattle, Wash., USA). Regional wall motion abnormality (RWMA) was calculated for the individual perfusion territory supplied by the target vessel. Severity of RWMA was computed by averaging chord motion of the most abnormal 50% of contracting chords of the perfusion territory [10]. A RWMA of 0 SD represents normokinesis, whereas a negative RWMA indicates hypokinesis and a positive RWMA expresses hyperkinesis. Reversible left ventricular dysfunction was assumed if RWMA improved >+1 SD after revascularization [11]. Collaterals to the occluded coronary artery were visually analyzed using the Rentrop score [12]. Restenosis of the target vessel at follow-up was quantified using a validated automatic contour detection program (AWOS™ System 3.01, Siemens Erlangen, Germany) [13].

Dobutamine Echocardiography

Transthoracic echocardiograms were performed at rest and with incremental dosages of 5, 10 and 20 μg/kg/min of dobutamine infused intravenously over a period of 3 min each. At each stage ECG-triggered echoscans of left ventricular contraction were acquired and stored digitally on a VINGMED CFM 800 echo scanner (VINGMED Sound, Horten, Norway). To facilitate comparison between stages, images were displayed in quadscreen format and were analyzed by a blinded experienced observer applying a 16-segment model and a 4-point scoring system [14]. Regional wall motion analysis was performed in nine anterior segments representing perfusion territory of the left anterior descending artery (LAD) or in nine inferior, posterior or lateral segments delineating perfusion territories of right coronary (RCA) or circumflex (CFX) arteries [14]. To reduce confounding effects of tethering, wall thickening was analyzed instead of improved wall motion. Dyskinetic segments were classified as viable when they exhibited increased wall thickening during dobutamine infusion. A change from dyskinesis to akinesis was not considered viable. Receiver-operating curve analysis was used to determine the optimal number of viable segments to predict functional recovery of the target perfusion territory.

PET and SPECT

Patients underwent PET and SPECT studies on a single day. A dose of 370 MBq (10 mCi) ^{99m}Tc sestamibi (Cardiolite, DuPont, Bad Homburg, Germany) was injected at rest. Patients received a standard meal after 20 min to promote clearance of ^{99m}Tc sestamibi from the hepatobiliary tract. Images were acquired 1 h after injection with a single-head γ-camera (Orbiter, Siemens Erlangen, Germany) equipped with a low-energy all-purpose collimator. Thirty-two projections were acquired over a 180° arc with acquisition time of 30 s each. Transaxial tomograms were reconstructed in 64 × 64 pixel matrix using a Butterworth 5th-order filter with a cutoff frequency of 0.3 cycles/pixel.

PET studies were performed using a dedicated full-ring whole-body tomograph (ECAT EXACT 921/47, Siemens/CTI, Knoxville, Tenn., USA). To enhance myocardial uptake, patients received an infusion of 10% glucose with a short-acting insulin and 10 mval potassium chloride 1 h before injection of 370 MBq (10 mCi) FDG. A 15-min transmission scan was acquired for attenuation correction. Dynamic images were obtained during a 60-min period. Transaxial data were reconstructed in 128 × 128 pixel matrix using a Hanning filter with a cutoff frequency of 0.4 cycles/pixel.

Quantitative Analysis

PET and SPECT studies were independently evaluated by use of a previously described semiautomatic analysis program [15]. In brief, a volumetric sampling algorithm was used to delineate a maximum count surface, which was transformed to a polar map. Each polar map was normalized to maximum uptake of each tracer. Attenuation correction was performed only on PET images, because transmission data were not available for SPECT. Polar maps were subdivided into basal, mid and apical regions and analysis was performed in 9 designated segments [16]. Perfusion territory of LAD was represented by apical, mid and basal anterior segments, where as territories of RCA and CFX were represented by mid and basal posterior or lateral segments, respectively [16]. Mean uptake of FDG and ^{99m}Tc sestamibi was calculated for each coronary perfusion territory and was used for receiver-operating characteristic curve analysis.

Statistical Analysis

Continuous data are expressed as means ± SD. Differences in continuous data were analyzed by Student's t test. Analysis of unpaired data for categorical variables was performed by χ^2 testing. Differences or agreement between imaging modalities were analyzed using the McNemar or κ test for paired data. Receiver-operating characteristic curve analysis was performed according to the method described by Hagen [17]. Multiple logistic regression analysis was used to determine independent indicators of functional recovery. $p < 0.05$ was required for statistical significance.

