Multimodality imaging of coronary artery bypass grafts
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CHAPTER 5

Functional significance of stenoses in coronary artery bypass grafts

Evaluation by single-photon emission computed tomography perfusion imaging, cardiovascular magnetic resonance, and angiography

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Abstract

Objectives: This study was designed to perform a head-to-head comparison between single-photon emission computed tomography (SPECT) and cardiovascular magnetic resonance (CMR) to evaluate hemodynamic significance of angiographic findings in bypass grafts.

Background: The hemodynamic significance of a bypass graft stenosis may not always accurately be determined from the coronary angiogram. A variety of diagnostic tests (invasive or noninvasive) can further characterize the hemodynamic consequence of a lesion.

Methods: Fifty-seven arterial and vein grafts in 25 patients were evaluated by angiography, SPECT perfusion imaging, and coronary flow velocity reserve determination by CMR. Based on angiography and SPECT, four different groups could be identified: 1) no significant stenosis (<50%), normal perfusion; 2) significant stenosis (≥50%), abnormal perfusion; 3) significant stenosis, normal perfusion (no hemodynamic significance); and 4) no significant stenosis, abnormal perfusion (suggesting microvascular disease).

Results: A complete evaluation was obtained in 46 grafts. SPECT and CMR provided similar information in 37 of 46 grafts (80%), illustrating good agreement (κ=0.61, $p<0.001$). Eight grafts perfused a territory with scar tissue. When agreement between SPECT and CMR was restricted to grafts without scar tissue, it improved to 84% (κ=0.68). Integration of angiography with SPECT categorized 14 lesions in group 1, 23 in group 2, 6 in group 3, and 3 in group 4. SPECT and CMR agreement per group was 86%, 78%, 100%, and 33%, respectively.

Conclusions: Head-to-head comparison showed good agreement between SPECT and CMR for functional evaluation of bypass grafts. CMR may offer an alternative method to SPECT for functional characterization of angiographic lesions.

Introduction

Determination of stenosis severity by coronary angiography has been considered the gold standard for the assessment of obstructive coronary artery disease, but the hemodynamic significance of a stenosis may not be determined accurately from the coronary angiogram (1;2). In order to decide whether conservative (medical) treatment or a percutaneous intervention is required, further clinical evaluation may be necessary.

A variety of tests have been proposed for the evaluation of the hemodynamic significance of a stenosis in native coronary arteries and bypass grafts. One method is flow velocity measurement during cardiac catheterization, using the Doppler flow wire at rest and during pharmacologic stress. Subsequent calculation of the coronary flow velocity reserve (CFVR) is an invasive method that can be performed to assess the hemodynamic significance of a stenosis, but its use remains limited to centers with experience (3;4). Alternatively, noninvasive techniques may be of value; myocardial perfusion imaging with single-photon emission computed tomography (SPECT) in particular is a well-established technique to evaluate the hemodynamic significance of a stenosis (5;6). Based on the integration of angiographic findings and SPECT results, four different categories can be identified: 1) no significant stenosis, normal perfusion; 2) a significant stenosis, abnormal perfusion; 3) a significant stenosis, normal perfusion (no hemodynamic significance); and 4) no significant stenosis, abnormal perfusion (suggesting microvascular disease). Thus, integration of anatomical information (angiography) and functional information (SPECT) may allow more precise characterization of lesions.

More recently, the feasibility of CFVR assessment using cardiovascular magnetic resonance (CMR) with velocity mapping in coronary arteries and bypass grafts was demonstrated (7;8). The relative merits of SPECT and CMR to provide noninvasive information in addition to angiography are unknown.

Accordingly, the aim of the present study was to perform a head-to-head comparison between SPECT and CMR to assess the hemodynamic significance of angiographic findings in bypass grafts.

Methods

Study Population

Consecutive patients with a history of bypass surgery who underwent elective coronary angiography for recurrent chest pain were invited to participate in the study. All patients gave informed consent. The protocol was approved by the medical ethics committee of our institution. Coronary angiography was performed according to a standard protocol using the femoral approach. In order to determine the stenosis severity objectively, quantitative coronary arteriography (QCA) was performed by an independent core lab (Heart Core, Leiden, the Netherlands). QCA was performed according to standardized methods (8-10). If two or more stenoses were present in either the graft or recipient vessels, the most severe lesion was taken into account.

