Multimodality imaging of coronary artery bypass grafts

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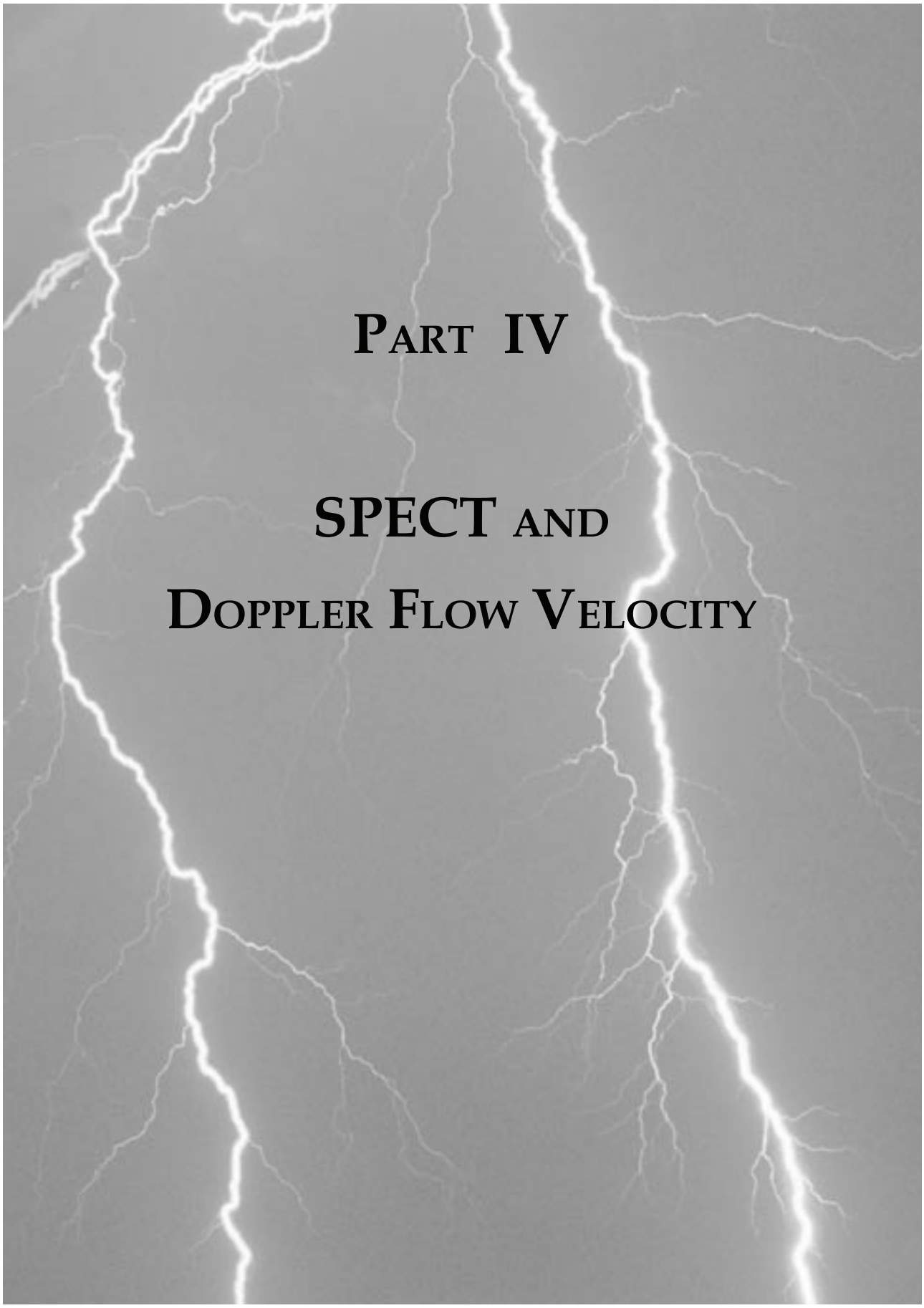

Part IV

SPECT and Doppler Flow Velocity

CHAPTER 9

Hemodynamic evaluation of saphenous vein coronary artery bypass grafts: relative merits of Doppler flow velocity and SPECT perfusion imaging

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ABSTRACT

Background: Coronary angiography is considered the gold standard in evaluating vein graft disease; however, angiography does not allow assessment of hemodynamic consequences of lesions. In this study, hemodynamic consequences of significant stenoses in vein grafts were evaluated by Doppler velocity assessment, and results were compared with single-photon emission computed tomography (SPECT) perfusion imaging.

Methods and Results: Angiography was performed in 58 patients after coronary artery bypass grafting because of recurrent chest pain. During the procedure, Doppler velocity measurements were acquired before and after administration of adenosine. Of 58 patients (with 78 vein grafts), 20 patients (with 24 vein grafts) underwent SPECT perfusion imaging.

