Journal of Cardiovascular Magnetic Resonance (2005) **7,** 631–637

ISSN: 1097-6647 print / 1532-429X online
DOI: 10.1081/JCMR-200065591

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MR ANGIOGRAPHY, FLOW, AND ENDOTHELIAL FUNCTION

Evaluation of saphenous vein coronary artery bypass graft flow by cardiovascular magnetic resonance

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Cardiovascular magnetic resonance (CMR) with flow velocity mapping has emerged as a noninvasive method to measure flow in saphenous vein coronary artery bypass grafts. The aim of the current study was to retrospectively test two previously described analysis methods on a large CMR data set and to compare their diagnostic accuracy in detecting diseased vein grafts. In 125 vein grafts of 68 patients, volume flow parameters (volume flow, systolic and diastolic peak flow, diastolic-to-systolic flow ratio at rest and during adenosine stress, and flow reserve) were derived from the velocity maps. Method 1 implemented basal flow < 20 ml/min or flow reserve < 2, yielding a sensitivity and specificity of 70% and 38% in the detection of a diseased graft or recipient vessel. Method 2 used receiver operating characteristic (ROC) curve analysis and implemented all significant volume flow parameters in a logistic regression model, yielding a sensitivity of 74% with a specificity of 68% in the detection of a diseased graft or recipient vessel. Evaluating single and sequential grafts separately, this method yielded a sensitivity and specificity of 79% and 87% for single grafts, and 62% and 94% for sequential grafts in the detection of $\geq$ 50% stenosis in grafts or recipient vessels. Cut-off values were formulated for the respective volume flow parameters, which maximally separate grafts with and without $\geq$ 50% stenosis. Using ROC curve analysis with logistic regression the specificity of the analysis method improved considerably. For the current data set the best results were acquired when single and sequential grafts were separately analyzed.

Key Words: Cardiovascular magnetic resonance; Saphenous vein coronary artery bypass grafts; Flow velocity mapping; Coronary flow reserve

1. Introduction

To determine the significance of a stenosis in coronary artery bypass grafts, flow velocity can be measured during catheterization using the Doppler flow wire (1). However, this invasive procedure carries a small risk of serious complications (2–4). Cardiovascular magnetic resonance (CMR) with flow velocity mapping has emerged as a potential noninvasive method to measure flow velocity in both arterial (5) and saphenous vein coronary artery bypass grafts (6–8). In one study (7), 40 vein grafts were analyzed by CMR and an algorithm was formulated to detect stenoses in vein grafts or recipient arteries by implementing basal volume flow < 20 ml/min or flow reserve < 2. Their algorithm yielded a sensitivity and specificity of 78% and 80%, respectively, in discrimination of grafts with a stenosis < 50% and normal recipient vessel and grafts with a stenosis $\geq$ 50% or a diseased recipient vessel. A graft supplying a region with a prior myocardial infarction, considered to have an impaired flow reserve, was defined in the algorithm as a graft with a diseased recipient vessel.

Langerak et al. (8) analyzed peak velocity of MR velocity maps in single and sequential vein grafts separately and described a model, developed using receiver operating characteristic (ROC) curve analysis and logistic regression, to detect a stenosis $\geq$ 50% and $\geq$ 70% in the graft or recipient vessel. For the detection of a stenosis $\geq$ 50%, sensitivity and specificity were 94% and 63% in single vein grafts and 91% and 82% in sequential vein grafts.

In native coronary arteries, many studies have researched an optimal cut-off value for the coronary flow reserve (CFR) to separate normal from diseased arteries (9–12). In these invasive studies, CFR cut-offs ranging from 1.7 to 2.0 have been used. An optimal cut-off value for CFR derived by CMR formulated to differentiate normal from diseased vein grafts has never been investigated.

Received 18 August 2004; accepted 26 February 2005.
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Accordingly, the aim of the current study was 1) to retrospectively test two previously described analysis methods on a large, well-documented CMR data set and to compare their diagnostic accuracy in detecting diseased vein grafts, and 2) to formulate cut-off values for the individual CMR flow parameters that maximally separate normal from diseased grafts.