Gated SPECT

For the gated SPECT examination a two-day stress-rest protocol was used (11). The stress protocol included a symptom-limited treadmill exercise test. Whenever possible, betablocking agents and calcium channel antagonists were discontinued at least 24 hours before scintigraphy. Test endpoints were physical exhaustion, dyspnea, angina pectoris, significant decrease in blood pressure (>10 mm Hg), or achievement of the maximum age-related heart rate. Blood pressure, heart rate, and electrocardiographic findings were monitored during the test. Technetium-99m tetrofosmin (500 MBq) was injected intravenously at peak exercise, which was continued for 1 minute after tracer injection. In patients unable to exercise (n = 11) adenosine stress was used. On the second day, resting images were obtained using 500 MBq technetium-99m tetrofosmin. The resting studies were acquired using electrocardiogram gating, allowing assessment of left ventricular (LV) ejection fraction and LV volumes (12).

Imaging was performed using a triple-head SPECT camera system (GCA 9300/HG, Toshiba Corp., Tokyo, Japan) equipped with low-energy, high-resolution collimators. A 20% window was used around the 140 keV energy-peak of technetium-99m tetrofosmin. A total of 90 projections (step-and-shoot mode, 35 s/projection, total imaging time 23 min) were obtained over a 360˚ circular orbit. Data were stored in a 64 x 64 matrix. The raw scintigraphic data were reconstructed by filtered back projection using a Butterworth filter (cutoff frequency at 0.26 cycle/pixel, of order 9). No attenuation correction was employed. Reconstruction of the images yielded standard long- and short-axis projections perpendicular to the heart axis. Reconstructed slices were 6.4 mm in all projections. The short-axis slices were displayed in polar map format, adjusted for peak myocardial activity (100%). The myocardium was divided into 17 segments, as recently proposed (13). Segmental tracer activity was expressed as percentage of maximum. Perfusion defects on stress images were considered present when tracer activity was <75% of maximum tracer uptake. Mild to moderate defects were defined as having 50% to 75% of normalized tracer uptake and severe defects as having <50% of normalized tracer uptake. When significant fill-in (>10% increase of normalized tracer activity) of perfusion defects was observed on the resting images, segments were classified as reversible (ischemic); defects without fill-in were classified as irreversible defects (scar) (14). The individual segments on the SPECT images were assigned to the distinct native coronary arteries, according to recently published guidelines (13). The anastomoses of the bypass graft on the different native coronary arteries then defined the vascular territory that the graft perfused.

Cardiovascular Magnetic Resonance

For the CMR examination a 1.5-T Gyroscan ACS-NT MR-scanner (Philips Medical Systems, Best, the Netherlands), equipped with Powertrak 6000 gradients, a cardiac research software patch, and five-element cardiac synergy coil was used. Transverse, electrocardiogram-gated, two-dimensional gradient-echo survey scans at the level of the ascending aorta were performed to localize the bypass grafts. A plane perpendicular to the proximal section of the graft was planned on two differently angulated survey scans, and for MR velocity mapping a fast breathhold Turbo field echo planar imaging (TFEPI) sequence was used at rest and during stress (adenosine 140 µg/kg/min intravenously). The TFEPI sequence is validated and described in more detail by Langerak et al. (15;16). Analyses of the velocity maps were performed with an analytic software package (FLOW, Medis, Leiden, the Netherlands) by an experienced investigator. A region

Number of patients (n)	25
Gender (M/F)	22/3
Age (years)	65 ± 9
Time after CABG (years)	11 ± 5
Hypercholesterolemia	22 (88%)
Diabetes mellitus	6 (24%)
Hypertension	15 (60%)
Current smokers	2 (8%)
Myocardial infarction	8 (32%)
Positive family history for cardiovascular disease	17 (68%)
Medication	
Beta-blockers	20 (80%)
Nitrates	19 (76%)
Calcium antagonists	18 (72%)
ACE inhibitors	10 (40%)
Statins	22 (88%)
Oral anticoagulants/aspirin	24 (96%)

Table 5.1
Patient Characteristics
CABG = coronary artery bypass grafting; ACE = angiotensin-converting enzyme

of interest of 2 x 2 pixels was placed in the center of the vessel in each phase image. The mean velocity of the four pixels was defined as the central velocity for that cardiac phase. The mean central velocity was regarded as the average peak velocity (APV; cm/s). CFVR was calculated as the ratio of APV during adenosine stress and APV at rest.

