Assessment of Coronary Artery Bypass Graft Disease Using Cardiovascular Magnetic Resonance Determination of Flow Reserve

Willeijn L. F. Bedaux, MD,*∥ Mark B. M. Hofman, PhD,† Stefan L. A. Vyt, MD,‡ Jean G. F. Bronzwaer, MD,* Cees A. Visser, MD, PhD,*§ Albert C. van Rossum, MD, PhD*§
Amsterdam and Utrecht, the Netherlands

OBJECTIVES The purpose of this study was to assess the value of cardiovascular magnetic resonance (CMR)–determined graft flow and flow reserve in differentiating significant from non-significant vein graft disease.

BACKGROUND In patients after coronary artery bypass grafting (CABG), non-invasive testing may be helpful in the detection of recurrent graft disease.

METHODS Randomly selected patients (n = 21) scheduled for X-ray angiography because of recurrent chest complaints after CABG were included for evaluation of vein grafts (n = 40) by CMR. Three-dimensional contrast-enhanced CMR angiography was performed and followed by flow measurements at rest and during hyperemia in patent grafts only. Flow reserve was calculated when resting flow exceeded 20 ml/min. Analysis was based on four categories defined by X-ray angiography: occluded grafts (n = 3), grafts with stenosis >50% (n = 19), grafts with stenosis <50% with diseased graft run-off (n = 8), and grafts with stenosis <50% and normal run-off (n = 10).

RESULTS The CMR angiography demonstrated occlusion of three grafts. In nine of the 37 patent grafts, basal blood flow was <20 ml/min, all demonstrating significant stenosis at X-ray angiography. In grafts with resting flow >20 ml/min (n = 28), flow reserve significantly differed between grafts without stenosis and grafts with significant stenosis or with diseased run-off (2.5 ± 0.7 vs. 1.8 ± 0.9, p = 0.04). An algorithm combining basal volume flow <20 ml/min and graft flow reserve <2 had a sensitivity and specificity of 78% and 80% respectively for detecting grafts with significant stenosis or diseased run-off.

CONCLUSIONS This feasibility study showed that quantification of flow and flow reserve by CMR may serve as a non-invasive adjunct to differentiate between vein grafts without stenosis and grafts with significant stenosis or diseased run-off.

After coronary artery bypass surgery, saphenous vein grafts demonstrate a high incidence of progressive atherosclerotic disease. Nearly 30% of the grafts are significantly diseased by one year, with an increasing incidence over the years after surgery (1,2). X-ray angiography is considered to be the standard procedure for evaluation of coronary artery bypass grafts as it provides excellent graft visualization, quantitative information on the degree of luminal obstructions, and access to immediate intervention. However, it carries the risk of adverse events related to the invasive character of the procedure and to administration of contrast agents (3). The capability of cardiovascular magnetic resonance (CMR) to assess patency of coronary artery vein grafts has been demonstrated (4–10). Limitations arise with regard to assessing obstructive disease and evaluating distal segments of sequential grafts, owing to insufficient spatial resolution, low signal-to-noise ratio, and cardiac motion. Adding information on flow (11–14) and flow reserve (15,16) using velocity-encoded cine CMR may help to detect the presence of hemodynamically significant graft stenosis.

The purpose of this study was to determine the feasibility of measuring volume flow and flow reserve of saphenous vein bypass grafts using CMR in patients suspected of graft disease, and to assess the value of CMR–determined graft flow reserve in differentiating non-diseased grafts from grafts with a significant stenosis or diseased run-off.

METHODS

Patient selection. Randomly selected patients referred for diagnostic X-ray angiography because of recurrent chest complaints after CABG were included during 21 months. Patients were ineligible for enrollment if they had a contra-indication for CMR (pacemaker, intracranial ferromagnetic clips, unstable medical condition, extreme obesity, or claus-
trophobia), cardiac arrhythmias interfering with adequate image acquisition, or a contraindication to receive adenosine (heart block or reactive respiratory disease). All substances that could interfere with the metabolism of adenosine, such as caffeine and other methylxanthine derivatives, were withheld 12 h before the study. The medication regimen was not changed, except for beta-blockers, which were withheld 24 h before CMR. Surgical records were reviewed to determine the number of grafts, the sites of distal anastomoses, and whether the grafts were single or sequential. This information was used to adjust the slice orientation of the imaging protocol. Because of CMR artifacts induced by clips, internal mammary grafts were excluded from the study. In patients with sustained myocardial infarction, the infarct region was identified from previously documented electrocardiographic, echocardiographic, and angiographic findings.