2. Materials and methods

2.1. *Patients*

A total of 68 patients with a history of bypass surgery underwent coronary angiography because of recurrent chest pain. Patient characteristics are summarized in Table 1. These patients were part of a study describing the diagnostic value of CMR in detecting significant stenosis in both vein and arterial grafts by analyzing peak velocity on MR velocity maps (8). In the current study, only vein grafts are described, and volume flow analysis has been used. Coronary angiography was performed according to a standard protocol using the Seldinger technique. In order to determine the stenosis severity of grafts and recipient vessels 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, 13, 14).

2.2. *CMR examination*

All patients underwent CMR examination, using a flow velocity mapping sequence to measure volume flow in bypass grafts. 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 5-element cardiac synergy coil was used. First, gross cardiac anatomy was visualized by means of a scout scan (Fig. 1). Then, transverse ECG-gated 2D gradient-echo survey scans at the level of the ascending aorta were performed to localize the grafts. When a graft was not visualized on the survey scan, it was considered occluded at CMR examination and defined to contain zero flow. When a graft was visualized, a plane perpendicular to the proximal section of the graft was planned on two differently angulated survey scans. A fast breathhold Turbo Field Echo Planar Imaging (TFEPI) sequence was used for the flow velocity mapping at rest and during stress (adenosine 140 μg/kg/min. intravenously), applying the following parameters: TR/TE of 11.0/4.6 ms, flip angle of 20°, temporal resolution of 23 ms, field of view of 200 × 100 mm, data acquisition matrix of 128 × 60 mm, in-plane spatial resolution of 1.6 × 1.6 mm, reconstructed to 0.8 × 0.8 mm by means of zero filling of k-space, section thickness of 6 mm, scan duration of 20 heart beats, velocity encoding of 75 cm/s and prospective ECG triggering. The CMR flow mapping sequence was previously validated against Doppler flow data in vitro, using a flow phantom, and in patients with vein grafts (15, 16).

Table 1. Patient and graft characteristics

Number of patients (n)	68
Male/female	57/11
Age (years)	66 ± 9
Time after CABG (years)	9 ± 5
Hypercholesterolemia	53 (77%)
Diabetes mellitus	13 (19%)
Hypertension	36 (52%)
Current smokers	9 (13%)
Positive family history for cardiovascular disease	42 (61%)
Bypass grafts included in analysis methods (n)	110
• Single vein grafts	72
• Sequential vein grafts	38
Bypass graft region	
• Left anterior descending artery	29
• Left circumflex artery	44
• Right coronary artery	37
Prior myocardial infarction in bypass graft region	50 (45%)
Percentage diameter stenosis (QCA)	53 ± 39%
• Stenosis < 50%	55 (50%)
• Stenosis ≥ 50%	55 (50%)

CABG = coronary artery bypass grafting, QCA = quantitative coronary arteriography.

2.3. *Image analysis*

Volume flow analysis of the bypass grafts was performed by means of an analytic software package (FLOW, Medis, Leiden, The Netherlands). Velocity maps consisted of paired modulus and phase images (Fig. 1). For volume flow analysis contours of the cross-sectional area of each graft were traced manually on the modulus images and transferred to the phase images. In the phase images each pixel contained a velocity value, and the average velocity of the cross-sectional area was defined as the average velocity of all the pixels within the contour. The position and size of each contour was adjusted according to the cardiac phase. The flow rate (mL/s) was then calculated by multiplying the average velocity of the cross-sectional area with the cross-sectional area for each cardiac phase. Flow rate versus time curves were reconstructed and volume flow (mL/min) was obtained by multiplying the integrated volumetric flow per heart beat with the heart rate. Systolic peak flow rate (SPF; mL/s) and diastolic peak flow rate (DPF; mL/s) were defined as maximal flow rate during systole and diastole, respectively. CFR was calculated as the ratio of volume flow during adenosine stress and volume flow at rest. The ratio between DPF and SPF was regarded as the diastolic-to-systolic flow ratio (DSFR).

