European Heart Journal (2008) **29**, 2000–2005
doi:10.1093/eurheartj/ehn266

Time course of functional recovery after revascularization of hibernating myocardium: a contrast-enhanced cardiovascular magnetic resonance study

Olga Bondarenko[1]*, Aernout M. Beek[1], Jos W.R. Twisk[2], Cees A. Visser[1†], and Albert C. van Rossum[1]

[1]Department of Cardiology, VU University Medical Centre, De Boelelaan 1117, Amsterdam HV 1081, The Netherlands; and [2]Department of Clinical Epidemiology and Biostatistics, VU University Medical Centre, Amsterdam, The Netherlands

Received 10 June 2007; revised 25 May 2008; accepted 29 May 2008; online publish-ahead-of-print 13 June 2008

Aims We sought to evaluate the relation between long-term functional outcome after revascularization in patients with chronic ischaemic left ventricular (LV) dysfunction and baseline extent of myocardial fibrosis.

Methods and results Thirty-five patients underwent cine and delayed contrast-enhanced cardiovascular magnetic resonance (deCMR) for the quantitative assessment of regional and global LV functions and segmental extent of hyperenhancement (SEH). Function was assessed 1 month before and 3, 6, and 24 $\pm$ 12 months after revascularization, and temporal changes were related to baseline extent of hyperenhancement. The likelihood of functional improvement was inversely related to the SEH during the entire follow-up: at the end of the study period, segments with 1–25, 26–50, 51–75, and 76–100% SEH were 2, 5, 11, and 86 times, respectively, less likely to have functional improvement than segments without hyperenhancement (multilevel analysis, $P < 0.001$). Although improvement continued over the whole study period in all SEH groups, the time course was significantly more delayed in segments with more extensive hyperenhancement at baseline (multilevel analysis, $P < 0.001$).

Conclusion In patients with chronic ischaemic LV dysfunction, improvement of dysfunctional but viable myocardium can be considerably delayed. Both the likelihood and the time course of long-term functional improvement are related to the baseline amount of scar, as visualized by deCMR.

Keywords Magnetic resonance imaging • Contrast media • Revascularization • Follow-up studies

Introduction

Functional outcome after revascularization of chronic ischaemic dysfunctional myocardium is related to the pre-operative regional extent of fibrosis and the presence of a sufficient number of residual viable myocytes.[1,2] However, functional recovery is often incomplete even in regions assessed as viable by a variety of techniques. Several studies using delayed contrast-enhanced cardiovascular magnetic resonance (deCMR) have shown that up to 22% of regions with little or no fibrosis do not improve.[1,3,4] Although this may be partly attributed to incomplete revascularization, or early or late graft failure, it may also be explained by the timing of the follow-up functional study. Functional recovery of hibernating regions, especially those with more advanced structural damage, may be considerably delayed. Functional outcome after revascularization is generally assessed after 3–6 months, whereas a longer interval would be more appropriate. So far, few reports have explored the time course of functional recovery in relation to baseline markers of viability.[5–7]

To address this issue, we used cine and deCMR to study a group of patients with chronic ischaemic dysfunction before and 3, 6, and 24 $\pm$ 12 months after revascularization. Using quantitative analysis

* Corresponding author. Tel: +31 20 4442244, Fax: +31 20 4442446, Email: o.bondarenko@vumc.nl

†Deceased in January 2007.

of left ventricular (LV) function and regional extent of hyperenhancement, long-term functional outcome and time course of functional changes were related to baseline extent of fibrosis.

Methods

Patients

All patients with known coronary artery disease and regional wall motion abnormalities on echocardiography or LV angiography, without CMR contraindications, who were scheduled to undergo surgical or percutaneous revascularization between April 2001 and February 2004, were study candidates. The Committee on Research Involving Human Subjects of the VU University Medical Centre, Amsterdam, approved the study protocol. All patients gave written informed consent.