The study was approved by the Medical Ethics Committee of the VU University Medical Center of Amsterdam, the Netherlands, and all participants gave informed consent.

**CMR technique.** The CMR was performed using a 1.5-Tesla whole body CMR system (Vision, Siemens, Germany), a phased array body receiver coil, and prospective electrocardiographic gating. First, a multislice two-dimensional breath-hold, double inversion, black blood turbo spin-echo sequence (repetition time 800 ms, echo time 44 ms; field of view 230 to 350 mm; matrix 176 × 256, slice thickness 5 mm) was applied in an axial plane at the level of the aortic root to visualize the origin of the grafts. The proximal segments of the grafts were identified from the typical sites of the aortotomy. The graft with the most superior origin from the aorta and coursing laterally from the main or left pulmonary artery was considered to anastomose with the circumflex artery or marginal branches. The next lower graft with a more anterior course immediately leftward from the main pulmonary artery was judged to anastomose with the left anterior descending artery or diagonal branches. The graft with the most inferior origin from the aorta, coursing next to the right atrium or atrioventricular groove was considered to anastomose with the right or posterior descending coronary artery.

Three-dimensional (3D) contrast-enhanced CMR angiography was applied using gadolinium–diethylene triamine pentacetic acid (dose 0.1 to 0.2 mmol/kg) for the assessment of the course and patency of the proximal parts of the grafts. More distal parts of sequential grafts were not visualized owing to limited coverage by the 3D volume slab or cardiac motion. Acquisition parameters used were repetition time 5 ms, echo time 2 ms, excitation angle 14°, matrix 96 × 256 to 124 × 256, slab thickness 100 to 110 mm, and 30 to 34 partitions. In-plane resolution ranged from 2.0 × 1.6 to 2.8 × 1.6 mm. A trigger-time delay of 50 to 250 ms was used to drive the acquisition toward diastole. For an optimal timing of the contrast arrival, the time to peak contrast was determined using a contrast test bolus in a transverse plane at the middle of the ascending aorta. When both 3D CMR angiography and turbo spin echo imaging showed an occlusion of the graft, flow measurements in this graft were not performed. Figure 1 shows the X-ray angiography (Fig. 1A) and the 3D contrast-enhanced CMR angiogram (Fig. 1B) of a patient with two stenoses in a jump graft anastomosed to the posterolateral branch of the circumflex and the posterior descending branch of the right coronary artery.

Phase-contrast velocity measurements were performed perpendicular to the proximal part of the saphenous vein graft of interest during breath holding. In a subset of sequential grafts, additional phase-contrast velocity measurements were acquired in the segments between subsequent anastomoses, but these were not used in the general analysis. A segmented k-space gradient echo pulse sequence was applied with five phase-encoding steps for each frame within the cardiac cycle (repetition time 10.5 ms, echo time 5 ms, excitation angle 30°, acquisition window 105 ms, spatial resolution 0.9 × 1.5 × 6 mm³). Other imaging parameters included a temporal resolution of 125 ms, a field of view of 200 × 200 mm, and scan duration of 27 heartbeats. Before every frame, a fat saturation pre-pulse was applied. The encoding velocity was set to 40 cm/s at baseline and 75 cm/s during hyperemia, resulting in a velocity window of −40 to 40 cm/s or −75 to 75 cm/s, respectively. Figure 2 shows an example of the anatomic image (Fig. 2A) and the phase-contrast velocity map (Fig. 2B), acquired perpendicular to grafts inserting to the obtuse marginal branch of the circumflex artery and the diagonal branch of the left anterior descending artery, respectively.

Then, adenosine was administered intravenously using a dose of 140 μg/kg/min during 6 to 10 min. After 2 min of infusion, CMR phase-contrast velocity measurements were repeated during maximal hyperemia. Heart rate and systemic arterial pressure were monitored and recorded at rest, and every 2 min during administration of adenosine. The total procedure was performed within 45 min.