2.4. *Assessment of prior myocardial infarction*

Myocardial infarction (MI) in the bypass graft region was evaluated by two cardiologists (HWV, JWJ) in consensus based on clinical investigations (patient history, electrocardiography, echocardiography, left ventricular contrast

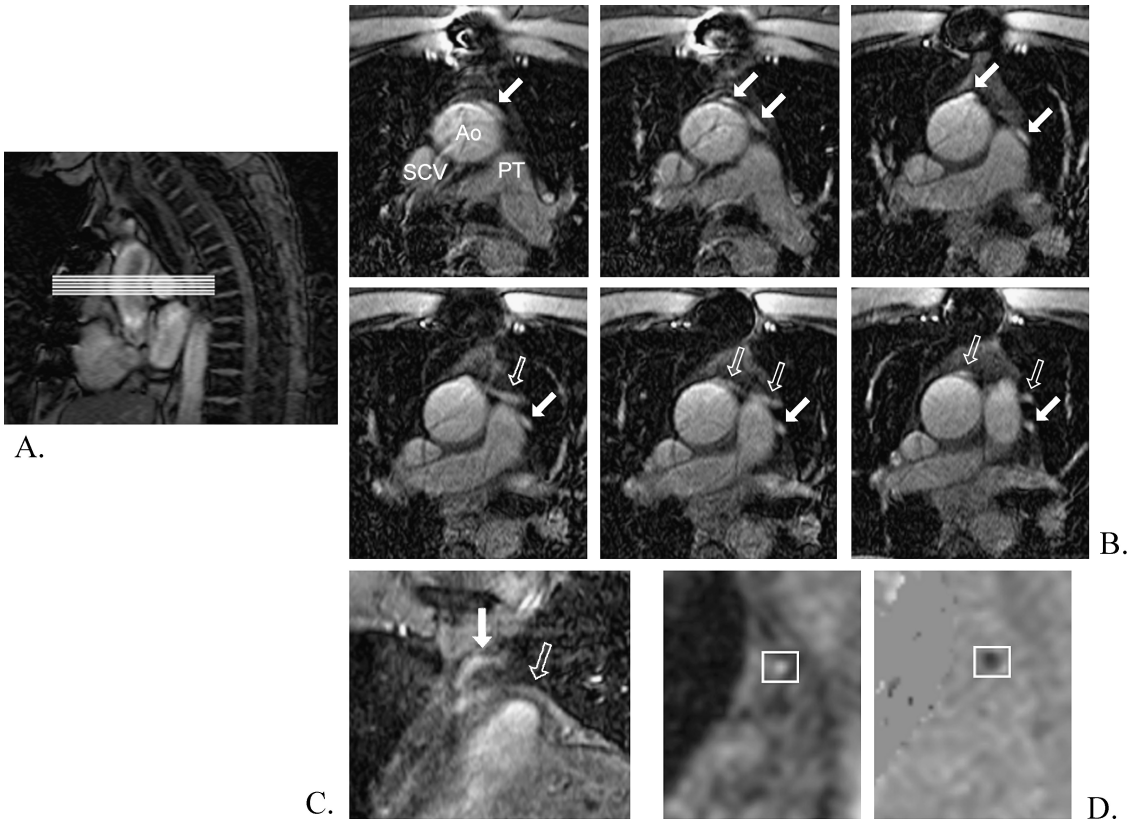

Figure 1. Example of a CMR study. Panel A shows a sagittal scout scan, on which the transversal survey scans at the level of the ascending aorta are planned. Panel B depicts the transversal survey scans showing two vein grafts, one sequential to the circumflex region (white arrow) and one single to the left anterior descending artery (outlined arrow). Ao = aorta, PT = pulmonary trunk, SCV = supra-caval vein. Panel C shows a coronal, oblique survey scan of the two vein grafts. Two differently orientated survey scans are used to plan the flow velocity scan. Panel D illustrates the flow velocity scan (modulus and phase image) in mid-diastole of the sequential graft at rest, which is used to obtain volume flow.

angiography, single photon emission computed tomography [$n = 20$], if available).