Results

The final study population consisted of 34 patients (31 men and 3 women, mean age 60 ± 9 years) with a patent target vessel at follow-up. Fifteen patients (31%) were excluded from the viability analysis because of unsuccessful revascularization in 5 (10%), missing follow-up in 3 (6%) subjects (2 died before the scheduled date and 1 refused to undergo repeat angiography), and reocclusion of the target vessel in 7 (17%) patients.

In the 34 patients with patent target vessel at follow-up, a history of myocardial infarction was present in 31 (92%), 27 of whom had Q-wave infarction. Exertional angina was manifest in 14 subjects (41%) and congestive heart failure with NYHA class ≥III was observed in 13 (39%). LAD occlusion was documented in 29 patients (85%), whereas 5 had occlusion of RCA or CFX. Multivessel coronary artery disease was present in 16 (47%) subjects. At baseline, ejection fraction was 42 ± 13% and RWMA was –2.77 ± 0.82 SD. The interval between infarction and study inclusion was 3.1 ± 4.8 years. Interventional revascularization was performed in 23 subjects (68%) including 11 patients with stent implantation. The remaining patients (32%) were revascularized by bypass surgery. Follow-up angiography was obtained 4.8 ± 2.5 months after revascularization.

Recovery of Left Ventricular Function

In the 34 patients with a patent target vessel at follow-up, RWMA improved from –2.77 ± 0.82 SD at baseline to –2.06 ± 1.63 SD at follow-up ($p < 0.01$). Reversible dysfunction >+1 SD was found in 9 (27%) patients whereas 25 patients revealed no change in RWMA and were classified as patients with irreversible dysfunction. No differences in baseline characteristics were found between both groups (table 1). In patients with reversible dysfunction, the ejection fraction markedly improved and the number of akinetic chords notably decreased (table 2). Patients with reversible dysfunction revealed more frequently collaterals to the occluded artery than patients with irreversible dysfunction ($p < 0.05$). At follow-up, minimal lumen diameter of the revascularized artery was identical in both groups, and no patient had a restenosis >50%. Patients with subsequent reocclusion revealed improvement in mean RWMA from baseline (–2.76 ± 1.15 SD) to follow-up (–2.37 ± 1.30 SD, $p < 0.05$). However, none of these patients achieved the required improvement in RWMA of >+1 SD.

Dobutamine Echocardiography

Twenty-six of 306 segments (8%) could not be adequately visualized and were excluded. Resting wall motion abnormalities were present in 250 segments representing 89 ± 17% of the perfusion territory. Of these segments, 63 were hypokinetic (23 ± 14% of perfusion territory) and 187 were akinetic or dyskinetic (66 ± 20% of perfusion territory). Functional improvement occurred more frequently in hypokinetic (48%) than in akinetic or

Table 1. Patient characteristics

Parameter	Reversible dysfunction (n = 9)	Irreversible dysfunction (n = 25)	p value
Age, years	57 ± 6	61 ± 9	NS
Sex, females/males	2/7	1/24	NS
Infarct location, anterior/inferoposterior or lateral	7/2	22/3	NS
Q-wave/non-Q-wave MI	7/2	20/5	NS
Revascularized vessel, LAD/RCA/CFX	7/1/1	22/3/0	NS
Interval between			
MI and DE, years	1.0 ± 1.3	3.9 ± 5.3	NS
MI and nuclear studies, years	1.0 ± 1.3	3.9 ± 5.3	NS
MI and revascularization, years	1.1 ± 1.3	4.0 ± 5.4	NS
Revascularization and follow-up, months	5.2 ± 2.2	4.7 ± 2.6	NS

MI = Myocardial infarction; DE = dobutamine echocardiography. Values are means ± SD or n.

Table 2. Angiographic characteristics

	Reversible dysfunction (n = 9)	Irreversible dysfunction (n = 25)	p value
Regional wall motion abnormality, SD			
Baseline	−2.34 ± 1.41	−2.93 ± 0.38	NS
Follow-up	−0.24 ± 2.13**	−2.75 ± 0.56	<0.0001
Δ Mean wall motion	+2.10 ± 1.00	+0.18 ± 0.38	<0.0001
Ejection fraction, %			
Baseline	48 ± 17	39 ± 12	NS
Follow-up	59 ± 17*	37 ± 17	<0.01
Δ Ejection fraction	+11 ± 14	−2 ± 8	<0.01
Akinetic chords, n			
Baseline	17 ± 18	20 ± 10	NS
Follow-up	3 ± 6*	18 ± 16	<0.05
Δ Akinetic chords	−14 ± 14	−2 ± 13	<0.05
Collaterals at baseline, yes/no	7/2	9/16	<0.05
Target vessel at follow-up			
Diameter stenosis, %	13 ± 14	17 ± 17	NS
Minimal lumen diameter, mm	2.7 ± 0.9	2.5 ± 0.7	NS

* $p < 0.05$ and ** $p < 0.01$ vs. baseline.

dyskinetic segments (32%, $p < 0.01$). Accordingly, reversible dysfunction was observed in 18 patients (53%) using improved wall thickening in ≥2 adjacent hypokinetic or akinetic segments, whereas improvement in ≥2 adjacent akinetic segments was present in 13 subjects (38%, $p < 0.01$).