**CMR flow analysis.** The images were evaluated without knowledge of the X-ray angiography results. In patent grafts, flow velocity analysis was performed with an analytic software package (FLOW, Medis, Leiden, The Netherlands). The contour of the cross-sectional graft was visually determined on a magnitude image. The area of the region of interest was kept constant over the cardiac cycle and repositioned at each time frame on the magnitude image. The phasic volume flow within the cross-sectional area was measured on the corresponding velocity image. Because a prospectively triggered electrocardiographic gating technique was applied, no measurements could be obtained.
during the final 50 to 100 ms of the cardiac cycle. To compensate for this lack of data, an interpolation was performed between the first and last phase. Volume flow was determined by averaging the phasic volume flow over the cardiac cycle. Graft flow reserve was calculated by the ratio of hyperemic volume flow divided by the basal volume flow. Graft flow reserve was not calculated when the absolute basal volume flow was below 20 ml/min as this would introduce relatively large errors at low flow values. The error in the flow reserve is determined by the relative error in the basal and stress flow measurements. These relative errors are large in the low velocity range because of absolute errors induced by limited signal-to-noise ratio and background noise. In a previously reported study, resting flow below 20 ml/min was indicative of significant graft disease (14). The total CMR flow analysis ranged from 5 to 10 min per graft.

**X-ray coronary angiography.** In all patients, conventional biplane angiography was performed with the Judkins technique. Grafts and native coronary arteries were imaged during the final 50 to 100 ms of the cardiac cycle. To compensate for this lack of data, an interpolation was performed between the first and last phase. Volume flow was determined by averaging the phasic volume flow over the cardiac cycle. Graft flow reserve was calculated by the ratio of hyperemic volume flow divided by the basal volume flow. Graft flow reserve was not calculated when the absolute basal volume flow was below 20 ml/min as this would introduce relatively large errors at low flow values. The error in the flow reserve is determined by the relative error in the basal and stress flow measurements. These relative errors are large in the low velocity range because of absolute errors induced by limited signal-to-noise ratio and background noise. In a previously reported study, resting flow below 20 ml/min was indicative of significant graft disease (14). The total CMR flow analysis ranged from 5 to 10 min per graft.

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**Figure 1.** X-ray coronary bypass angiogram (A), and 3D contrast-enhanced cardiovascular magnetic resonance angiogram obtained through post-processing using a maximum intensity projection (B) of a patient with a sequential graft with anastomoses to the posterolateral branch of the circumflex and the posterior descending branch of the right coronary artery. The open arrow points to a stenosis with 59% luminal narrowing, the white arrow to a stenosis with 73% luminal narrowing. Luminal stenosis was determined by quantitative coronary angiography on two orthogonal projections. Ao = aorta.

**Figure 2.** Images obtained simultaneously in an orientation perpendicular to grafts inserted to the obtuse marginal branch of the circumflex artery (white arrow) and the diagonal branch of the left anterior descending artery (open arrow). (A) The anatomic image. (B) The corresponding velocity map in diastole. Ao = aorta.
using manual contrast media injections in orthogonal views. Where graft narrowing was observed, percent lumen diameter stenosis was calculated from the cineangiograms using quantitative measurements on two orthogonal projections. Based on X-ray angiography, a classification was made into the following categories: I) occluded grafts; II) patent grafts with <50% luminal narrowing; III) grafts with luminal narrowing <50% and distal run-off to a coronary artery with a significant stenosis (>50%) or to a myocardial perfusion territory with old infarction (diseased graft run-off); and IV) grafts with luminal narrowing <50% and normal run-off.