Grafts were divided into those with non-significant percent diameter stenosis (<50%, n = 49), and those with significant percent diameter stenosis (≥50%, n = 29). When a cut-off value for coronary flow velocity reserve (CFVR) of 1.8 was applied, modest agreement (69%, $\kappa = 0.25$, $p<0.05$) between CFVR and angiography was shown. Agreement between SPECT and angiography was also modest (63%, $\kappa = 0.28$, p = NS). SPECT and CFVR provided comparable information in 20 of 24 grafts with available SPECT, illustrating good agreement (83%, $\kappa = 0.61$, $p = 0.001$).

Conclusions: Significant stenoses in vein grafts require further exploration to assess their hemodynamic significance. The Doppler velocity results agreed better with SPECT perfusion imaging than with percent diameter stenosis in the evaluation of vein graft function.

Introduction

Determination of stenosis severity by coronary angiography is considered the gold standard for the assessment of obstructive coronary artery disease, but the hemodynamic significance of a stenosis cannot be derived from the coronary angiogram (1;2), and additional diagnostic testing is required. Invasively, the hemodynamic consequences can be determined by flow velocity measurements by use of the Doppler flow wire at rest and during hyperemia, as well as calculation of the coronary flow velocity reserve (CFVR) (3;4). This technique has been extensively explored in native coronary arteries (5-8), but studies in bypass grafts are limited. In vein grafts in particular, discordance between the angiographic severity of the stenosis and the hemodynamic consequences occurs (4).

Myocardial perfusion imaging with single-photon emission computed tomography (SPECT) is a noninvasive imaging technique that also allows evaluation of the hemodynamic significance of stenotic lesions in coronary arteries or bypass grafts (9;10). For clinical routine use, noninvasive testing may be preferred. However, direct comparisons between the invasive flow wire measurements and noninvasive SPECT imaging for assessment of the hemodynamic significance of lesions in patients with vein grafts are lacking. Accordingly, the aim of this study was to evaluate the relationship between angiographic stenosis severity and CFVR in a large number of vein grafts, as well as to perform a comparison between the Doppler flow wire and SPECT perfusion imaging to evaluate the hemodynamic consequences of stenoses in vein grafts.

Methods

Study Population

A total of 58 patients with a history of coronary artery bypass grafting (CABG) underwent coronary angiography because of recurrent chest pain. All underwent Doppler flow velocity measurements, and in 20 patients SPECT perfusion imaging was performed. The protocol was approved by the local medical ethics committee and informed consent was obtained from all patients.

Coronary Angiography and Doppler Flow Velocity Measurements

Routine coronary angiography procedures were performed; vascular access was obtained via the femoral approach. Doppler flow velocity measurements were performed in vein grafts only. A 0.014-inch Doppler guide wire (FloWire, Cardiometrics, Mountain View, CA) was advanced proximal into the graft and adjusted until a stable blood flow velocity signal was acquired (3;4). After the bolus injection of 18 µg adenosine directly into the graft, hyperemic velocity was measured (11). When velocity returned to baseline, measurements were repeated. When two baseline measurements differed by more than 10%, a third measurement was obtained and values were averaged. Doppler flow velocity measurements were previously validated by comparison with flow meters (12;13) and good reproducibility of measurements was demonstrated (14).

Subsequently, angiography of the graft was performed according to the standard protocol. All percent diameter stenoses and percent area stenoses in either bypass graft or distal coronary arteries supplied by the graft were analyzed objectively by use of

quantitative coronary arteriography (QCA) by an independent core laboratory (Heart Core, Leiden, the Netherlands). If two or more stenoses were present in either graft or recipient vessels, the most severe lesion was considered the most flow limiting stenosis. Coronary bypass graft flow velocity was digitized offline by use of a computer with a custom-made software program. Digitized peak flow velocity from at least three cardiac cycles was averaged to calculate the average peak velocity (APV; cm/s), systolic peak velocity (SPV; cm/s), and diastolic peak velocity (DPV; cm/s) at baseline and during hyperemia by use of adenosine. CFVR was computed as the ratio of hyperemic to baseline APV, and diastolic-to-systolic velocity ratio (DSVR) as the ratio of DPV and SPV.

Gated SPECT Perfusion Imaging

For the gated SPECT examination, a 2-day stress-rest protocol was used (15). The stress protocol included a symptom-limited treadmill exercise test. Test endpoints were physical exhaustion, dyspnea, angina pectoris, significant decrease in blood pressure (>10 mmHg), or achievement of the maximum age-related heart rate. 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 = 10), adenosine stress was used. On the second day, resting images were obtained by use of 500 MBq Tc-99m tetrofosmin. The resting studies were acquired by use of electrocardiography gating, allowing assessment of left ventricular ejection fraction (LVEF) and left ventricular volumes (16).