FDG and ^{99m}Tc Sestamibi Uptake

The mean FDG uptake of the target perfusion territory was 53.5 ± 16.4% which was not different from the mean ^{99m}Tc sestamibi uptake (51.0 ± 11.4%, p = NS). To examine differences between FDG and ^{99m}Tc sestamibi uptake, a threshold of >50% was used for both tracers to differentiate reversible from nonreversible dysfunction. An FGD uptake of >50% was present in 18 patients and a ^{99m}Tc

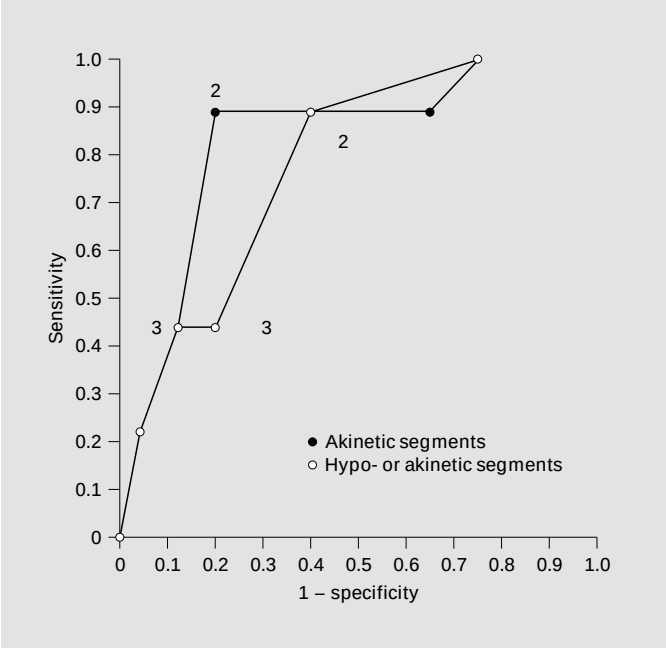

Fig. 1. Receiver-operating characteristic curve analysis to predict reversible dysfunction in 34 patients with patent target vessel at follow-up by the number of viable segments by low-dose dobutamine echocardiography. Test performance was optimized by exclusion of hypokinetic segments from the analysis which increased the area under the curve from 0.78 for hypokinetic or akinetic segments to 0.83 for akinetic segments only.

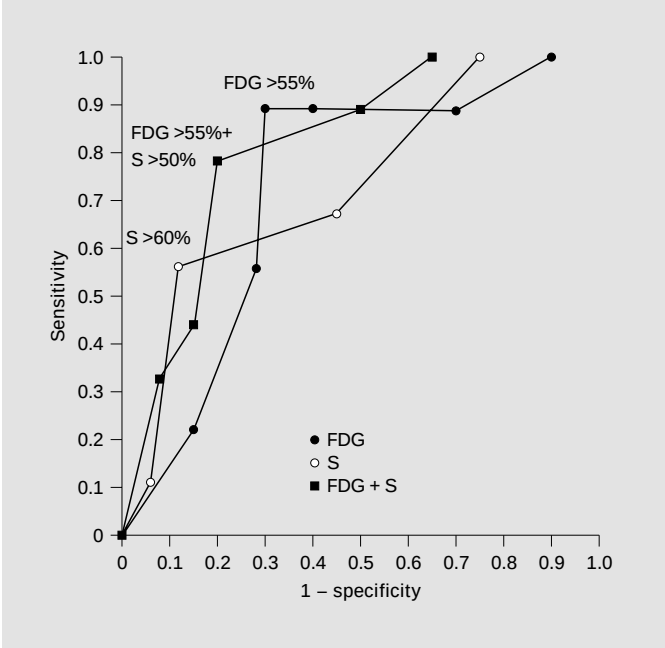

Fig. 2. Receiver-operating characteristic curve analysis to predict functional recovery in 34 patients with patent target vessel at follow-up by nuclear studies. For glucose metabolism, an FDG uptake >55% was the optimal cutoff. For imaging of perfusion, a ^{99m}Tc sestamibi (S) uptake >60% was the best cutoff to predict functional recovery. Interestingly, a similar test performance was found for FDG and ^{99m}Tc sestamibi imaging with an area under the curve of 0.73 and 0.74, respectively. Test accuracy was optimized by a concordant match of both tracers, resulting in an area under the curve of 0.81.