Initially, 120 study candidates were prospectively earmarked as potential study candidates from the coronary artery bypass surgery (CABG) and PCI waiting lists at our hospital. Patients were initially contacted by phone and were offered study information by mail. Ten patients could not be reached in time before the revascularization, 12 patients refused to participate directly without giving any reason, 14 patients were already participating in another study, and five other patients spoke neither Dutch nor English. The remaining 79 patients received the study information. They were contacted by phone again a week later and asked whether they would like to participate in the study. Seventeen patients refused to give their consent. Six patients were willing but could not participate for logistical reasons, e.g. scanner availability. One patient forgot his first MRI appointment three times in a row and was excluded by us from further participation. Another two patients appeared claustrophobic at the very beginning of the first examination and were not able to complete the study. Fifty-three patients completed CMR examination 4 $\pm$ 2 weeks before revascularization. Three of them appeared not to be suitable for the study owing to absence of wall motion abnormalities in two cases and no revascularization in one case. CMR was repeated 3, 6, and 24 $\pm$ 12 months (median 26 months, range 13–44 months) after revascularization in 45, 41, and 35 patients, respectively. No patient died. Six patients were excluded from the study: in one patient, the CABG was accompanied by LV aneurysmectomy, four patients had electrocardiographic and/or biochemical evidence of peri-procedural myocardial infarction, and one patient had a permanent pacemaker implanted. Two patients suffered a cerebrovascular accident. Follow-up was incomplete in the remaining seven patients: no follow-up in four patients [(newly developed) claustrophobia in two, fear of needles in one, lack of motivation in one], and two patients declined to return after the 3 month study, and one for the 3 and the 6 month study. The baseline characteristics of the 35 patients, who underwent all four CMR examinations, are listed in *Table 1*.

CABG was performed in 25 patients and percutaneous transluminal coronary angioplasty (PTCA) in 10. All patients were in stable clinical condition at the time of the CMR examinations and there was no clinical evidence of ischaemic events in the period between the CMR examinations and revascularization. Complete revascularization was defined as revascularization of all major epicardial vessels or first generation side branches with >50% diameter stenosis. For patients in whom revascularization was incomplete, only segments in revascularized coronary artery territories were considered.[8]

Table 1 Patients characteristics

Males/females, *n*	29/6
Age, years	63 $\pm$ 11
Risk factors, %	
Systemic hypertension	45
Diabetes mellitus	17
Hypercholesterolaemia	31
Smoking	41
Positive family history	12
Coronary angiography, %	
Single-vessel disease	14
Two-vessel disease	14
Three-vessel disease	72
History of myocardial infarction, %	59
Previous revascularization, %	
CABG	7
PTCA	3
Ejection fraction at baseline, %	39 $\pm$ 11
Months between infarction and baseline CMR (range)	53 (2–177)

Cardiovascular magnetic resonance

All scans were performed on a 1.5 T scanner (Sonata, Siemens, Erlangen, Germany), with the patient in a supine position, using a four-element phased array cardiac receiver coil. ECG-gated cine images were acquired using a breath-hold-segmented steady-state free precession sequence (true FISP; echo time/repetition time of 1.2/3.2 ms; resolution of 1.3 $\times$ 1.8 $\times$ 5 mm^3). Per patient, eight to 10 short-axis views were obtained every 10 mm starting from the mitral valve insertion and covering the entire left ventricle.

A gadolinium-based contrast agent (Magnevist, Schering AG, Berlin, Germany; 0.2 mmol/kg) was then administered intravenously with a power injector through a peripheral vein. After 10–15 min, contrast-enhanced images were acquired in the same orientation as the cine images, using a two-dimensional segmented inversion recovery gradient-echo pulse sequence triggered to end-diastole (repetition time/echo time = 9.6/4.4 ms, flip angle 25°, matrix 208 $\times$ 256, and a typical voxel size of 1.6 $\times$ 1.3 $\times$ 5.0 mm^3).

Data analysis

All data were analysed on a separate workstation (Sun Microsystems, Inc., Santa Clara, CA, USA), using a dedicated software package (MASS 5.1, Medis, Leiden, The Netherlands).