Imaging was performed with a triple-head SPECT camera system (GCA 9300/HG, Toshiba Corporation, Tokyo, Japan) equipped with low-energy, high-resolution collimators. A 20% window was used around the 140-keV energy-peak of Tc-99m tetrofosmin. A total of 90 projections (step-and-shoot mode, 35 s/projection, total imaging time of 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 backprojection via a Butterworth filter (cutoff frequency at 0.26 cycle/pixel; order 9). No attenuation correction was used. 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 (17). Segmental tracer activity was expressed as percentage of maximum. Perfusion defects on stress images were considered to be 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 (scar) (18). The individual segments on the SPECT images were assigned to the distinct native coronary arteries, according to recently published guidelines (17). The anastomoses of the bypass graft on the different native coronary arteries then defined the vascular territory that the graft perfused.

Statistical Analysis

Data are presented as mean ± SD. On the basis of QCA analysis, grafts were divided into two categories: those with nonsignificant percent diameter stenosis (<50%; n = 49), and those with significant percent diameter stenosis (≥50%; n = 29) in either graft or recipient vessel. Grafts were also divided into those with nonsignificant percent area stenosis (<80%; n = 52), and those with significant percent area stenosis (≥80%; n = 26).

Mean Doppler parameters were compared by Student t-test. A previously reported cut-off value for CFVR of 1.8 was used to distinguish between normal and diseased grafts (19). Agreements between the diagnostic modalities were assessed by use of κ statistics, with a κ value <0.4, between 0.4 and 0.75, and >0.75 representing modest, fair to good, and excellent agreement, respectively. The association between CFVR and percent diameter stenosis, and between CFVR and percent area stenosis on angiography was also assessed by use of Pearson correlation. A p-value <0.05 was considered statistically significant.

RESULTS

Study Population

A total of 58 patients were included in the study. Patient characteristics are presented in Table 9.1. Coronary angiography and Doppler velocity assessment was performed in 78 vein grafts. Mean time after CABG was 10.2 ± 5.2 years, ranging from 1 to 23 years. Bypass graft characteristics are shown in Table 9.2. The characteristics of the 20 patients who underwent SPECT imaging resembled those of the overall patient group. With regard to these 20 patients, the mean time after CABG was 10.3 ± 5.0 years, 30% of them had diabetes, and 60% were treated for hypertension. The time interval between the coronary angiography and SPECT imaging was 3.4 ± 2.8 months. No events happened between the examinations.

Number of patients	58
Male/female	48/10
Age (years)	66.4 ± 8.7
Diabetes mellitus	13 (22%)
Currently smoking	5 (9%)
Hypertension	30 (52%)
Hypercholesterolemia	45 (78%)
Prior myocardial infarction in bypass graft region	22 (38%)
Time after CABG (years)	10.2 ± 5.2

Table 9.1
Patient Characteristics
CABG = coronary artery bypass grafting

Number of bypass grafts	78
Single/sequential grafts	47/31
Vascular territory perfused by graft	
LAD	26 (33%)
LCX	29 (37%)
RCA	23 (30%)
Percentage diameter stenosis (QCA)	40 ± 33%
<50%	49
≥50%	29
Percent area stenosis (QCA)	52 ± 39%
<80%	52
≥80%	26

Table 9.2
Bypass Graft Characteristics
LAD = left anterior descending artery; LCX = left circumflex artery; RCA = right coronary artery

Coronary Angiography and Doppler Flow Velocity Measurements
In all 78 vein grafts coronary angiography was successfully performed. Stenosis severity, as measured by QCA, ranged from 0% to 100%, with a mean percent diameter stenosis of 40 ± 33% and a mean percent area stenosis of 52 ± 39%. On the basis of the QCA results, grafts were divided into those with angiographically nonsignificant percent diameter and area stenoses and those with significant percent diameter and area stenosis (Table 9.2).
Successful flow velocity signals were acquired in all bypass grafts. A biphasic flow velocity pattern, typical for vein grafts, was demonstrated in all 78 grafts. During Doppler velocity assessment, the heart rate and mean aortic pressure at baseline were 67 ± 12 beats/min and 97 ± 15 mm Hg, respectively. After adenosine injection, heart rate and mean aortic pressure did not change significantly. Mean Doppler velocity parameters per category are displayed in Table 9.3. Baseline peak velocities did not show a statistically significant difference between the significantly and nonsignificantly stenosed vessels, except for DPV. Doppler peak velocities with adenosine stress demonstrated significantly decreased values at ≥50% diameter stenosis, and ≥80% area stenosis. Accordingly, CFVR was significantly decreased in ≥50% diameter stenosis, and ≥80% area stenosis in vein grafts. These results are in concordance with those in previously reported studies on Doppler flow velocity in native coronary arteries (3;4).