**Table 1. Clinical Characteristics of the Patients**

<table>
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*Data from 21 patients (A–U) with a total of 40 saphenous vein grafts. †Classification I—occluded grafts; II—patent grafts with >50% luminal narrowing; III—grafts with luminal narrowing <50% and distal run-off to a coronary artery with a significant stenosis (>50%) or to a myocardial perfusion territory with old infarction (diseased graft run-off); IV—grafts with luminal narrowing <50% and normal run-off.

a = anterolateral branch; am = acute marginal branch; ant = anterior; cx = circumflex artery; d = diagonal branch; F = female; inf = inferior; lad = left anterior descending artery; lat = lateral; lpl = left posterolateral branch; M = male; om = obtuse marginal branch; post = posterior; QCA = quantitative coronary angiography; rca = right coronary artery; rpd = right posterior descending artery; rpl = right posterolateral branch.

**Data analysis.** All results are presented as mean ± standard deviation. Measurements on separate grafts within one patient are considered as independent in the analysis, because separate CMR acquisitions were performed for each graft. Statistical significance of differences between categories was determined with an unpaired Student t test; p < 0.05 was considered statistically significant.

**RESULTS**

Twenty-one patients (mean age 61 ± 9 years, 20 male) were included in the study. Patient characteristics and results of
quantitative coronary angiography are described in Table 1. In none of the patients, stent implantation had occurred at the time of the CMR. The CMR was performed of 40 saphenous vein grafts (18 single and 22 sequential grafts) within 24/11006-49 days of the X-ray angiography. No adverse cardiovascular events occurred between CMR and X-ray angiography. During adenosine infusion seven patients suffered from chest pain, immediately subsiding after terminating the infusion. Significant rhythm or conduction abnormalities did not occur.

Three grafts were occluded according to 3D CMR angiography, which was confirmed by X-ray angiography. Figure 3 shows the basal volume flow measurements in all non-occluded grafts (n = 37). Volume flow at rest was <20 ml/min in nine grafts, all demonstrating a significant stenosis (>50%) by X-ray angiography. In 28 grafts with basal volume flow >20 ml/min, volume flow increased from 53 ± 26 ml/min at rest to 98 ± 49 ml/min during administration of adenosine. The calculated flow reserve ranged from 0.8 to 3.8. For subcategories, flow reserves in grafts without stenosis and normal run-off (n = 10), in grafts with a diseased graft run-off (n = 8), and in grafts with stenosis >50% (n = 10) demonstrated a gradual decrease from 2.5 ± 0.7, to 2.0 ± 1.0, and to 1.6 ± 0.8, respectively (Fig. 4).

For clinical decision making, it is important to differentiate between open grafts with a good run-off that do not need further invasive work-up and diseased grafts or coronary arteries distal from the anastomosis that require a further invasive evaluation. To that end, a significant difference was found between flow reserve in the grafts with stenosis <50% and a normal run-off (n = 10) and grafts with stenosis >50% or diseased run-off (n = 18) (2.5 ± 0.7 vs. 1.8 ± 0.9, p = 0.04) (Fig. 5). An algorithm combining an absolute basal volume flow <20 ml/min or graft flow reserve <2 had a sensitivity and specificity of 78% and 80%, respectively (positive predictive value 91%, negative predictive value 57%) for detecting a stenosis >50% or a diseased run-off.

In six sequential grafts, flow measurements were determined at multiple levels. The following observations are exemplary cases meant to illustrate the potential of the technique. In Patient U (Table 1) with a sequential bypass graft to the obtuse marginal branch and right coronary artery, one measurement was performed in the proximal graft segment before the anastomosis with the obtuse marginal branch. A second measurement was performed in the segment leading to the right coronary artery. A graft flow reserve of 3.6 and 2.7 was obtained, respectively. X-ray angiography of the same patient demonstrated a non-diseased graft with a normal caliber. In Patient S with a sequential graft to the anterolateral, obtuse marginal, and posterior descending branch, X-ray angiography demonstrated a 100% stenosis at the anastomosis with the obtuse marginal branch. A second measurement was performed in the segment leading to the right coronary artery. A graft flow reserve of 3.6 and 2.7 was obtained, respectively. X-ray angiography of the same patient demonstrated a non-diseased graft with a normal caliber. In Patient S with a sequential graft to the anterolateral, obtuse marginal, and posterior descending branch, X-ray angiography demonstrated a 100% stenosis at the anastomosis with the obtuse marginal branch. Graft flow reserve of the proximal segment from aorta to anterolateral branch was 2.3. Graft flow reserve of the segment from anterolateral to obtuse marginal branch was 1.1, and for the most distal segment flow reserve was not calculated because basal volume flow was 17.4 ml/min, probably due to collateral filling (i.e. <20 ml/min). The other four cases showed similar results, but the pathology in this small group was too heterogeneous to draw any conclusions.