Segmental function

Segmental wall thickness was measured at end-systole and end-diastole after manual tracing of endocardial and epicardial borders in stop-frame images, excluding trabeculations and papillary muscles. The contours were drawn blinded to patient identity, clinical history, and scan time point. The analysis program used the modified centreline method[9] along 100 chords per short-axis slice and allowed the automatic segmentation, in which the number of chords per segment depended on the number of segments chosen (number of chords per segment = 100/number of segments). Segmental wall thickness was calculated as the average of the chords within one segment. Segmental wall thickening (SWT) in millimetres was calculated as: end-systolic wall thickness minus end-diastolic wall thickness. The normal range of SWT was defined in a group of 10 healthy volunteers (age 50–75 years): 4.4 $\pm$ 0.7 mm. Segments with SWT < 3 mm (mean – 2SD) were considered

dysfunctional. Registration of follow-up cine images was achieved using standard imaging procedure and various anatomical landmarks such as right ventricle septal insertion sites, papillary muscle location, and trabecularization patterns in the right and left ventricles. Functional improvement was defined as an increase in SWT of $\geq$1.5 mm compared with baseline, based on the in-plane spatial resolution of the cine sequence. The results of intraobserver and interobserver (by two observers) variabilities of SWT were determined in 10 randomly chosen patients. The time period between the repeated readings was 2 weeks.

Images were evaluated using a 16-segment model.[8] Using the full coverage cine short-axis data set, six basal, six mid-ventricular, and four distal segments were composed by averaging the data of a maximum of three short-axis slices. The most basal short-axis slice used for the composition of the basal segments was located just below the LV outflow tract. The two most apical slices were excluded, because short-axis images at this level preclude a reliable segmental evaluation owing to small diameter.

Global function

LV end-diastolic and end-systolic volumes (LVEDV and LVESV, respectively) were determined by planimetry of all short-axis images in each patient. LV ejection fraction (LVEF, in percentage) was calculated as (LVEDV – LVESV)/LVEDV.

Segmental hyperenhancement

Hyperenhanced regions were quantified after standardization by thresholding signal intensity contrast-enhanced images as described previously.[10] Areas of hyperenhancement were quantified by computer-assisted planimetry on each of the short-axis images, and segmental extent of hyperenhancement (SEH) was expressed as percentage of segmental area. Images were evaluated according to the same 16-segment model as described earlier. All segments were assigned to one of the following SEH groups: 1–0, 2–1 to 25, 3–26 to 50, 4–51 to 75, and 5–76 to 100% hyperenhancement.

Statistical analysis

All values are expressed as mean $\pm$ SD. The paired sample *t*-test and the independent samples *t*-test were used to compare means within the study group or between subgroups. We used multilevel logistic regression (MlwiN, version 1.02.0007, Centre for Multilevel Modelling, London, UK)[11,12] to adjust for the non-independence of the data to evaluate the relation between baseline extent of hyperenhancement and change in SWT. In this analysis, we added a random intercept and we estimated the regression coefficients (as fixed effects and transformed them into the odds ratios) for the dummy variables, reflecting the different groups of hyperenhancement. We used the 0% SEH group as a reference, so all other groups were related to this one. The dummy variables for SEH were in the model as fixed effects. Because we had only two levels (segments clustered within patients) and no random slopes, there was no covariance of the random effects, so no particular structure was chosen. The regression equation was used to calculate odds ratios, which expressed the likelihood of improvement relative to functional outcome of segments without any hyperenhancement. The multilevel logistic regression was also used to evaluate time course of regional functional improvement in relation to segmental extent of myocardial fibrosis. ANOVA for repeated measurements (using univariate estimation approach with the Greenhouse Geisser adjustment and testing the difference between baseline and post-baseline measurements) was applied to analyse changes in global ventricular function. We used linear regression analysis to assess the relation between viability at baseline and changes in ejection fraction at late follow-up. Intraclass correlation coefficients were used for the assessment of intra- and interobserver variabilities. All statistical tests were two-tailed, and *P*-values $<$0.05 were considerate to indicate statistical significance.