2.5. *Statistical analysis*

2.5.1. *Method 1*

The aforementioned algorithm stated that basal volume flow < 20 mL/min or CFR < 2 would indicate a diseased graft or recipient vessel (7). A diseased graft or recipient vessel was defined as either showing a stenosis $\geq$ 50% or perfusing a region with previous MI. Grafts were not divided into single and sequential grafts. This algorithm was applied to our data set. Sensitivity and specificity were calculated in a 2×2 cross tabulation, in which sensitivity was defined as the proportion of diseased grafts that are correctly identified by the algorithm and specificity as the proportion of normal grafts that are correctly identified by the algorithm.

2.5.2. *Method 2*

According to the second method (8), ROC curve analysis with logistic regression was performed on the CMR data set. To quantify the diagnostic performance of the individual flow parameters (volume flow, SPF, DPF, DSFR at rest and during stress, and CFR), ROC areas-under-the-curve (AUC) were calculated for each parameter (univariate analysis). Logistic regression analysis was performed using the parameters with significant AUC in univariate analysis to determine the diagnostic performance of the volume flow parameters (multivariate analysis). First, single and sequential grafts combined were analyzed in order to compare methods 1 and 2. A diseased graft or recipient vessel was defined as either showing a stenosis $\geq$ 50% or perfusing a region with previous MI. Sensitivities and specificities of methods 1 and 2 were compared by a McNemar test. Since prior MI may only partially compromise vein graft flow, ROC curve analysis with logistic regression was performed on the data set in separating grafts (and recipient vessels) with mild (< 50%) and significant ($\geq$ 50%) stenosis. Since significant differences in vein graft flow for single and sequential grafts were demonstrated previously (17), vein grafts were then divided into single and sequential grafts and separately analyzed. Using the univariate ROC curves, a cut-off value for each parameter with significant AUC was formulated,

Table 2. 2 × 2 table of CMR volume flow and QCA according to method 1

	QCA		
Method 1	Diseased grafts	Nondiseased grafts	Totals
CMR volume flow			
Basal volume flow < 20 ml/min or CFR < 2	51	23	74
Basal volume flow ≥ 20 ml/min and CFR ≥ 2	22	14	36
Totals	73	37	110

Diseased grafts are defined as vein grafts or recipient vessels with a stenosis severity ≥ 50% or a prior myocardial infarction in the bypass graft region. Nondiseased grafts represent vein grafts and recipient vessels with a stenosis < 50%. QCA = quantitative coronary arteriography, CFR = coronary flow reserve.

defined as the intersection of sensitivities and specificities. Sensitivities and specificities are presented with their 95%-confidence intervals (95%-CI).

2.6. *Influence of prior myocardial infarction*

In order to assess whether a MI had an impact on the flow parameters as formulated in method 1, single and sequential vein grafts with a stenosis < 50% were divided into grafts supplying a region with and without MI, and the CMR flow parameters were compared using a Student *t*-test.

A *P*-value < 0.05 was considered statistically significant.

3. Results

3.1. *Method 1*

A total of 125 vein grafts were investigated by coronary angiography and CMR flow velocity mapping, including single and sequential grafts (Table 1). Of the 125 vein grafts, CMR flow velocity mapping either at rest or during stress was not completed in 15 grafts, due to artefacts or minor adenosine side-effects. Accordingly, these 15 grafts were discarded since calculation of CFR requires both measurements at rest and during stress. On the 110 remaining grafts, the algorithm could be applied, discriminating between grafts and recipient vessels with a stenosis < 50%, and grafts or recipient vessels with a stenosis severity ≥ 50% or a MI in the perfused region. The 2 × 2 cross tabulation is displayed in Table 2. Method 1 yielded a sensitivity of 70% (95%-CI 61–79%) and a specificity of 38% (95%-CI 29–47%).