Statistical Analysis

Results are displayed as mean ± SD. Based on the integration of angiographic findings and SPECT results, four categories were distinguished: 1) a stenosis <50% on angiography and normal perfusion on SPECT; 2) a stenosis ≥50% and abnormal perfusion on SPECT, indicating a stenosis with hemodynamic consequences; 3) a stenosis ≥50% and normal perfusion on SPECT, indicating a stenosis without hemodynamic consequences; and 4) a stenosis <50% and abnormal perfusion, implying microvascular disease.
The agreement between SPECT and CMR results was evaluated using kappa statistics, with a kappa value <0.4, between 0.4 and 0.75, and >0.75 representing poor, fair to good, and excellent agreement, respectively. Grafts in which CFVR was not available were discarded. A p value <0.05 was considered significant.

Results

Study Population

A total of 25 patients were included in the study. Patient characteristics are presented in Table 5.1. Fifty-seven bypass grafts were evaluated. Bypass graft characteristics are presented in Table 5.2. Stenosis severity, as measured by QCA, ranged from 0% to 100%

Number of bypass grafts (n)	57
Arterial/vein grafts	12/45
Single/sequential grafts	39/18
Vascular territory perfused by graft	
LAD	26 (46%)
LCX	13 (23%)
RCA	18 (32%)
Percentage diameter stenosis (QCA)	55 ± 36%
<50%	23
≥50%	34
Minimal luminal diameter (mm)	1.26 ± 0.50

Table 5.2

Bypass Graft Characteristics

LAD = left anterior descending artery; LCX = left circumflex artery; RCA = right coronary artery; QCA = quantitative coronary arteriography

with a mean percentage diameter stenosis of 55 ± 36%. Based on the QCA results, the grafts were divided into grafts with angiographically nonsignificant (<50%, n = 23), and significant stenoses (≥50%, n = 34).

Gated SPECT

Gated SPECT demonstrated an average LV ejection fraction of 53 ± 17% (range 24% to 85%). Mean end-systolic and end-diastolic volumes were 65 ± 50 ml and 122 ± 64 ml, respectively.

In the vascular territories supplied by the 57 grafts, stress myocardial perfusion was normal in the territories allocated to 25 grafts, mild or moderately reduced in territories of 17 grafts, and severely reduced in territories of 15 grafts. Rest perfusion was normal in 39 grafts, mild to moderately reduced in 15 grafts, and severely reduced in three grafts. Accordingly, perfusion was normal in the vascular territory of 25 grafts, ischemia was present in the territory of 22 grafts, and irreversible defects (indicating scar tissue) were present in the territory of 10 grafts. Perfusion defects per vascular territory are summarized in Table 5.3.

	Normal perfusion (n = 25)	Ischemia (n = 22)	Scar (n = 10)
LAD territory (n = 26)	13	9	4
LCX territory (n = 13)	4	5	4
RCA territory (n = 18)	8	8	2

Table 5.3

SPECT Perfusion Results per Vascular Territory of the Bypass Graft

SPECT = single-photon emission computed tomography; other abbreviations as in Table 5.2

SPECT Perfusion versus Angiographic Stenosis

Based on integration of the angiographic findings and SPECT results, 18 of 57 grafts (32%) were classified as stenosis <50% with normal perfusion; 27 (47%) had a stenosis ≥50% with abnormal perfusion, seven (12%) had a stenosis ≥50% with normal perfusion, indicating no hemodynamic significance of the stenosis; and five (9%) grafts had a stenosis <50% with abnormal perfusion, indicating microvascular disease. Mean percent diameter stenosis for the four categories were 16 ± 20%, 79 ± 20%, 65 ± 18%, and 36 ± 20%, respectively. Differences in percent diameter stenosis between the categories with equivalent stenosis percentages (<50% or ≥50%) were not significant. Mean minimal luminal diameter for the four categories were 1.51 ± 0.52 mm, 1.14 ± 0.50 mm, 1.33 ± 0.54 mm, and 1.03 ± 0.28 mm, respectively (p = NS).

Cardiovascular Magnetic Resonance

In 46 of 57 grafts, full CMR with velocity mapping at rest and during adenosine stress was successful. In 11 grafts velocity mapping failed for the following reasons. In one graft, the baseline velocity map could not be analyzed because of insufficient technical quality. In four grafts, stress velocity maps could not be obtained because of minor adverse reactions to adenosine, such as chest pain, dyspnea, headache, and flushing. All adverse reactions resolved within a few minutes after termination of adenosine infusion. In six grafts, velocity mapping could not be completed because of limitation of total research time, reserved for the CMR examination. One full CMR examination took approximately 1.5 hours to complete.