Results

Regional function

At baseline, 560 segments (35 patients $\times$ 16 segments) were available for analysis. 518 segments were successfully revascularized. Almost 50% of these segments ($n = 258$) had a baseline SWT of $<$3 mm (mean 1.2 $\pm$ 1.0 mm) and were considered dysfunctional. The interobserver variability for SWT was 0.1 $\pm$ 0.7 mm [mean difference between values of observer 1 (OB) and 2 (AMB); intraclass correlation coefficient 0.89, 95% confidence interval 0.55–0.98]. The intraobserver variability for SWT was 0.0 $\pm$ 0.4 mm [mean difference between two measurements (OB); intraclass correlation coefficient 0.97, 95% confidence interval 0.86–0.99].

Functional improvement

At the end of the study period, functional improvement was seen in 93, 70, 66, 36, and 5% of segments with no, 1–25, 26–50, 51–75, and 75–100% SEH, respectively (*Table 2*, *Figure 1A*). The likelihood of functional improvement was inversely related to the SEH during the entire follow-up: at the end of the study period, segments with 1–25, 26–50, 51–75, and 76–100% SEH were 2 (1.1–3.6), 5 (2.5–8.6), 11 (5.0–20.1), and 86 (11.0–682.0) times less likely to have functional improvement than segments without hyperenhancement (multilevel analysis, $P < 0.001$).

Table 2 Regional functional improvement

MRI	SEH				
	0%	1–25%	26–50%	51–75%	76–100%
Baseline	$n = 62$	$n = 57$	$n = 59$	$n = 59$	$n = 21$
3 months	35 (56%)	19 (33%)	13 (22%)	4 (7%)	0
6 months	15 (24%)	16 (28%)	15 (25%)	7 (12%)	0
24 months	8 (13%)	5 (9%)	11 (19%)	10 (17%)	1
Total	58 (93%)	40 (70%)	39 (66%)	21 (36%)	1 (5%)

Regional functional improvement, expressed in absolute numbers of improved segments and a percentage of baseline, for every MRI examination according to SEH; *n*, number of dysfunctional segments at baseline.

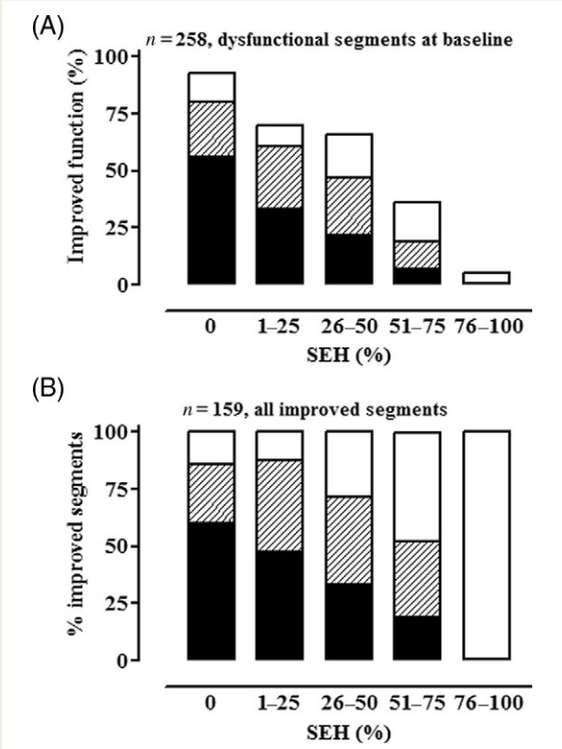

Figure 1 (*A*) Likelihood of functional improvement after revascularization in relation to baseline segmental extent of hyperenhancement (SEH), expressed as a percentage of total number of dysfunctional segments, at 3 months (black bars), 6 months (striped bars), and 2 years (white bars) follow-up. All dysfunctional segments are included ($n = 258$). (*B*) Time course of regional functional improvement in relation to baseline segmental extent of hyperenhancement, shown as the relative percentage of improvement at 3 months (black bars), 6 months (striped bars), and 2 years (white bars) follow-up. Only segments with functional improvement are included ($n = 159$).

