Resting Myocardial Blood Flow Is Impaired in Hibernating Myocardium
A Magnetic Resonance Study of Quantitative Perfusion Assessment

Joseph B. Selvanayagam, MBBS, FRACP, DPhil; Michael Jerosch-Herold, PhD; Italo Porto, MD; David Sheridan, BSc; Adrian S.H. Cheng, MRCP; Steffen E. Petersen, MD; Nick Searle, DCR(R); Keith M. Channon, MD, FRCP; Adrian P. Banning, MD, FRCP; Stefan Neubauer, MD, FRCP

Background—Although impairment in perfusion reserve is well recognized in hibernating myocardium, there is substantial controversy as to whether resting myocardial blood flow (MBF) is reduced in such circumstances. Quantitative first-pass cardiovascular magnetic resonance (CMR) perfusion imaging allows absolute quantification of MBF. We hypothesized that MBF assessed at rest by quantitative CMR perfusion imaging is reduced in hibernating myocardium.

Methods and Results—Twenty-seven patients with 1 or 2-vessel coronary disease and at least 1 dysfunctional myocardial segment undergoing PCI were studied with preprocedure, early (24 hours), and late (9 months) postprocedure CMR imaging. First-pass perfusion images at rest were acquired in 3 short-axis planes by use of a T1-weighted turboFLASH sequence. In each slice, MBF was determined for 8 myocardial segments in mL·min⁻¹·g⁻¹ by deconvolution of signal intensity curves with an arterial input function measured in the left ventricular blood pool. Cine MRI for assessment of global and segmental function and delayed enhancement MRI for detection of viability were also obtained. All coronary lesions were 80% to 95% stenosis in severity. Over all segments, mean MBF normalized by rate-pressure product (“corrected MBF”) was 1.2±0.3 mL·min⁻¹·g⁻¹·(mm Hg·bpm/10⁴)⁻¹ in segments without significant coronary stenosis and 0.7±0.2 mL·min⁻¹·g⁻¹·(mm Hg·bpm/10⁴)⁻¹ in segments with coronary stenosis before PCI (mixed model controlling for slice and segment z=-23.9, P<0.001). Early after the procedure, the MBF was 1.2±0.2 mL·min⁻¹·g⁻¹·(mm Hg·bpm/10⁴)⁻¹ in revascularized segments and 1.3±0.2 mL·min⁻¹·g⁻¹·(mm Hg·bpm/10⁴)⁻¹ in nondiseased segments (z=-6.1, P<0.001). Late after PCI, the systolic wall thickening and end-diastolic wall thickness both increased significantly more (both P<0.001) in the myocardial segments subtended by severe coronary stenosis (8±17% to 40±19% and 6.5±1.1 to 9.3±2 mm, respectively) than in the myocardial segments supplied by nondiseased vessels. Mean MBF in dysfunctional segments with significantly improved contraction after revascularization was 0.8±0.2 mL·min⁻¹·g⁻¹·(mm Hg·bpm/10⁴)⁻¹ before PCI and 1.2±0.2 mL·min⁻¹·g⁻¹·(mm Hg·bpm/10⁴)⁻¹ after PCI (z=2.0, P=0.04).

Conclusions—CMR perfusion imaging detects impaired resting MBF in hibernating myocardial segments. (Circulation. 2005;112:3289-3296.)

Key Words: imaging | hibernation | blood flow | heart failure | perfusion

Hibernating myocardium has been defined as a state of downregulated contractile function in noninfarcted myocardium in the setting of severe coronary stenosis that improves after revascularization.1–3 Although impairment in perfusion reserve is well recognized in hibernating myocardium, there is substantial controversy as to whether resting myocardial blood flow (MBF) is reduced in such circumstances.4 Some studies using positron emission tomography (PET) with oxygen-labeled water ([¹⁸O]H₂O) for absolute quantification of regional MBF have shown that resting flow is not impaired in hibernating myocardium compared with flow in remote myocardium or in myocardium of age-matched normal control subjects.5–7 In contrast, other studies using the same methodology have found that MBF in hibernating myocardium is significantly reduced (by 20% to 30%) compared with MBF in the remote normal myocardium.8,9

Editorial p 3222

quantification of regional MBF have shown that resting flow is not impaired in hibernating myocardium compared with flow in remote myocardium or in myocardium of age-matched normal control subjects.5–7 In contrast, other studies using the same methodology have found that MBF in hibernating myocardium is significantly reduced (by 20% to 30%) compared with MBF in the remote normal myocardium.8,9