DISCUSSION

So far, spatial resolution and consistency of CMR for detecting coronary artery bypass stenosis have not reached the level of reliability required for clinical use (7–10). Graft stenosis often occurs at the site of the anastomosis with the native coronary artery, a location where CMR encounters similar problems induced by cardiac and respiratory motion.

Figure 3. Plot of mean basal volume flow measurements as a function of stenosis severity in all patent grafts. In nine grafts a basal volume flow of <20 ml/min was measured. X-ray angiography demonstrated a significant stenosis in each graft.
as for imaging native coronary artery stenosis. In a recent study applying one of the most advanced imaging approaches, diagnostic accuracy of approximately 80% was observed after exclusion of patients with stents and another 11% of patients with insufficient image quality (17).

Only a few studies concerning the functional evaluation of grafts have been performed. Galjee et al. (7, 12) and Hoogendoorn et al. (14) provided basal flow quantification in normal and dysfunctional saphenous vein grafts, but their technique was limited by respiration movements. It appeared that a volume flow less than 20 ml/min was an indicator of early graft dysfunction (14). Single and sequential grafts are functionally different grafts as sequential grafts show significantly higher volume flow (7). In this study we found the same trend, but no differentiation in single and sequential grafts was performed to define a separate cutoff value for sequential grafts, because of the limited number of patients.

Differentiation between blood-flow limiting and non-limiting stenosis may be achieved by flow reserve measurements. Langerak et al. (15) described the correlation between Doppler and CMR velocity reserve for non-diseased grafts (n = 20) and stenotic grafts (n = 4) or grafts with a diseased run-off (n = 3). No significant difference was found because of the limited number of diseased grafts.

Other non-invasive tests have shown efficacy in the detection of ischemia, such as dobutamine stress echocardiography (18) and CMR (19), CMR first pass perfusion imaging with dipyridamole (20), and stress scintigraphy (21). As these approaches determine the myocardial contractile reserve and perfusion reserve respectively, they fundamentally differ from flow reserve measurements at the blood flow conduits.

This study shows the combined use of CMR angiography and quantification of basal volume flow and flow reserve in differentiating between non-significantly and significantly diseased venous grafts or graft run-offs. CMR is of potential value in the non-invasive evaluation of patients with previous bypass graft surgery and may help to decide whether to postpone or to proceed to X-ray angiography. In patients with angiographically proven graft stenosis, it may help to assess the functional severity of the graft stenosis, i.e., whether the graft stenosis is flow-limiting and requires revascularization.

**Limitations and potential improvements.** The CMR flow velocity measurements in multiple grafts during a 6 to 10-min stress test using short-acting adenosine require fast data acquisition, preferably within a breath-hold. The technique of breath-hold phase velocity quantification as used in this study has certain limitations, which may lead to variability of the results. First, it requires a long breath holding (20 to 35 s), which is difficult to obtain in every patient, especially during adenosine administration. The position of breath holding may vary, which can result in a

**Figure 4.** Plot of graft flow reserves in three different groups: grafts with stenosis <50% (n = 10), grafts with diseased graft run-off (n = 8), and grafts with stenosis >50% (n = 10). Flow reserves in these groups were 2.5 ± 0.7, 2.0 ± 1.0, and 1.6 ± 0.8, respectively (*p = 0.02).
In conclusion, this study shows the feasibility of CMR flow quantification to non-invasively differentiate between non-significantly diseased grafts and grafts that are significantly diseased or have a diseased graft run-off. The technique may become of clinical value to help in deciding whether or not to proceed to a further invasive evaluation.

Reprint requests and correspondence: Dr. Willemijn L. F. Bedaux, Department of Cardiology, VU University Medical Center, Amsterdam, De Boelelaan 1117, 1081 HV Amsterdam, the Netherlands. E-mail: wlf.bedaux@VUmc.nl.

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