Table 3. Accuracy of viability tests to predict left ventricular recovery in 34 patients

	Sensitivity	Specificity	Accuracy	PPV	NPV
DE ≥2 akinetic segments	89	80	82	62	95
DE ≥2 hypo- or akinetic segments	89	60	68	44	94
PET >55%	89	68	74	50	94
SPECT >60%	56	88	79	63	85
PET >55% + SPECT >50%	78	80	79	58	91

DE = Dobutamine echocardiography; PPV = positive predictive value; NPV = negative predictive value.

sestamibi uptake of >50% in 19 patients (p = NS). FDG and ^{99m}Tc sestamibi uptake were concordant in 27 patients (79%, κ = 0.59). Discordant findings were present in 7, of whom 3 (9%) revealed ^{99m}Tc sestamibi uptake <50% but had preserved FDG uptake >50%. Four patients (12%) showed a pattern of preserved ^{99m}Tc sestamibi uptake >50%, but reduced FDG uptake <50%.

Prediction of Functional Recovery

The accuracy of each viability test to predict functional recovery is summarized in table 3. Receiver-operating characteristic curve analysis revealed improvement of ≥2 adjacent segments as optimal threshold for dobutamine echocardiography (fig. 1). The use of a threshold of ≥3 adjacent segments slightly increased specificity, but low-

ered sensitivity. A better test performance was achieved by exclusion of hypokinetic segments from the analysis. The area under the curve increased from 0.78 for hypokinetic or akinetic segments to a value of 0.83 for only akinetic segments (fig. 1). At the threshold of ≥2 segments, exclusion of hypokinetic segments reduced false-positive findings in 5 patients and increased specificity from 60 to 80%. In all 5 patients, hypokinetic segments were located at the border zone between akinetic and normal-contracting myocardium.

An FDG uptake >55% resulted in optimal test performance for PET (fig. 2). The >50% FDG uptake resulted in lower specificity without gain in sensitivity. The optimal threshold of ^{99m}Tc sestamibi was an uptake >60% (fig. 2). A similar test performance was found for FDG and ^{99m}Tc sestamibi with an area under the curve of 0.73 and 0.74, respectively. Test performance was optimized by a concordant match of both tracers, resulting in an area under the curve of 0.81 (fig. 2). The use of FDG uptake >55% and ^{99m}Tc sestamibi uptake >50% improved sensitivity and specificity to 78 and 80%, respectively.

Multiple Logistic Regression Analysis

Improvement of ≥2 adjacent akinetic segments under dobutamine stimulation was the most accurate predictor of functional recovery after revascularization (table 4). Perfusion imaging with ^{99m}Tc sestamibi emerged as a useful and independent predictor of reversible dysfunction. However, the combined use of both nuclear tracers increased the accuracy of PET and SPECT studies.

Table 4. Multiple logistic regression analysis

	χ^2	p value
DE ≥2 akinetic segments	13.94	<0.001
PET >55% + SPECT >50%	9.43	<0.01
PET >55	9.39	<0.01
DE ≥2 hypokinetic or akinetic segments	7.09	<0.01
SPECT >60%	6.38	<0.05

DE = Dobutamine echocardiography.

Discussion

The current data revealed that FDG and ^{99m}Tc sestamibi provided concordant information on viability in 79% of patients. However, when both nuclear studies were validated by improved wall motion after revascularization, FDG revealed high sensitivity (89%) and moderate specificity (68%), whereas ^{99m}Tc sestamibi achieved intermediate sensitivity (56%) but high specificity (88%). A concordant match of preserved glucose uptake and myocardial perfusion improved sensitivity and specificity of nuclear imaging to 78 and 80%, respectively. The performance of low-dose dobutamine echocardiography was improved by exclusion of hypokinetic segments from the analysis increasing sensitivity and specificity to 89 and 80%, respectively.

Incidence of Functional Recovery

Left ventricular recovery occurred in 27% of patients, a proportion similar to previous studies with a comparable set of patients [11, 18, 19]. However, most previous studies are devoid of any angiographic follow-up information about restenosis or reocclusion and the relation to functional recovery [18–21]. In the current study, left ventricular recovery only occurred in patients with successful revascularization and unrestricted perfusion at follow-up. Patients with subsequent reocclusion failed to show functional recovery of more than 1 SD in RWMA. This finding underlines the importance of sustained perfusion for functional recovery and the importance of angiographic follow-up to exclude restenosis or reocclusion as a cause of failed recovery.