Similar results were found when analysing the data with different cut-offs for segmental functional improvement (2, 2.5, and 3 mm SWT change), although the odds ratios were lower due to the lower number of improving segments at these higher cut-offs.

Time course

The time course of functional improvement was considerably protracted: at 3 months, improvement was seen in less than half of all segments that eventually improved (71 of 159; 45%). Although improvement continued over the whole study period in all SEH-groups, the time course was significantly more delayed in segments with more extensive hyperenhancement at baseline (multilevel logistic regression, $P < 0.001$; *Figure 1B*). At 3 months, the major part (54/98, 55%) of improvement in segments with no or minimal ($\leq$25%) hyperenhancement was found in the first 3 months, vs. only 28% (17/61) of improvement in segments with >25% hyperenhancement. Conversely, more than one-thirds (22/61, 36%) of total improvement in segments with >25% hyperenhancement occurred between 6 months and the final follow-up, vs. only a small fraction (13/98, 13%) in segments with no or minimal hyperenhancement.

A total of 75 segments became dysfunctional at late follow-up. Twenty-two (18%) of 124 segments that initially improved (mean SWT at baseline 1.8 ± 0.8 mm, 3 months follow-up 3.2 ± 1.3 mm, 6 months follow-up 3.3 ± 1.8 mm) showed a decrease in SWT >1.5 mm at late follow-up ending up as dysfunctional (mean SWT 1.4 ± 1.0 mm). At baseline, 10 of these showed no hyperenhancement, and nine, two, and one segments had 1–25, 26–50, and 51–75% SEH, respectively. A similar proportion of revascularized segments with normal SWT at baseline [49 of 260 (19%)] became dysfunctional 2 years after revascularization (mean SWT 4.4 ± 0.9 mm at baseline vs. 1.7 ± 0.9 mm at late follow-up). The long-term follow-up also revealed worsening of regional function in four of 25 (16%) initially normokinetic, non-revascularized segments (mean SWT 4.1 ± 1.0 vs. 2.6 ± 0.4 mm).

Global left ventricular function

Both end-diastolic and end-systolic LV volumes showed small but significant improvements at 3 months follow-up, with no additional changes at 6 months and 2 years. The ejection fraction showed a small increase at all follow-up time points, which reached statistical significance only at 6 months. There were no statistically significant changes in LV mass. Data are shown in *Figure 2A–C*.

For each patient, we calculated a viability index by adding the number of dysfunctional segments with SEH $\leq$ 50% and then dividing this by the total number of dysfunctional segments in the left ventricle. There was a significant, positive relation between the viability index and improvement in ejection fraction at late follow-up (regression coefficient $r = 0.47$, $P = 0.005$).

Discussion

This is the first study that used CMR imaging to evaluate long-term follow-up after revascularization in patients with chronic ischaemic myocardial dysfunction. Our results showed that both likelihood and time course of functional improvement were related to the amount of baseline myocardial scar.

Long-term functional outcome after revascularization

Previous studies have shown a variety of degenerative changes at cellular and subcellular levels in histological assessment of targeted biopsies taken at the time of CABG.[13,14] Increased extracellular matrix, with replacement of cardiomyocytes by fibrosis, is considered to have a central role in the likelihood and time course of functional recovery after restoration of blood flow. Although the exact mechanism of hibernation is still not fully understood, several investigators have found a relation between functional outcome after revascularization and the degree of these morphological changes.[7,13–17] Delayed contrast-enhanced CMR allows the accurate visualization and quantification of regional scar and is of proven value in the assessment of myocardial viability.[1,3,18,19]

Extending previous work, our results showed that functional outcome was inversely related to the baseline SEH at every time