Received March 15, 2005; revision received July 13, 2005; accepted August 8, 2005.
From the University of Oxford Centre for Clinical Magnetic Resonance Research (J.B.S., A.S.H.C., S.E.P., S.N.) and Department of Cardiovascular Medicine (J.B.S., A.S.H.C., S.E.P., K.M.C., S.N.), University of Oxford, Department of Cardiology (I.P., A.P.B.) and Department of Radiology (N.S.), John Radcliffe Hospital, Oxford, UK, and the Advanced Imaging Research Center (M.J.-H., D.S.), Oregon Health and Science University, Portland.
Correspondence to Joseph B. Selvanayagam, MBBS, FRACP, DPhil, Department of Cardiovascular Medicine, John Radcliffe Hospital, Oxford, OX3 9DU, UK. E-mail joseph.selvanayagam@cardio.vox.ac.uk
© 2005 American Heart Association, Inc.
Circulation is available at http://www.circulationaha.org
DOI: 10.1161/CIRCULATIONAHA.105.549170

3289
Cardiovascular magnetic resonance (CMR) imaging during the first pass of an injected tracer permits assessment of myocardial perfusion both at rest and during pharmacological stress and gives superior spatial resolution compared with nuclear imaging methods. CMR perfusion results from animal experiments have shown a strong correlation with microspheres for the assessment of blood flow. Although clinical CMR perfusion studies to date in coronary artery disease (CAD) have used semiquantitative methods of assessment, recent developments in CMR perfusion imaging permit absolute quantification of blood flow per gram of myocardial tissue (in mL·min⁻¹·g⁻¹). Absolute quantification of myocardial perfusion and perfusion reserve might be particularly crucial in multivessel CAD patients, in whom perfusion reserve is globally reduced, and hence qualitative and semiquantitative methods might well be inadequate for determining the severity of coronary stenosis.

In the present study, we assessed the issue of blood flow reduction in hibernating myocardium using high-resolution quantitative CMR. In a population of patients undergoing percutaneous coronary intervention (PCI), we prospectively quantified resting MBF using perfusion CMR in dysfunctional myocardial segments affected by severe coronary stenosis and compared it with MBF in remote normal myocardium. Furthermore, we repeated the MR studies both 24 hours and several months after revascularization for repeat stenosis and compared it with MBF in remote normal myocardial segments affected by severe coronary artery disease. Finally, we repeated the MR studies both 24 hours and several months after revascularization for repeat stenosis and compared it with MBF in remote normal myocardial segments.

**Methods**

**Ethics**
The study was approved by our institutional ethics committee, and informed written consent was obtained from each patient.

**Patient Population**
Twenty-seven consecutive patients with severe coronary artery stenosis (as defined by >80% stenosis on quantitative coronary angiography) involving either 1- or 2-vessel CAD and scheduled for PCI were included. Patients needed to demonstrate at least 1 dysfunctional myocardial segment on their baseline CMR scan. We excluded patients with a clinical history of myocardial infarction or dysfunctional myocardial segment on their baseline CMR scan. We also excluded patients with a clinical history of myocardial infarction or functional, 4), and quantitatively, using automated computer software scoring system (normal, 1; hypokinetic, 2; akinetic, 3; and dyskinetic, 4), and quantitatively, using automated computer software (MMASS, Medis), to determine end-diastolic wall thickness (mm) and systolic wall thickening (%) by the center-line method. For perfusion analysis, the endocardial and epicardial contours were traced by an examiner blinded to angiography (MMASS, Medis) and corrected manually for displacements (eg, breathing). The myocardium was divided into 8 equiangular segments per slice. LV signal intensity of the basal slice and myocardial signal intensity were determined for all time points. In each short-axis slice, MBF was determined for 8 myocardial segments in mL·min⁻¹·g⁻¹ by deconvolution of signal intensity curves with an arterial input function measurement in the LV blood pool, with explicit accounting for any delay in the arrival of the tracer. Because basal MBF is closely related to the rate-pressure product, an index of LV oxygen consumption, values for basal flow in each patient were also corrected for the respective rate-pressure product (ie, the absolute values of flow were divided by rate-pressure product/10 000).