Prediction of Functional Recovery

This study compared head-to-head the accuracy of various viability tests to predict contractile recovery after revascularization. Care was taken to eliminate potential bias in favor of any viability test. First, in all patients, revascularization was performed blinded to and irrespective of any test results to exclude preselection by evidence of viability. Second, left ventricular angiography was used as an independent method to document contractile recovery. This approach avoids a bias by using the same method both for prediction of viability and for subsequent validation, which represents a potential limitation of previous echocardiographic viability studies [1].

Dobutamine Echocardiography

The incidence of functional improvement with dobutamine was higher in hypokinetic as compared to akinetic segments. This finding is in line with previous studies in patients with acute myocardial infarction [22, 23] and is explained by a mixture of scar, normal and viable myocardium in hypokinetic segments whereas in akinetic seg-

ments the amount of scar is predominant. Interestingly, Bolognese et al. [23] also found lower specificity to predict later functional recovery in hypokinetic as compared to akinetic segments. The authors concluded that in some hypokinetic segments the underlying mechanism for resting dysfunction might be related to tethering rather than stunned or hibernating myocardium [23]. In the current study, specificity and accuracy of low-dose dobutamine echocardiography was improved by exclusion of hypokinetic segments from the analysis. All excluded hypokinetic segments were located in the borderzone between normal and infarcted myocardium. Although in the presence of borderzone viability, the amount of viable myocardium may not be sufficient to ensure recovery of the entire perfusion territory. The current findings suggest that hypokinetic border zone segments should be excluded if recovery of a large perfusion territory is at issue rather than changes in small segments.

FDG and ^{99m}Tc Sestamibi Uptake

Recent quantitative blood flow measurements have challenged the model of chronic myocardial underperfusion as the main cause of hibernating myocardium [5–7]. Marinho et al. [7] found that chronic dysfunctional segments with functional recovery after revascularization had normal perfusion compared to remote normal contracting myocardium. Only dysfunctional segments without functional recovery had a significantly reduced myocardial perfusion at rest. Similarly, Gerber et al. [6] found normal myocardial perfusion and preserved glucose uptake in reversibly dysfunctional segments, whereas persistent dysfunctional segments had concordantly reduced myocardial perfusion and glucose uptake.

The current data suggest that sustained perfusion is an important and independent predictor of functional recovery after revascularization with a diagnostic accuracy similar to that of preserved glucose metabolism by FDG-PET. Furthermore, our data revealed for the first time that a concordant match of preserved myocardial metabolism and perfusion was the best indicator of functional recovery. The current findings underline the importance of preserved perfusion to maintain myocardial viability and emphasize the diagnostic impact of perfusion imaging to detect viable myocardium.

Angiographic analysis of the collateral flow at baseline revealed that 78% of patients with later functional recovery had collaterals to the occluded coronary artery. Conversely, only 36% of patients without functional recovery had such collateral vessels ($p < 0.05$). These collaterals are most likely responsible for preservation of myocardial perfusion in patients with occluded epicardial arteries. The blood supply via collaterals may be sufficient to maintain cellular viability but may be insufficient to meet the demand during exercise resulting in recurrent ischemia and loss of contractile function.

Limitations

In contrast to the SPECT technique, PET and nuclear tracers such as ^{13}N-ammonia or $H_2{}^{15}O$ enable absolute quantification of regional myocardial perfusion. These tracers may be better suited to study perfusion in chronic hibernating myocardium, because they have a short half-time and no redistribution. Redistribution of the nuclear tracer may represent a potential problem of perfusion imaging with ^{99m}Tc sestamibi [24]. However, ^{99m}Tc sestamibi images were acquired early after injection, when distribution of this tracer is comparable and proportional to flow measurement by ^{13}N-ammonia PET [8]. No attenuation correction was performed on SPECT images potentially resulting in underestimation of tracer uptake. However, 85% of our patients were revascularized in the anterior perfusion territory where attenuation is a less relevant problem [25].

Conclusions

Dobutamine echocardiography or nuclear imaging techniques predict recovery of contractile function of chronically dysfunctional myocardium with high accuracy. Improvement of ≥ 2 adjacent akinetic segments on dobutamine echocardiography was the most accurate predictor of functional recovery after revascularization. Imaging of myocardial perfusion using ^{99m}Tc sestamibi emerged as a useful and independent predictor of reversible dysfunction. A concordant match of sustained glucose metabolism and preserved myocardial perfusion increased the accuracy of the nuclear modalities.

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