Fourteen of 57 grafts (25%) were not found in their expected course on the survey scan (zero flow) and were considered to be occluded.

Mean APV increased from 6.9 ± 5.5 cm/s (range 0 to 19.5 cm/s) at baseline to 15.2 ± 12.0 cm/s (range 0 to 35.6 cm/s) during stress, resulting in a mean CFVR of 1.7 ± 1.3 (range 0 to 3.7). When a cutoff value for CFVR of 2.0 was used (17), normal CFVR (≥2.0) was found in 25 grafts with a mean CFVR of 2.7 ± 0.5 and reduced CFVR (<2.0) in 21 grafts with a mean CFVR of 0.5 ± 0.8.

		CMR		
		CFVR ≥2.0	CFVR <2.0	Total
SPECT	Normal perfusion	18	2	20
	Abnormal perfusion	7	19	26
	Total	25	21	46

Table 5.4

Agreement of SPECT Perfusion and CMR

Only grafts with available CFVR (n = 46) were included.

SPECT = single-photon emission computed tomography; CMR = cardiovascular magnetic resonance; CFVR = coronary flow velocity reserve

SPECT/Angiography	CMR		
	CFVR ≥2.0	CFVR <2.0	Total
Stenosis <50% / normal SPECT perfusion	12	2	14
Stenosis ≥50% / abnormal SPECT perfusion	5	18	23
Stenosis ≥50% / normal SPECT perfusion	6	0	6
Stenosis <50% / abnormal SPECT perfusion	2	1	3
Total	25	21	46

Table 5.5
Agreement Between SPECT and CMR in Four Categories
Only grafts with available CFVR (n = 46) were included. Abbreviations as in Table 5.4

Relation between SPECT Perfusion and CMR
Grafts for which CFVR was not available (n = 11) were discarded. In 18 of the 20 grafts (90%) with normal perfusion on SPECT, CFVR was preserved (Table 5.4). Conversely, in 19 of 26 grafts (69%) with abnormal perfusion on SPECT, CFVR was reduced. Accordingly, SPECT and CMR provided similar information in 37 of 46 grafts (80%; κ = 0.61), illustrating a good agreement between SPECT and CMR ($p<0.001$).
The relation between SPECT and CMR in the four categories (see Statistical Analysis section) is depicted in Table 5.5. Grafts (n = 14) with a stenosis <50% and normal perfusion on SPECT had normal CFVR in 86%; 78% of grafts (n = 23) with a stenosis ≥50% and abnormal perfusion had reduced CFVR. Grafts with a stenosis ≥50% and normal perfusion, indicating no hemodynamic significance of the stenosis, also had normal CFVR in 100%. Finally, 33% of grafts with a stenosis <50% and abnormal perfusion (suggesting microvascular disease) also had reduced CFVR.

Influence of Scar Tissue
According to the SPECT results, scar tissue was present in the perfused territory of 8 of 46 grafts with available CFVR. When the analysis was restricted to grafts without scar tissue on SPECT, the agreement between SPECT and CMR improved to 84% (32 of 38 grafts; κ = 0.68).

Discussion
In the present study a head-to-head comparison between SPECT and CMR to evaluate the hemodynamic significance of angiographic findings in bypass grafts was performed. Similar results of SPECT perfusion and CFVR assessed by CMR were demonstrated in 80% of grafts (κ = 0.61), indicating that both noninvasive approaches provide similar information concerning the hemodynamic significance of the lesions detected invasively. Integration of an invasive and a noninvasive approach may allow optimal characterization of lesions.

Characterization of Angiographic Lesions by SPECT

SPECT perfusion imaging is a well-established technique to evaluate ischemic heart disease by assessing regional perfusion. A wealth of data is present demonstrating excellent sensitivities and specificities of (gated) SPECT to detect stenoses in native coronary arteries using coronary angiography as the gold standard (5;14). Less data are available in patients who underwent bypass surgery. A sensitivity of 80% with a specificity of 87% for the detection of >50% bypass graft stenosis has been reported (6). However, the hemodynamic significance of an angiographic stenosis cannot be determined on the coronary angiogram alone (1;2). A different approach is to use functional testing to further characterize the hemodynamic significance of an angiographic lesion. Chamuleau et al. (18) used this concept to further characterize intermediate stenoses (40% to 70%) in native coronary arteries by SPECT and by invasively acquired CFVR and used the results of the functional testing for deferral of a percutaneous coronary intervention in 191 patients. Safe deferral was demonstrated, when CFVR was ≥2.0 (event rate 6%). Both CFVR and SPECT were predictive of subsequent cardiac events. In the present study, SPECT was used to characterize angiographic findings into four categories: 1) both tests show normal results (n = 18); 2) both tests show abnormal results (n = 27); 3) discordance: angiographic significant stenosis but normal SPECT results, implying no hemodynamic consequence of the lesion (n = 7); and 4) discordance: no stenosis, but perfusion defects on SPECT, implying microvascular disease (n = 5).