The diagnostic coronary angiogram was used as the “gold standard” in defining affected myocardial segments. As illustrated in Figure 1, each myocardial segment in 3 (basal, midventricular, and apical) short-axis slices was ascribed a coronary artery territory according to standard criteria. A right dominant was assumed when the right coronary artery supplied the inferior parts of the ventricular septum and at least 1 posterolateral branch to the diaphragm wall of the left ventricle. A left dominant was determined when the right coronary artery did not exceed the crux cordis and the left branches supplied the inferior septum (modified according to Schiller et al17). All data were analyzed in a blinded manner. Coronary stenoses >80% were deemed to be severely diseased, and myocardial segments subtended by such vessels were labeled as “affected” and myocardial subtended by normal/non-diseased coronary arteries was labeled as “unaffected.”

**Statistical Analysis**
Values are expressed as mean±SD or median (interquartile range) as appropriate. Mixed-effects models with a random intercept for patient, controlling for slice and segment number both as categorical fixed effects, were performed using Stata Version 8.0 (StatCorp LP) so as to take account of within-patient clustering and to test for the...
significance of any interactions. Student t tests were used to compare changes in global LV function before and after revascularization. Statistical significance was taken throughout at the 5% level (P<0.05).

Results

Patient Characteristics and Follow-Up

The mean age of the study patients was 60±11 years; 21 (78%) were male. The median interval between the first CMR scan and PCI was 1 (0–2) day, and the median intervals between the PCI and early and late follow-up CMR scans were 1 (1–3) day and 9 (7–12) months, respectively.

Quantitative Coronary Angiography

The median diameter severity of coronary lesions assessed by quantitative coronary angiography was 90% (range, 5%). All patients had stenosis diameter severity of between 80% and 95%. Twenty-two (81%) of the study patients had single-vessel disease. The left anterior descending coronary artery was the most frequently involved, being affected in 20 of 32 vessels (63%).

Changes in MBF

Of the total of 648 myocardial segments analyzed, 308 segments (47.5%) were in territories subtended by a severely diseased coronary vessel (referred to as “affected”), and 340 (52.5%) segments were supplied by non-diseased coronary arteries (referred to as “unaffected”). When all patients were considered, mean baseline MBF normalized by rate-pressure product (“corrected MBF”) was 1.2±0.3 mL · min⁻¹ · g⁻¹ · (mm Hg · bpm/10⁴)⁻¹ in segments without significant coronary stenosis and 0.7±0.2 mL · min⁻¹ · g⁻¹ · (mm Hg · bpm/10⁴)⁻¹ in segments with coronary stenosis before PCI (mixed model z=23.9, P<0.001). After the procedure, the corrected MBF was 1.2±0.2 mL · min⁻¹ · g⁻¹ · (mm Hg · bpm/10⁴)⁻¹ in revascularized segments and 1.3±0.2 mL · min⁻¹ · g⁻¹ · (mm Hg · bpm/10⁴)⁻¹ in non-revascularized segments (z=6.1, P<0.001). There was a significantly greater increase in the corrected MBF in revascularized myocardial segments (0.5±0.3 mL · min⁻¹ · g⁻¹ · (mm Hg · bpm/10⁴)⁻¹) than in non-revascularized segments (0.1±0.2 mL · min⁻¹ · g⁻¹ · (mm Hg · bpm/10⁴)⁻¹) (z=19.2, P<0.001). The mean rate-pressure product/10 000 during the baseline scan was 0.88 and in the follow-up scan was 0.84 (P<0.05). Figure 2 shows an example of changes in resting MBF in a patient with severe left anterior descending coronary artery disease.
MBF Changes in Hibernating Myocardium

In a subset analysis, MBF before intervention and after intervention was evaluated only in those segments without hyperenhancement (HE) that exhibited either marked improvement in function or normalization of function after the intervention and compared with remote normal myocardium. We predefined significant improvement in function after revascularization as an increase in subjective regional wall motion index (RWMI) score by at least 1 grade and/or percentage systolic wall thickening of at least 15%.21 Of 151 dysfunctional, viable myocardial segments, 132 (87%) demonstrated significant improvement in contraction after PCI. This change in MBF was statistically significant after control for slice and segment number (mixed model z=2.0, P=0.04; Figure 3). In contrast, mean MBF in remote myocardium (ie, not subtended by a stenosis) with normal function and no HE was not significantly changed after revascularization (1.5±0.2 mL·min⁻¹·g⁻¹·(mmHg·bpm/10⁴)⁻¹ before PCI versus 1.4±0.2 mL·min⁻¹·g⁻¹·(mmHg·bpm/10⁴)⁻¹ after PCI. This change in MBF was statistically significant after control for slice and segment number (mixed model z=2.0, P=0.04; Figure 3). In contrast, mean MBF in remote myocardium (ie, not subtended by a stenosis) with normal function and no HE was not significantly changed after revascularization (1.5±0.2 mL·min⁻¹·g⁻¹·(mmHg·bpm/10⁴)⁻¹ before PCI versus 1.4±0.2 mL·min⁻¹·g⁻¹·(mmHg·bpm/10⁴)⁻¹ after PCI, P=0.4).