3.2. *Method 2*

For method 2, the same 15 of 125 grafts were discarded as in method 1 because either rest or stress flow velocity mapping was not completed. First, the remaining 110 grafts were analyzed to differentiate grafts with < 50% stenosis from grafts with ≥ 50% or a MI in their perfused region. In univariate analysis all parameters had a significant AUC and were included in the multivariate analysis. Using ROC curve analysis with logistic regression an AUC of 0.72 ($P < 0.001$) was found with a sensitivity of 74% (95% CI 66–82%) and a specificity of 68% (95% CI 59–78%). Compared with method 1, method 2 yielded a similar sensitivity with a significantly higher specificity.

Table 3. Optimal cut-offs of significant flow parameters of vein grafts derived from univariate analysis

Single vein grafts			Sequential vein grafts		
Flow parameter	Cut-off	AUC	Flow parameter	Cut-off	AUC
Volume flow baseline (mL/min)	22.7	0.79†	Volume flow baseline (mL/min)	40.9	0.75*
Volume flow stress (mL/min)	47.9	0.82†	Volume flow stress (mL/min)	93.6	0.77*
SPF baseline (mL/s)	0.73	0.78†	SPF baseline (mL/s)	1.17	0.80*
SPF stress (mL/s)	1.49	0.81†	SPF stress (mL/s)	2.28	0.78*
DPF baseline (mL/s)	1.15	0.79†	DPF stress (mL/s)	3.60	0.75*
DPF stress (mL/s)	2.03	0.84†			
CFR	1.56	0.81†			
DSFR baseline	0.93	0.79†			
DSFR stress	1.05	0.82†			

AUC = area-under-the-curve, SPF = systolic peak flow, DPF = diastolic peak flow, CFR = coronary flow reserve, DSFR = diastolic-to-systolic flow ratio.
†$P < 0.001$.
*$P < 0.01$.

Second, the diagnostic performance of CMR volume flow was analyzed by determining its ability to separate grafts with $< 50\%$ stenosis from grafts with $\geq 50\%$ stenosis. In multivariate analysis, an AUC of 0.80 ($P < 0.001$) was demonstrated, yielding a sensitivity of 65% (95% CI 56–74%) and a specificity of 85% (95% CI 78–92%).

Third, grafts were divided into single (n = 72) and sequential grafts (n = 38). For single vein grafts in univariate analysis, significant AUC, were demonstrated for all parameters. For sequential vein grafts, significant AUC, were found for volume flow baseline and stress, SPF baseline and stress, and DPF stress. AUC and optimal cut-off values are shown in Table 3. In multivariate analysis using ROC curve analysis with logistic regression, implementing CMR flow parameters with significant AUC, the following regression equation was formulated for single vein grafts:

$$\begin{aligned}\text{logit}(P) = {} & 0.009 * \text{volume flow}_{\text{baseline}} - 0.002 \\ & * \text{volume flow}_{\text{stress}} + 0.042 * \text{SPF}_{\text{baseline}} \\ & - 1.48 * \text{SPF}_{\text{stress}} + 1.44 * \text{DPF}_{\text{baseline}} \\ & + 0.056 * \text{DPF}_{\text{stress}} + 0.10 * \text{CFR} - 0.35 \\ & * \text{DSFR}_{\text{baseline}} - 1.68 * \text{DSFR}_{\text{stress}} + 2.34 \quad (1)\end{aligned}$$

in which P is the predicted probability for the presence of a stenosis $\geq 50\%$ in the graft or recipient vessel. Optimal cut-off for P is for single vein grafts 0.411, yielding a sensitivity of 79% (95%-CI 70–88%) and specificity of 87% (95%-CI 79–95%). In the ROC curve analysis, an AUC of 0.87 was found ($P < 0.001$).