Agreement between Coronary Angiography and Doppler Velocity
Percent diameter stenosis on angiography versus Doppler velocity
The individual data (except for 8 grafts with a total occlusion in the graft or recipient vessel) for CFVR as compared with percent diameter stenosis on angiography are shown in Figure 9.1 A. In all 70 grafts, CFVR ranged from 0.98 to 5.8. A moderate, inverse

correlation between percent diameter stenosis and CFVR existed (y = -0.0085x + 2.53; r = 0.30; p<0.05). In 49 grafts with <50% diameter stenosis, CFVR ranged from 1.4 to 5.8. In grafts with ≥50% stenosis, CFVR ranged from 0.98 to 3.4, demonstrating that percentage diameter stenosis on the coronary angiogram does not reliably reflect hemodynamic consequences of vein graft lesions. When the cut-off value for CFVR of 1.8 was applied, a modest agreement of 69% (κ = 0.25; p<0.05) between CFVR and percent diameter stenosis at coronary angiography was shown (Table 9.4). Disagreement between the two parameters was observed in 11 of 49 (22%) grafts with a stenosis <50%, and in 11 of 21 (52%) grafts with a stenosis ≥50%. The distribution of CFVR in categories with increasing percent diameter stenosis is shown in Figure 9.2 A.

	<50% DS	**≥50% DS**	**<80% AS**	**≥80% AS**
APV baseline (cm/s)	17.6 ± 9.2	14.4 ± 7.9	17.4 ± 9.3	14.6 ± 7.7
APV stress (cm/s)	38.6 ± 14.2	26.9 ± 12.8 †	37.8 ± 14.7	27.1 ± 12.4 §
CFVR	2.40 ± 0.79	1.99 ± 0.65 *	2.38 ± 0.77	1.97 ± 0.68 ‡
SPV baseline (cm/s)	13.7 ± 7.3	11.6 ± 7.3	13.4 ± 7.4	11.9 ± 7.2
SPV stress (cm/s)	29.9 ± 12.9	21.4 ± 10.1 †	29.3 ± 13.3	21.7 ± 9.2 §
DPV baseline (cm/s)	22.0 ± 12.4	16.5 ± 9.5 *	21.7 ± 12.4	16.6 ± 9.4 ‡
DPV stress (cm/s)	46.5 ± 17.0	30.9 ± 16.0 †	45.5 ± 17.4	31.1 ± 16.0 §
DSVR baseline	1.76 ± 0.77	1.76 ± 1.07	1.77 ± 0.75	1.73 ± 1.12
DSVR stress	1.67 ± 0.48	1.50 ± 0.57	1.68 ± 0.48	1.46 ± 0.56

Table 9.3

Mean Values of Flow Velocity Parameters

** p<0.05; † p<0.01 versus <50% diameter stenosis; ‡ p<0.05; § p<0.01 versus <80% area stenosis; DS = diameter stenosis; AS = area stenosis; APV = average peak velocity; SPV = systolic peak velocity; DPV = diastolic peak velocity; CFVR = coronary flow velocity reserve; DSVR = diastolic-to-systolic velocity ratio*

Doppler velocity	Coronary angiography			
	%DS <50%	%DS ≥50%	%AS <80%	%AS ≥80%
CFVR ≥1.8	38	11	41	8
CFVR <1.8	11	10	11	10
Total	49	21	52	18

Table 9.4

Agreement between CFVR and Percent Diameter and Area Stenoses on Coronary Angiography
Only patent grafts were included (n = 70). %DS = percent diameter stenosis; %AS = percent area stenosis; CFVR = coronary flow velocity reserve

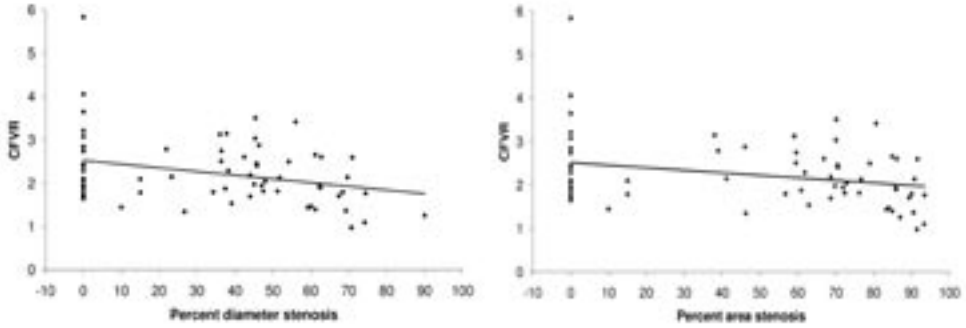

Figure 9.1

Scatterplot of CFVR versus percent diameter stenosis (A), and versus percent area stenosis (B). Grafts without a total occlusion are included (n = 70). Regression line for CFVR versus percent diameter stenosis represents the following: y = -0.0085x + 2.53, pearson regression coefficient r = 0.30, p<0.05. CFVR versus percent area stenosis yielded the following: y = -0.0085x + 2.52, r = 0.28, p<0.05.