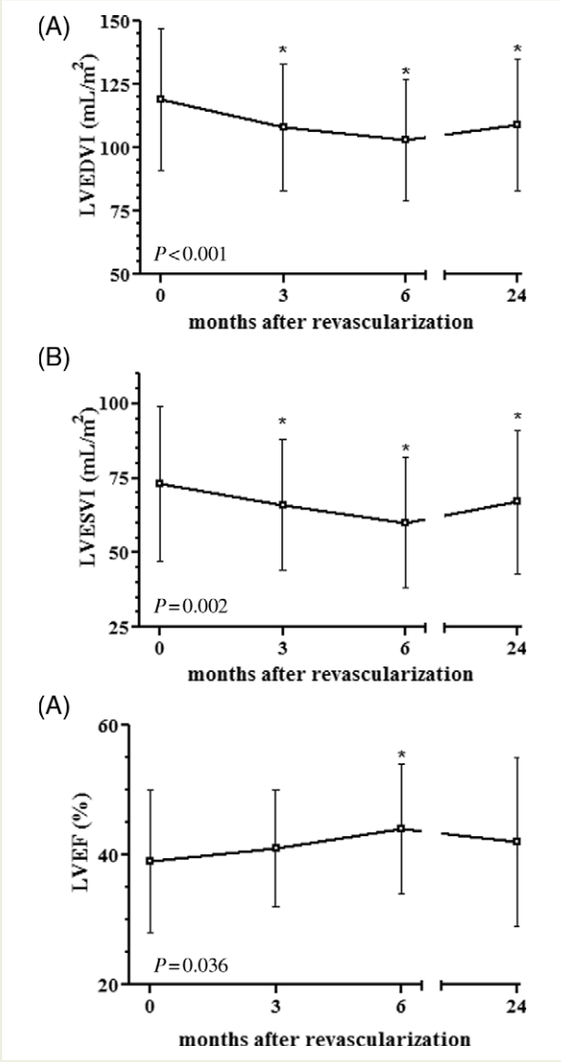

Figure 2 Changes in global left ventricular parameters. LVEDVI, left ventricular end-diastolic volume index (*A*); LVESVI, left ventricular end-systolic volume index (*B*); LVEF, left ventricular ejection fraction (*C*). Asterisk indicates statistically significant difference compared with baseline value. Bars represent standard deviation. *P*-values are given for linear trend over time analysis.

point of the study. Compared with earlier studies using deCMR, we found a relatively low improvement rate at 3 months; for example, only 56% of segments without hyperenhancement improved vs. 78% reported by Kim *et al.*[1] However, at the end of the study period, improvement rate was higher than previously reported in all groups with less than transmural (<75%) enhancement. For example, after 2 years, almost all segments without hyperenhancement (93%) showed functional improvement.

Time course of recovery

Our results clearly show that delayed recovery is common in successfully revascularized hibernating myocardium, and that this was not limited to regions with more extensive structural damage, but that it also occurred in regions with no hyperenhancement. In all SEH groups, a comparable number of segments continued to show improvement throughout the study period. However, the relative time course differed considerably and, in fact, was inversely related to the SEH. Thus, both long-term likelihood and time course of functional improvement were predicted by the degree of morphological changes at baseline.

Previous reports have shown that morphological changes are paralleled by metabolic alterations: regional scar extent was inversely related to FDG uptake by PET.[2,20] Outcome was best in segments with both a thick viable rim >4.5 mm (indicating limited scar extent) and preserved FDG uptake, whereas segments with impaired FDG uptake (indicating more severe metabolic disturbance) had low likelihood of recovery despite the presence of thick viable rim.[2] However, follow-up in this study was shorter (11 ± 2 months) and our data suggest that segments with a higher degree of metabolic disturbance may require a longer time to recover.

In line with previous studies, we found that the negative predictive value of (almost) transmural hyperenhancement was high: only one segment with >75% SEH improved after revascularization. Apparently, extensive morphological changes preclude functional improvement, although technically we cannot rule out the possibility that some improvement would have occurred at an even longer follow-up time in segments with only little residual non-enhancing myocardium (>75 to <100% transmurality).