Pre-PCI Delayed Enhancement-MRI Findings and Relationship to Changes in MBF

Overall, 11 patients (31%) had evidence of myocardial HE in their pre-PCI scan. The mean mass of HE per patient was 9.1±7.0 g. Out of a total of 641 myocardial segments (7 segments were excluded from analysis), 521 (81%) had no HE, 91 (14%) had 1% to 50% HE, and 29 (5%) had >50% HE. HE transmurality grade is shown according to stenosis severity in Figure 4. Nonstenosed segments were significantly more likely to have no HE and less likely to have both 1% to 50% and >50% HE (z=3.7, P<0.001).

To assess the blood flow changes in scarred myocardial segments, we subdivided the MBF results according to transmural extent of delayed HE (Figure 5). Both the extent of HE (z=−10.3, P<0.001) and the presence of significant stenosis (z=−11.1, P<0.001) were significantly associated with MBF before PCI. In segments with no HE, the mean corrected MBF before PCI was 1.2±0.2 mL·min⁻¹·g⁻¹·(mmHg·bpm/10⁴)⁻¹ in segments without significant coronary stenosis and 0.8±0.2 mL·min⁻¹·g⁻¹·(mmHg·bpm/10⁴)⁻¹ in segments with coronary stenosis before PCI (z=−23.9, P<0.001). In the 91 segments with 1% to 50% HE, the mean corrected MBF was 1.0±0.4 mL·min⁻¹·g⁻¹·(mmHg·bpm/10⁴)⁻¹ in segments without significant coronary stenosis and 0.6±0.1 mL·min⁻¹·g⁻¹·(mmHg·bpm/10⁴)⁻¹ in segments with coronary stenosis before PCI (z=−7.2, P<0.0001). In the segments with >50% HE, the respective corrected MBFs were 0.4±0.1 mL·min⁻¹·g⁻¹·(mmHg·bpm/10⁴)⁻¹ and 0.3±0.2 mL·min⁻¹·g⁻¹·(mmHg·bpm/10⁴)⁻¹ (z=−1.09, P=0.28). Thus, the presence of large amounts of myocardial scar attenuated the differences in MBF between stenosed and nonstenosed coronary territories (z=−1.9, P=0.049).

Cine MRI

The mean preprocedural ejection fraction was 47±10% (composed of mean end-diastolic volume index of 76±16 mL/m² and mean end-systolic volume index of 41±13 mL/m²). At 9-month follow-up scanning, across the whole group, the global ejection fraction had improved to 57±7% (P=0.03). Cardiac index improved from 2.3±0.7 L·min⁻¹·m⁻² to 2.6±0.5 L·min⁻¹·m⁻² (P=0.04), whereas LV mass index was unchanged (pre-PCI, 63±11 g/m² and 61±10 g/m²; P=0.6). This improvement in global LV function was a result of a significant (P=0.009) reduction in end-systolic volumes after revascularization (post-PCI end-diastolic volume index of 74±19 mL/m² and end-systolic volume index of 31±15 mL/m²).
Late Functional Changes After Revascularization