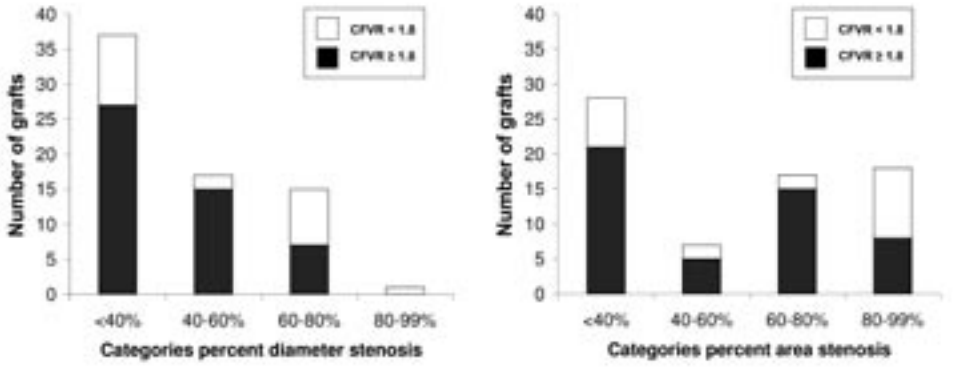

Figure 9.2

Distribution of CFVR (<1.8 versus ≥1.8) in grafts according to percent diameter stenosis (A), and percent area stenosis (B).

Percent area stenosis on angiography versus Doppler velocity

A moderate correlation was also demonstrated between percent area stenosis and CFVR ($y = -0.0058x + 2.52$; $r = 0.28$; $p<0.05$, Figure 9.1 B). When the cut-off value for CFVR of 1.8 for percent area stenosis of 80% were applied, a modestly improved agreement of 73% ($\kappa = 0.33$; $p<0.01$) as compared with percent diameter stenosis was shown. CFVR and percent area stenosis disagreed in 11 of 52 grafts (21%) with an area stenosis <80%, and in 8 of 18 grafts (44%) with an area stenosis ≥80%. In categories with an increasing percent area stenosis, allocation of CFVR is depicted in Figure 9.2 B.

Gated SPECT Perfusion Imaging

Gated SPECT in 20 patients demonstrated a mean LVEF of 54 ± 18% (range 24-85%). Mean left ventricular end-systolic and end-diastolic volumes were 66 ± 56 ml and 123 ± 70 ml, respectively. In the vascular territories supplied by 24 grafts, stress myocardial perfusion was normal in the territories allocated to 15 grafts, mildly to moderately reduced in territories of 4 grafts, and severely reduced in territories of 5 grafts. Rest perfusion was normal in 19 grafts, mildly to moderately reduced in 3 grafts, and severely reduced in 2 grafts. Accordingly, perfusion was normal in the vascular territory of 15 grafts, ischemia was present in the territory of 6 grafts, while irreversible defects (indicating scar tissue) were present in the territory of 3 grafts.

Agreement between Coronary Angiography and SPECT

Percent diameter stenosis on angiography versus SPECT

A modest agreement of 63% (15 of 24 grafts; $\kappa = 0.28$; $p = 0.13$) was demonstrated between SPECT and percent diameter stenoses on coronary angiography (Table 9.5). SPECT perfusion and percent diameter stenosis did not agree in 2 of 10 grafts (20%) with nonsignificant stenosis, and in 7 of 14 grafts (50%) with significant stenosis.

	Coronary angiography			
SPECT	%DS <50%	%DS ≥50%	%AS <80%	%AS ≥80%
Normal perfusion	8	7	10	5
Abnormal perfusion	2	7	2	7
Total	10	14	12	12

Table 9.5

Agreement between SPECT Perfusion and Coronary Angiography

Only grafts with available SPECT (n = 24) were included. %DS = percent diameter stenosis; %AS = percent area stenosis; SPECT = single-photon emission computed tomography

	Doppler velocity		
SPECT	CFVR ≥1.8	CFVR <1.8	Total
Normal perfusion	15	0	15
Abnormal perfusion	4	5	9
Total	19	5	24

Table 9.6

Agreement between CFVR and SPECT Perfusion

Only grafts with available SPECT (n = 24) were included. SPECT = single-photon emission computed tomography; CFVR = coronary flow velocity reserve

Percent area stenosis on angiography versus SPECT
SPECT and percent area stenoses showed fair agreement (17 of 24 grafts; 71%), when area stenoses <80% and ≥80% were considered nonsignificant or significant ($\kappa = 0.42$; $p<0.05$). Disagreement between SPECT and percent area stenosis occurred in 2 of 12 (17%) grafts with an area stenosis <80%, and in 5 of 12 grafts (42%) with an area stenosis ≥80%.