Significant improvement in global LV function after revascularization requires a substantial amount of viable myocardium.[21] Long-term data are scarce, since most viability studies have focused on short-term (≤6 months after revascularization) changes in regional function. In our study group, there was a significant positive relation between the amount of dysfunctional but viable myocardium at baseline, estimated per patient, and improvement in the ejection fraction at late follow-up. However, we found only small changes in the mean global LV function after revascularization, even at late follow-up, which suggests that the improvement in regional function may not have been enough for global improvement. Alternatively, the regional improvement may have been partly offset by the 72 newly dysfunctional segments (13% of total) at late follow-up. Changes in global function are also influenced by several other factors, such as baseline volumes and ejection fraction, peri-procedural ischaemic accidents, and long-term graft failure or restenosis.

Limitations

Only 35 patients completed the whole study protocol, however this sample size is comparable with previously published studies that used deCMR and cine imaging in patients with chronic ischaemic heart disease and a revascularization procedure.[1,2]

We chose a 16-segment model for the regional evaluation of LV function, because this can be directly translated into clinical practice. Transforming the CMR data into a limited number of segments involves averaging information of several slices. Although averaging data has the obvious disadvantage that some detail may be lost, it may at the same time help to prevent misregistration of follow-up scans, which is an important potential limitation in any long-term follow-up study of regional function.

Although observers were unaware of patient identity during analysis of the cine data, follow-up studies could be identified by the presence of sternal wire or stent artefacts. It was not possible to differentiate between the various post-procedural time points.

Conclusions

In patients with chronic ischaemic LV dysfunction, improvement of dysfunctional but viable myocardium after revascularization can be considerably delayed. Both the likelihood and the time course of long-term functional improvement are related to the baseline amount of scar, as visualized by deCMR.

Conflict of interest: none declared.

Funding

This work was supported by grant 2001.158 from the Netherlands Heart Foundation.