For sequential vein grafts, the regression equation was formulated as follows:

$$\begin{aligned}\text{logit}(P) = {} & -0.019 * \text{volume flow}_{\text{baseline}} + 0.01 \\ & * \text{volume flow}_{\text{stress}} - 0.40 * \text{SPF}_{\text{baseline}} \\ & - 0.87 * \text{SPF}_{\text{stress}} + 0.005 * \text{DPF}_{\text{stress}} + 2.42 \quad (2)\end{aligned}$$

Optimal cut-off for P is 0.696 for sequential vein grafts, generating a sensitivity and specificity of 62% (95%-CI 47–77%) and 94% (95%-CI 86–100%) with an AUC of 0.81 ($P = 0.001$). ROC curves of the multivariate analysis are presented in Fig. 2.

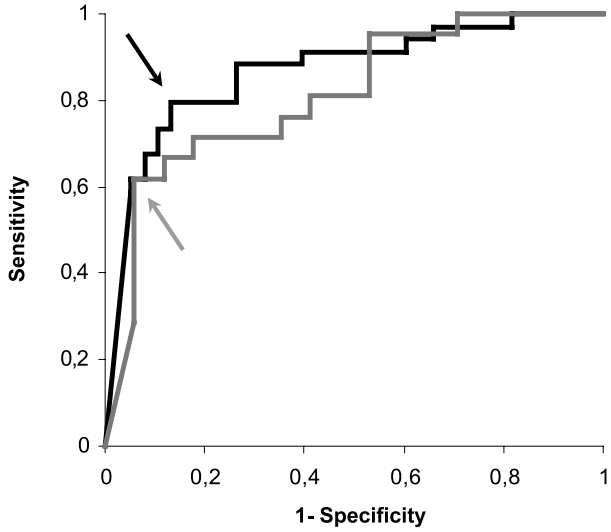

Figure 2. ROC curves of the multivariate analysis, including all significant CMR flow parameters from the univariate analysis, of single vein grafts (black line; AUC 0.87) and sequential vein grafts (grey line; AUC 0.81) in the detection of a stenosis $\geq 50\%$. Optimal cut-offs are indicated by an arrow. For single vein grafts the cut-off yielded a sensitivity and specificity of 79% and 87%, and for sequential vein grafts 62% and 94%, respectively. ROC = receiver operating characteristic; AUC = area-under-the-curve.

3.3. *Influence of prior myocardial infarction*

When grafts with and without a MI in their vascular area were compared for single and sequential grafts, respectively, no statistically significant differences were found for the flow parameters. In single vein grafts without a significant stenosis and without a MI in their perfused territory (n = 25), mean CFR was 2.9 ± 2.9 versus 2.8 ± 0.9 in patients with sustained MI (n = 11; $P = 0.84$). When a vein graft has a sustained MI in its vascular area, vein graft flow is not necessarily impaired.

4. Discussion

This is the first study that compares two previously described analysis methods for the analysis of vein graft flow with CMR. The two analysis methods were retrospectively tested on a large, well-documented CMR data set, and their diagnostic accuracy in detecting diseased vein grafts was compared. Method 1, using a previously described algorithm (7), yielded a sensitivity and specificity of 70% and 38% for discriminating between grafts without a significant stenosis (< 50%) and grafts with a significant stenosis or a diseased recipient vessel. Using ROC curve analysis with logistic regression, method 2 yielded a sensitivity and specificity of 74% and 68% in the detection of a diseased graft. For the present data set the optimal approach for evaluating vein graft flow by CMR would be to analyze single and sequential grafts separately. For single grafts, a sensitivity and specificity of 79% and 87% was demonstrated in the detection of $\geq 50\%$ stenosis in grafts or recipient vessels. And for sequential grafts a sensitivity of 62% with a specificity of 94% was found.

4.1. *Method 1*

Method 1 stated that basal volume flow < 20 ml/min or CFR < 2 would indicate a diseased graft or recipient vessel, yielding a sensitivity of 78% and a specificity of 80% (7).

When applied to a different, larger data set, similar sensitivity with a much lower specificity was demonstrated.