Agreement between Doppler Velocity and SPECT
In 15 of the 15 grafts (100%) with normal perfusion on SPECT, CFVR was ≥1.8 (Table 9.6). Conversely, in 5 of 9 grafts (56%) with abnormal perfusion on SPECT, CFVR showed a value <1.8. SPECT and Doppler velocity provided similar information in 20 of 24 grafts (83%; $\kappa = 0.61$), illustrating good agreement between SPECT and CFVR ($p = 0.001$).
Because the influence of scar tissue on CFVR is unpredictable, agreement between SPECT and CFVR was also established after exclusion of 3 grafts showing an irreversible perfusion defect. Of these 3 grafts, one had a CFVR <1.8, and 2 grafts had a CFVR >1.8. Agreement then improved to 90% (19 of 21 grafts; $\kappa = 0.74$).

Discussion
In this study the hemodynamic consequences of angiographically significant stenoses in vein grafts were explored by Doppler flow velocity assessment and SPECT perfusion imaging. The nonsignificant percent diameter stenoses on angiography showed a reduced CFVR in 22% and an abnormal SPECT study in 20%, indicating that these stenoses were hemodynamically significant. Alternatively, the angiographically significant percent diameter stenoses exhibited a normal CFVR in 52% and a normal SPECT in 50%, indicating that these stenoses were hemodynamically nonsignificant. In addition, agreements between angiography and CFVR or SPECT were only modest. Accordingly, the results demonstrate that the angiographic stenosis severity did not correctly reflect the presence or absence of hemodynamic consequences in vein grafts, indicating the need for additional testing to assess the hemodynamic significance of the angiographic findings. CFVR agreed better with SPECT perfusion imaging than with percent diameter stenosis, suggesting that CFVR may also be used to assess the hemodynamic significance of a vein graft lesion.

Doppler Flow Velocity Assessment in Vein Grafts
In early studies the coronary flow reserve (CFR) was introduced in order to evaluate the physiology of coronary artery stenoses, visualized at angiography (20;21). At that time, absolute coronary blood flow could only be measured by perivascular flow transducers in "open chest" procedures. CFR was therefore validated in animal models and patients undergoing open heart surgery (1;20;22), though clinical use remained limited. When the diameter of intravascular catheter-based Doppler ultrasound devices could be reduced to 0.018 inch, measurement of flow velocity and CFVR in coronary arteries in patients during catheterization was realized. Absolute blood flow correlated well with Doppler-derived flow velocity both in vitro and in vivo (12;13;23). Thereafter the value of Doppler CFVR was extensively researched in native coronary arteries (4;8;24;25). However, studies focusing on the use of Doppler measurements in vein grafts are limited. In our

study, the mean resting flow (APV) was not different in the grafts with ≥50% diameter stenosis (or ≥80% area stenosis) or without a significant stenosis on angiography, confirming that resting flow frequently remains normal despite the presence of stenoses, as demonstrated previously for native coronary arteries (3;20). However, the mean CFVR was significantly lower in the grafts with a significant stenosis on angiography (Table 9.3). Still, only a moderate inverse correlation was demonstrated for CFVR and quantitative analysis of the coronary angiogram (r = 0.30 for percent diameter stenosis; r = 0.28 for percent area stenosis) with a wide range for CFVR in both nonsignificant and significant stenoses. Indeed, when individual data were analyzed, many grafts with an angiographically significant stenosis had preserved CFVR and some grafts without a significant stenosis had reduced CFVR indicating the relative inability to determine the hemodynamic significance from angiography alone.

Value of SPECT Perfusion Imaging

SPECT perfusion imaging is a well-established technique by which to detect obstructive coronary artery disease by evaluating regional myocardial perfusion at rest and during stress. Excellent sensitivities and specificities of SPECT to detect stenoses in native coronary arteries were demonstrated (9;18;26). In addition, studies evaluating patients after CABG with SPECT showed good results for the assessment of graft disease. In 50 patients with 119 bypass grafts a sensitivity of 80% with a specificity of 87% for the detection of >50% stenosis have been reported (10). In another study 88 grafts were studied late after surgery (4.0 ± 1.2 years) by SPECT, and a comparable sensitivity and specificity (83% and 88%, respectively) for the detection of >50% stenosis were shown (27).