Of the affected myocardial segments, 79% (243) demonstrated resting wall motion abnormalities at rest before PCI: 70% hypokinesis, 28% akinesis, 2% dyskinesis. Quantitatively, the systolic wall thickening was lower in the affected segments compared with the unaffected segments (8±17% versus 46±16%; z=-35.71, P<0.001) before revascularization. Late after PCI, the systolic wall thickening increased notably and significantly more in the myocardial segments subtended by severely stenosed coronary arteries (from 8±17% to 40±19%) than in the unaffected segments (from 46±12% to 48±10%; z=26.83, P<0.001; Figure 6A), confirming that a large proportion of these segments were hibernating. Similarly, the end-diastolic wall thickness also increased significantly more in the affected myocardial segments (an increase of 2.8±1.9 mm, from 6.5±1.1 to 9.3±2.0, Figure 6B) than in the myocardial segments supplied by nondiseased vessels (10.4±1.2 to 10.7±1.1 mm) (z=20.3, P<0.001). This improvement in regional wall motion late after PCI in affected myocardial segments was confirmed on visual scoring assessment with mean RWMI score decreasing significantly, from 2.2±0.4 to 1.3±0.5 (P=0.02). In contrast, the regional function of the unaffected segments remained normal in the late follow-up scan (Figure 7).

Discussion

Using quantitative CMR perfusion imaging, our study shows that resting MBF is reduced in dysfunctional myocardial segments supplied by severely stenosed coronary arteries. The majority of these segments showed clear evidence of myocardial hibernation, because there was functional improvement in systolic wall thickening and end-diastolic wall thickness in the late follow-up CMR scan. To the best of our knowledge, this is the first study reporting on the use of quantitative CMR perfusion imaging to evaluate resting MBF in patients with CAD. Our study findings may have important implications for understanding the pathophysiology of resting blood flow changes in states of myocardial hibernation and the relationship between MBF and scar tissue.

The mechanisms underlying hibernating myocardium are controversial. Although several studies support the traditional view that underperfusion downregulates local contractile performance, recent studies have questioned this concept by demonstrating relatively normal regional perfusion in hibernating segments as well as normal oxidative metabolism. All of these studies used PET to evaluate MBF. In this study, we have found using quantitative CMR perfusion imaging that dysfunctional but viable myocardial segments have significantly lower resting MBF compared with blood flow in remote myocardial segments. A number of reasons may explain the differences between our findings and some of the previous studies.
results using PET. First, compared with those studies, the severity of coronary stenoses was significantly higher in our population. In their seminal paper investigating the relationship between MBF and the severity of coronary artery stenosis using $^{15}$O$\text{H}_2\text{O}$ PET, Uren and colleagues$^{27}$ found that the baseline MBF remained constant regardless of the severity of coronary stenosis. However, of the 35 patients examined in their study, only 4 patients had coronary stenosis greater than 80% diameter stenosis, whereas our entire study cohort was in this severe coronary stenosis category. Other PET studies, such as those by Fath-Ordoubadi and colleagues,$^7$ do not report a detailed breakdown of the severity of coronary lesions, and quantitative coronary angiography was not used for coronary stenosis assessment in these early studies. Second, our imaging methodology used to assess changes in MBF is fundamentally different from previous studies. Although to the best of our knowledge, no study so far has directly compared quantitative CMR perfusion imaging with PET, both of these imaging modalities have been independently validated in animal models. PET assessment, both in the 2D and more recently in the 3D mode has had extensive validation as an accurate measure of absolute regional MBF over a wide range of blood flow when using radioisotope-labeled microspheres as the gold standard.$^{28-31}$ CMR first-pass technique combined with the model-independent deconvolution method used in this study has also been well validated by use of radioisotope-labeled microspheres.$^{11}$ Third, the control baseline MBF values in the study by Uren et al were derived from age- and sex-matched healthy control subjects, whereas in our study and in those by Conversano et al$^8$ and de Silva et al,$^{22}$ the myocardial segment supplied by a nondiseased artery in the same individual served as the control. It is conceivable that the differences in regional MBF observed in our study between affected and unaffected myocardial segments might be explained, at least in part, by a higher MBF in the remote normally contracting regions rather than by an absolute reduction in hibernating segments. This explanation would be consistent with the higher oxygen consumption reported in regions remote from segments with severe wall motion abnormalities.$^{35}$

On average, we found a 40% reduction in baseline MBF in affected compared with unaffected myocardial segments. Previous work in animals would indicate that this degree of reduction in transmural MBF can result in significantly impaired myocardial contraction. Gallagher and coworkers$^{32}$ have shown in the dog model that there is a linear relation between reductions in subendocardial blood flow and myocardial contractility. Vatner$^{33}$ measured subendocardial blood flow in dogs and found that MBF reductions by as low as 10% to 20% resulted in severely impaired regional function. Even with the superior spatial resolution of CMR perfusion imaging over PET, we could not determine subendocardial blood flow in our cohort because of the thinness of the myocardium at end diastole. However, on the basis of animal data, we would expect that when transmural MBF falls by ~40%, subendocardial blood flow would decrease even further (by ~50% to 70%$^{32}$).