References

1. Kim RJ, Wu E, Rafael A, Chen EL, Parker MA, Simonetti O, Klocke FJ, Bonow RO, Judd RM. The use of contrast-enhanced magnetic resonance imaging to identify reversible myocardial dysfunction. *N Engl J Med* 2000;**343**:1445–1453.
2. Knuesel PR, Nanz D, Wyss C, Buechi M, Kaufmann PA, von Schulthess GK, Luscher TF, Schwitter J. Characterization of dysfunctional myocardium by positron emission tomography and magnetic resonance: relation to functional outcome after revascularization. *Circulation* 2003;**108**:1095–1100.
3. Selvanayagam JB, Kardos A, Francis JM, Wiesmann F, Petersen SE, Taggart DP, Neubauer S. Value of delayed-enhancement cardiovascular magnetic resonance imaging in predicting myocardial viability after surgical revascularization. *Circulation* 2004;**110**:1535–1541.
4. Wellnhofer E, Olariu A, Klein C, Grafe M, Wahl A, Fleck E, Nagel E. Magnetic resonance low-dose dobutamine test is superior to SCAR quantification for the prediction of functional recovery. *Circulation* 2004;**109**:2172–2174.
5. Bax JJ, Visser FC, Poldermans D, Elhendy A, Cornel JH, Boersma E, van Lingen A, Fioretti PM, Visser CA. Time course of functional recovery of stunned and hibernating segments after surgical revascularization. *Circulation* 2001;**104**:I314–I318.
6. Haas F, Augustin N, Holper K, Wottke M, Haehnel C, Nekolla S, Meisner H, Lange R, Schwaiger M. Time course and extent of improvement of dysfunctioning myocardium in patients with coronary artery disease and severely depressed left ventricular function after revascularization: correlation with positron emission tomographic findings. *J Am Coll Cardiol* 2000;**36**:1927–1934.
7. Shivalkar B, Maes A, Borgers M, Ausma J, Scheys I, Nuyts J, Mortelmans L, Flameng W. Only hibernating myocardium invariably shows early recovery after coronary revascularization. *Circulation* 1996;**94**:308–315.
8. Cerqueira MD, Weissman NJ, Dilsizian V, Jacobs AK, Kaul S, Laskey WK, Pennell DJ, Rumberger JA, Ryan T, Verani MS. Standardized myocardial segmentation and nomenclature for tomographic imaging of the heart: a statement for healthcare professionals from the Cardiac Imaging Committee of the Council on Clinical Cardiology of the American Heart Association. *Circulation* 2002;**105**:539–542.
9. van Rugge FP, van der Wall EE, Spanjersberg SJ, de Roos A, Matheijssen NA, Zwinderman AH, van Dijkman PR, Reiber JH, Bruschke AV. Magnetic resonance imaging during dobutamine stress for detection and localization of coronary artery disease. Quantitative wall motion analysis using a modification of the centerline method. *Circulation* 1994;**90**:127–138.
10. Bondarenko O, Beek AM, Hofman MB, Kuhl HP, Twisk JW, van Dockum WG, Visser CA, van Rossum AC. Standardizing the definition of hyperenhancement in the quantitative assessment of infarct size and myocardial viability using delayed contrast-enhanced CMR. *J Cardiovasc Magn Reson* 2005;**7**:481–485.
11. Goldstein H. *Multilevel Statistical Models*. London: Edward Arnold; 2003.
12. Twisk JWR. *Applied Multilevel Analysis. A Practical Guide*. Cambridge, UK: Cambridge University Press; 2005.
13. Elsasser A, Schlepper M, Klovekorn WP, Cai WJ, Zimmermann R, Muller KD, Strasser R, Kostin S, Gagel C, Munkel B, Schaper W, Schaper J. Hibernating myocardium: an incomplete adaptation to ischemia. *Circulation* 1997;**96**:2920–2931.
14. Schwarz ER, Schoendube FA, Kostin S, Schmiedtke N, Schulz G, Buell U, Messmer BJ, Morrison J, Hanrath P, vom DJ. Prolonged myocardial hibernation exacerbates cardiomyocyte degeneration and impairs recovery of function after revascularization. *J Am Coll Cardiol* 1998;**31**:1018–1026.
15. Depre C, Vanoverschelde JL, Melin JA, Borgers M, Bol A, Ausma J, Dion R, Wijns W. Structural and metabolic correlates of the reversibility of chronic left ventricular ischemic dysfunction in humans. *Am J Physiol* 1995;**268**:H1265–H1275.
16. Haas F, Jennen L, Heinzmann U, Augustin N, Wottke M, Schwaiger M, Lange R. Ischemically compromised myocardium displays different time-courses of functional recovery: correlation with morphological alterations? *Eur J Cardiothorac Surg* 2001;**20**:290–298.
17. Vanoverschelde JL, Depre C, Gerber BL, Borgers M, Wijns W, Robert A, Dion R, Melin JA. Time course of functional recovery after coronary artery bypass graft surgery in patients with chronic left ventricular ischemic dysfunction. *Am J Cardiol* 2000;**85**:1432–1439.
18. Beek AM, Kuhl HP, Bondarenko O, Twisk JW, Hofman MB, van Dockum WG, Visser CA, van Rossum AC. Delayed contrast-enhanced magnetic resonance imaging for the prediction of regional functional improvement after acute myocardial infarction. *J Am Coll Cardiol* 2003;**42**:895–901.
19. Kim RJ, Fieno DS, Parrish TB, Harris K, Chen EL, Simonetti O, Bundy J, Finn JP, Klocke FJ, Judd RM. Relationship of MRI delayed contrast enhancement to irreversible injury, infarct age, and contractile function. *Circulation* 1999;**100**:1992–2002.
20. Kuhl HP, Beek AM, van der Weerdt AP, Hofman MB, Visser CA, Lammertsma AA, Heussen N, Visser FC, van Rossum AC. Myocardial viability in chronic ischemic heart disease: comparison of contrast-enhanced magnetic resonance imaging with (18)F-fluorodeoxyglucose positron emission tomography. *J Am Coll Cardiol* 2003;**41**:1341–1348.
21. Bax JJ, Poldermans D, Elhendy A, Boersma E, Rahimtoola SH. Sensitivity, specificity, and predictive accuracies of various noninvasive techniques for detecting hibernating myocardium. *Curr Probl Cardiol* 2001;**26**:147–186.

The above article uses a new reference style being piloted by the EHJ that shall soon be used for all articles.