As a reference for the cut-off values, the study performed by Hoogendoorn et al. (18) was used, in which 23 vein grafts were investigated by CMR with flow mapping. Of the 23 grafts, 6 were occluded, and one graft had stenosis. The quantity of affected grafts in that study was too low to calculate cut-off values. In the present study, a cut-off point of 22.7 ml/min was calculated for single vein grafts (n = 72), and 40.9 ml/min for sequential vein grafts (n = 38), underscoring the need to use separate reference values for single and sequential grafts, as was recently shown (17).

4.2. *Method 2*

The cut-off value < 2 for CFR is commonly used when native coronary arteries are examined by Doppler flow wire (19, 20). However, vein grafts display a different physiology than native coronary arteries (21, 22), and therefore different cut-off values should be used. Using method 2, the best cut-off for CFR was demonstrated at 1.56 for single vein grafts. Several studies found a lower flow reserve in non-stenotic saphenous vein grafts, intra-operative, early and late after surgery, in comparison with non-stenotic native coronary arteries (23, 24). Thus, a lower cut-off than 2 could be expected.

For sequential vein grafts, CFR did not show a significant AUC at ROC analysis ($P = 0.09$). Absolute parameters (rest and stress volume flow, rest and stress SPF, stress DPF) did show significance in detecting bypass graft stenosis $\geq$ 50%, suggesting that absolute flow parameters, rather than relative parameters (CFR, DSFR), should be used in the evaluation of sequential vein grafts.

4.3. *Influence of prior myocardial infarction*

In method 1 (7), a diseased graft run-off was defined as a distal coronary artery run-off with significant stenosis ($\geq$ 50%) or a prior MI in the perfusion territory of the graft. However, the perfused territory may only partially be compromised by the MI, in particular in sequential grafts where the perfused area is large. In method 1, no distinction was made between subendocardial or transmural myocardial infarctions. In a study using a canine model small and large infarctions were induced and volume flow was measured invasively before occlusion and reperfusion of the left anterior descending artery and one week after occlusion (25). Between the large and small infarctions (transmural extent 67–100% versus < 50%) there was a significant difference in mean CFR after one week. Between small infarctions and the control group, no significant differences in mean CFR were found. In our study, no significant differences were found for the CMR flow parameters with or without sustained MI, in both single and sequential vein grafts. When a prior MI was not taken into account in method 2, the regression model improved for the data collected in the present study. Further research is required to quantify the extent of MI in the graft vascular area combined with a CFR determination, which could both be acquired by CMR (26, 27).

It would have been preferable to measure flow velocity distal to the stenosis. However this was not possible with the technique that we used since distal flow velocity measurement is associated with severe motion artefacts. Faster imaging techniques or higher field strength might overcome this problem in the future.

5. Conclusion

Two previously described methods to evaluate vein graft flow by CMR display different results when subjected to retrospective testing. Using ROC curve analysis and logistic regression the specificity of the analysis method improved considerably. For the current data set the best results were acquired when single and sequential grafts were separately analyzed, demonstrating a sensitivity of 79% and specificity of 87% for single grafts and a sensitivity of 62% with a specificity of 94% for sequential grafts. Moreover, different cut-off values may be used for the individual CMR flow parameters in single and sequential vein grafts. Absolute parameters appear to be more discriminative than relative parameters.

6. Abbreviations

CMR	cardiovascular magnetic resonance
ROC	receiver operating characteristic
CFR	coronary flow reserve
QCA	quantitative coronary arteriography
TFEPI	Turbo Field Echo Planar Imaging
TR	repetition time
TE	echo time
SPF	systolic peak flow
DPF	diastolic peak flow
DSFR	diastolic-to-systolic flow ratio
MI	myocardial infarction
AUC	area-under-the-curve
95%-CI	95%-confidence interval

Acknowledgment

The Netherlands Heart Foundation, The Hague, the Netherlands, supported J.W. Jukema (established clinical investigator; grant 2001D032).

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