Patients with hibernating myocardium may also present with some degree of irreversible myocardial injury (ie, infarction), even in the absence of a clinical history. This is supported by our finding of 40% (11/27) of patients demonstrating some evidence of delayed HE, even when only those patients with an absence of a clinical history of myocardial infarction are included. We found that, although the mean MBF is lower in myocardial segments with scar (and this reduction being incrementally related to the transmural extent of scar), even areas with >50% transmural extent of scar still show 30% of normal (compared with normally contracting, nonscar segments) MBF. This has not been studied previously by use of any other imaging technique that measures scar directly, although indirect support for our findings is provided by studies using PET (with either $^{15}$N$\text{NH}_3$ or $^{15}$O$\text{H}_2\text{O}$), which have found higher MBF values in reversibly dysfunctional segments compared with persistently dysfunctional segments.$^5$ Furthermore, there was no significant difference between the mean MBF in affected and unaffected coronary territories in significantly scarred myocardium. This finding is not surprising, however, because the flow reduction in these areas will be determined primarily by the amount of scar rather than by the presence or absence of epicardial stenosis. The ability of CMR to assess both myocardial scar and perfusion concurrently with high spatial resolution is one of the major strengths of the technique and allows us for the first time to report absolute MBF in regions of scarred myocardium.

Our results indicate that a substantial proportion of revascularized segments improved regional contractility at 9 months after PCI, despite the fact that before PCI, the affected myocardium was significantly thinned (mean end-diastolic wall thickness, 6.5 mm). This demonstration of functional recovery after revascularization is vital, because it is the definitive criterion to define a dysfunctional segment subtended by a stenotic artery as “hibernating.” This functional improvement was confirmed both on semiquantitative visual score index and quantitatively.

![AFICTED SEGMENTS vs UNAFFECTED SEGMENTS](image-url)
using end-diastolic wall thickness and percentage change in systolic wall thickening. Reflecting this improvement in regional wall motion, global LV ejection fraction also improved at late follow-up.

Study Limitations

The number of patients in the study was relatively small. This disadvantage, however, was compensated for by the highly selective patient recruitment and successful follow-up. Even with the superior spatial resolution of CMR (at 1.5 T) over PET, we were unable to distinguish between subendocardial versus subepicardial MBF because of low signal-to-noise ratio. Whether or not subendocardial blood flow is reduced further in hibernating myocardium awaits verification by direct measurement, and it is likely that the higher signal-to-noise ratio provided by high-field CMR systems will make further in hibernating myocardium waits verification by direct measurement, and it is likely that the higher signal-to-noise ratio provided by high-field CMR systems will make this possible in the near future. Perfusion measurements in 3 short-axis slices did not give complete coverage of the LV myocardium in this study. However, we do not believe that this would have influenced our results, because the ischemic area induced by most coronary artery stenoses is unlikely to be limited to a small basal or apical area and, furthermore, Nagel and colleagues\(^1\) have shown that evaluating only the 3 inner (ie, excluding the most basal and apical) short-axis slices by CMR perfusion resulted in a higher diagnostic accuracy for the detection of significant CAD than evaluating 5 short-axis slices.

In conclusion, using quantitative CMR perfusion imaging, we have shown that resting MBF is abnormal in hibernating myocardial segments supplied by severely stenosed coronary arteries. The sensitivity of CMR in the assessment of cardiac function and in the quantification of both myocardial scar and blood flow makes it a powerful tool in the investigation of pathophysiological mechanisms of dysfunctional myocardium and in assessing the effectiveness of medical and interventional therapies in CAD and cardiomyopathy.

Acknowledgments

This work was supported by the British Heart Foundation (BHF), the Medical Research Council, and an unrestricted research donation from Guidant, UK. Dr Selvanayagam is funded by a BHF Intermediate Fellowship. Dr Jerosch-Herold gratefully acknowledges support for his work by National Institutes of Health grant RO1-HL65394-01. The authors thank Jane Francis for help with patient scanning and Dr Helen Doll for statistical input.

References


Circulation. 2005;112:3289-3296; originally published online November 14, 2005; doi: 10.1161/CIRCULATIONAHA.105.549170

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2005 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/112/21/3289

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org/subscriptions/