However, the agreement between SPECT and angiography is not perfect (5). In this study SPECT perfusion imaging agreed moderately with percent diameter stenosis (63%; $\kappa = 0.28$; p = NS). In particular, 20% of nonsignificant stenoses on angiography had abnormal SPECT perfusion results, and 50% of the angiographically significant stenoses had normal SPECT results.

Agreement between Doppler CFVR and SPECT

More recently, for SPECT imaging the emphasis has shifted from detection of coronary artery disease to hemodynamic evaluation of stenoses. Comparative studies between SPECT imaging and Doppler assessment have been performed, demonstrating a good agreement (ranging from 72% to 96%) between these two techniques for the assessment of the hemodynamic consequence of an intermediate native coronary artery stenosis (5;19;28-30). In these studies, the cut-off value for CFVR to predict an abnormal SPECT study varied from 1.7 to 2.0. The best concordance (96%) between between Doppler assessment and SPECT imaging was obtained when a cut-off value for CFVR of 1.8 was used (19).

Studies evaluating the hemodynamic consequences of bypass graft lesions are lacking. In this study, good agreement between Doppler assessment (with the use of the cut-off value of 1.8 for CFVR) and SPECT imaging was demonstrated in vein grafts (83%; $\kappa = 0.61$; p = 0.001), suggesting that both SPECT imaging and CFVR assessment may be used

to characterize the hemodynamic consequences of vein graft stenoses. The agreement increased to 90% ($\kappa = 0.74$) when grafts subtending an area with infarcted tissue were excluded. In these regions SPECT findings are abnormal (irreversible defects), whereas CFVR may be preserved, if an intact graft subtends a partially infarcted region.

Clinical Implications

Vein graft disease occurs frequently after CABG, affecting 48% of grafts at 5 years and 81% at ≥15 years (31). Still, revascularization after initial CABG is required in 19% of patients by 10 years (32). Our study shows that coronary angiography alone, currently widely used as gold standard, does not reliably reflect the hemodynamic consequences of stenoses in vein grafts. Thus further assessment of stenoses in vein grafts or recipient vessels is required. This study suggests that either SPECT perfusion imaging or CFVR assessment may be used to characterize the hemodynamic consequence of a vein graft lesion.

Limitations

SPECT perfusion imaging was not available in all patients who underwent coronary angiography with Doppler velocity measurements. For logistical reasons, this was only performed in 20 patients; in particular, the number of graft-related region with ischemia was small. However, the characteristics of the patients who underwent SPECT imaging resembled those of the entire population.

No attenuation correction was performed with SPECT imaging, and therefore, some SPECT perfusion defects with normal CFVR may have been caused by attenuation.

Pressure measurements were not performed. The fractional flow reserve can be calculated as the ratio of distal coronary and aortic pressure during maximal hyperemia (33). Large studies investigating the fractional flow reserve in vein or arterial grafts are lacking.

Conclusion

Significant stenoses in vein grafts require further exploration to assess their hemodynamic significance. The Doppler velocity results agreed better with SPECT perfusion imaging than with percent diameter stenosis in the evaluation of vein graft function.

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EDITORIAL

Defining the "gold standard": A changing paradigm

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At the inception of nuclear cardiology, the accuracy of perfusion (planar and single-photon emission computed tomography [SPECT]) and function (first-pass and gated equilibrium radionuclide angiography) was assessed against percent diameter stenosis (DS) by coronary angiography, a tradition that has changed very little over the past three decades and has spilled over to other imaging methods such as stress two-dimensional echocardiography and magnetic resonance (1). The foundation for such an approach was deeply rooted on the elegant work by Gould et al (2;3) showing a decline in the hyperemic coronary blood flow at approximately 50% DS of a coronary vessel in the animal model. Scores of articles using this threshold have not only shown that imaging works but, in the process, have reinforced the validity of DS as a measure of stenosis severity (1).

Then came the revelations that DS did not agree well with physiologic severity of stenosis when the latter was assessed by catheter-based techniques or by positron emission tomography. The pioneer work of many groups, notably those from the same institution as the authors of the current article in the Journal (4), showed a significant scatter between measures of physiologic severity (flow velocity reserve ratio, fractional flow reserve, and stenosis resistance) with DS, even when measured quantitatively by state-of-the-art methods (4-10).

These results, as important as they are, are not unexpected, as coronary atherosclerosis in humans differs from ligature-induced stenosis in animal models in multiple ways. These include the presence of diffuse disease and differences in diameter of the vessel, length of stenosis, entrance and exit stenosis angles, location, serial lesions, endothelial dysfunction, microvascular dysfunction, vasomotion, and collaterals. It is intuitive to conclude that, if there is discordance between catheter-based physiologic measures of coronary stenosis and DS, then there must also be discordance between DS and imaging methods that reflect the physiologic relevance of stenosis severity, such as gated SPECT perfusion imaging. Such a confirmation has been previously reached in native coronary vessels and in the current study in bypass grafts after coronary artery bypass graft surgery (CABG).