Agreement between SPECT and CMR

It was previously demonstrated that SPECT perfusion imaging agreed well with CFVR established during cardiac catheterization using the Doppler guide wire. An agreement of 76% between SPECT perfusion and invasively acquired CFVR was demonstrated in patients with two-vessel coronary artery disease (17).

CMR with flow velocity mapping is a new noninvasive technique to assess CFVR, and evaluate the functional significance of a stenosis. Recently, the value of CMR with velocity mapping in the detection of stenoses in bypass grafts and recipient vessels was demonstrated. A sensitivity of 94% with a specificity of 63% for the detection of angiographically significant stenoses in single vein grafts has been reported (8). In another study, CMR with velocity mapping yielded a sensitivity and specificity of 78% and 80% for detecting vein grafts with a significant stenosis (19).

In the present study, agreement between SPECT perfusion imaging and CFVR acquired by CMR was assessed, showing both diagnostic tests to agree well in the identification of the hemodynamic significance of a stenosis in bypass grafts. In the aforementioned four categories of functional characterization of angiographic lesions, the agreement of SPECT and CMR results was evaluated. When angiography showed a nonsignificant (<50%) stenosis and SPECT showed normal perfusion, the agreement with CMR was good. Also, when angiography showed a significant stenosis and SPECT showed abnormal perfusion, the majority of lesions had reduced CFVR on CMR. Most importantly, 100% of the lesions with a significant stenosis on angiography but normal perfusion on SPECT (indicating no hemodynamic significance) had preserved CFVR on CMR, underscoring the capability of CMR with flow velocity mapping to accurately characterize angiographic lesions. The category without a significant stenosis on angiography and abnormal SPECT, suggesting microvascular disease, contained few grafts. To draw any conclusions on this particular group, a larger sample size is needed.

Influence of Scar Tissue

A prior myocardial infarction, as evidenced by scar tissue on SPECT perfusion imaging, is known to affect CFVR (20;21). The extent of infarcted myocardium is an important factor in the impairment of CFVR. Conversely, when a graft is placed on a partially infarcted area, it can still display a preserved CFVR. Accordingly, when grafts with scar tissue in their perfused territory were eliminated from the analyses in the present study, agreement of SPECT and CFVR increased to 84%.

Study Limitations

Several limitations of the study need to be addressed. First, the current study did not investigate the safety of deferral of patients with significant stenoses in bypass grafts when negative test results were demonstrated by SPECT or CMR.

Full CMR examination with baseline and stress velocity mapping could not be completed in 11 grafts. In 10 grafts this was due either to minor adverse reactions to adenosine or a short period of time available for research in between the standard scanning procedures; only in one graft was it technically unfeasible to acquire CFVR.

Both exercise-induced and adenosine-induced stressors were used at SPECT imaging. However, previous studies with thallium-201 or technetium-99m tetrofosmin SPECT demonstrated comparable accuracies for both stressors to detect coronary artery disease (22;23). In the current study, exercise-induced and adenosine-induced stressors were equally distributed in the four distinguished categories and provided no source of disagreement between SPECT and CMR results.

In the present study sequential stenoses within a graft were not separately investigated. The most severe graft stenosis was considered the most flow-limiting lesion. Additional research is required to evaluate the influence of sequential stenoses in bypass grafts on SPECT perfusion imaging and CMR.

Our sample size is small. The category of grafts with a stenosis <50% and abnormal perfusion contained three grafts, which is inadequate to formulate a conclusion. Differences between groups based on specific disease categories could not be assessed.

In the current study multiple grafts in a single patient were investigated. A possible correlation of these grafts was not taken into account in the analysis.

Conclusions

The integration of anatomical and functional information obtained with angiography and SPECT, respectively, allows precise characterization of lesions. Head-to-head comparison showed good agreement between SPECT and CMR for this purpose in bypass grafts. CMR may offer an alternative method to SPECT for characterization of angiographic lesions.

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