Obviously, with SPECT perfusion imaging, several factors affect regional myocardial tracer concentration in addition to myocardial blood flow (MBF) or, more precisely, myocardial blood volume. These include the changes in first-pass extraction fraction in relation to flow (which is tracer-dependent and has considerable species and individual differences), type of stress, type of imaging protocol, relative changes in MBF in relation to changes in cardiac output, myocardial viability, tracer kinetics, metabolic alterations, attenuation, scatter, and depth resolution (1). The differences in regional tracer concentration reflect relative flow differences rather than absolute or hyperemic MBF (relative flow reserve ratio [peak/resting flow] in culprit lesion compared with a normal zone). Given this complexity in the interrelationship between MBF and tracer concentration, it is not unexpected that imaging could not identify all coronary lesions or all patients with coronary lesions by coronary angiography. Experience has taught us another valuable lesson: interventions (such as statin therapy or conventional antianginal medications) that have little effect on DS could remarkably alter the perfusion results.

One final point worth mentioning is that catheter-based methods for assessing stenosis severity do not provide information on the area of myocardium at risk. Studies during stress, during rest, or with temporary balloon occlusion at the time of angioplasty have consistently shown a wide variability between coronary angiography and the area of ischemic myocardium or size of myocardial infarction (1). It would seem that those who try hard to show a perfect correlation between DS and imaging are indeed missing the point that a perfect correlation is neither logical nor expected and the beauty of imaging is the fact that it provides independent and complementary information to coronary angiography. And thank goodness for that; otherwise, it would have merely provided redundant information (11). These features of perfusion imaging explain very well why and how SPECT imaging works so well in risk assessment. Our challenges are to better understand the mechanisms of why few patients with left-main or three-vessel disease show no reversible perfusion abnormalities, to determine how to define ischemia in regions with prior partial-thickness infarcts, and to keep the pressure on industry about our needs for perfusion tracers with improved physical and biologic kinetics.

With regard to patients with prior coronary revascularization, both percutaneous coronary interventions and CABG have witnessed major changes in the past decade. The number of percutaneous coronary intervention procedures now exceeds those with CABG, and those patients referred to CABG are likely to be sicker, with more advanced disease and poorer target vessels. This shift is important to keep in mind, as American College of Cardiology/American Heart Association guidelines cite studies from a much earlier time with a different patient mix. It is not unusual now to see patients with recurrent symptoms at one year or earlier after CABG, and the five-year honeymoon period cited in these guidelines may apply to fewer patients (12-14).

In this issue of the *Journal*, Salm et al (4) examined the correlation between DS, Doppler flow velocity (78 grafts in 58 patients), and SPECT results (24 grafts in 20 patients) in patients after CABG. On the basis of 50% DS and a flow velocity reserve ratio of 1.8,

there was only a modest correlation between DS and reserve ratio or between SPECT and DS (4). However, SPECT and reserve ratios provided comparable data in 20 of 24 grafts (83%). This study therefore extends the concepts gained in patients with native coronary stenosis to those with graft lesions. There are a few features of the study worth mentioning. First, this must have been an unusual group of patients who had CABG because there were only 1.2 grafts per patient among those who had SPECT imaging. Second, the use of 50% DS by the group who defamed this measurement appears to be interesting especially in vein grafts, which are known to be of larger diameter than native vessels. Third, we do not know from this study how to interpret the data in patients with more grafts and more severe disease such as stenosis in a graft to one branch of the left circumflex artery but no disease in a second branch, or vice versa (or any similar scenario in a different vascular bed). Fourth, we have no information on flow velocity reserve ratio in a control vessel for reasons discussed previously (perfusion pattern reflects relative rather than absolute flow reserve ratio). Finally, we do not know whether the adenosine dose was optimal in all grafts in all locations to produce a maximal response.

Nevertheless, the importance of this study rests on the need for a constant reminder that DS should be abandoned as a gold standard and future studies should use physiologic measures of coronary stenosis, which unfortunately are invasive and not that easy to perform by less expert individuals than those in the current study. This should not, however, be a green light signal that any discordance between SPECT and coronary angiography, which is still the most widely available method, should be explained by limitations of coronary angiography in every patient. The truth is probably that no single method has a monopoly on how to define the "gold standard" of ischemia, but at least there has been a shift in the paradigm and SPECT results are not always made the scapegoat (false positive or false negative). This observation did not go unnoticed by the Food and Drug Administration, which now does not insist on using coronary angiography as the "gold standard" for approving new products of interest to our field.

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