MYOCARDIAL VIABILITY: BEYOND IMPROVEMENT OF FUNCTION

Myocard vitaliteit: meer dan functie verbetering alleen?

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For My Family
Alla Mia Famiglia

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Part 2. Beneficial Effects of Coronary Revascularization: Beyond Improvement in LVEF

CHAPTER 1

Introduction and Overview of the Thesis

Assessment of myocardial viability in chronic ischemic heart disease: current status

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Assessment of myocardial viability is clinically important in the work-up of patients with ischemic cardiomyopathy. Numerous studies in the past 2 decades demonstrated that revascularization improves left ventricular ejection fraction (LVEF), heart failure symptoms and prognosis in patients with viable myocardium. Conversely patients without viable tissue do not benefit from revascularization. Also, a substantial amount of viable myocardium (at least 25% of the left ventricle) is needed to result in improvement of LVEF. Hence, both identification and quantification of the extent of viable myocardium are required for a careful selection of candidates for revascularization. Indeed, the presence of a substantial amount of viable myocardium decreases the risk of surgery in patients with reduced LVEF. Several diagnostic techniques are available to identify myocardial viability. Positron emission tomography (PET), myocardial perfusion imaging, and stress echocardiography are considered the traditional techniques to evaluate myocardial viability. Recently, newer techniques including cardiac magnetic resonance (CMR), myocardial contrast echocardiography (MCE) and electromechanical mapping have been introduced. In this manuscript the status of the currently available techniques to assess viability was reviewed. Also the relative merits of each technique for prediction of functional recovery and prognosis was addressed. The available retrospective data support the clinical use of viability assessment. Patients with ischemic cardiomyopathy should undergo viability testing to determine therapeutic strategy. In the presence of substantial amount of viable myocardium, patients should undergo revascularization since benefits in terms of left ventricular function, remodeling, symptoms and prognosis may be anticipated. However, prospective randomized trial are needed to confirm these data.

KEY WORDS: Myocardium - Myocardial ischemia - Radionuclide imaging.

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Assessment of myocardial viability is clinically important in the management of patients with ischemic cardiomyopathy. The awareness that left ventricular (LV) dysfunction may be reversed after revascularization, when dysfunctional but viable myocardium is present, has resulted in an increased interest of cardiologists to refer these patients for surgery, despite the associated high risks.[1-4] Even though data from randomized clinical trials are still awaited, numerous studies over the past 2 decades have demonstrated that revascularization improves left ventricular ejection fraction (LVEF), heart failure symptoms and prognosis predominantly in patients with viable myocardium.[5-13] In contrast, revascularization of patients without viable tissue, did not result in improvement of function, symptoms, or prognosis.[5-13] Preliminary studies reported that about 50% of patients with chronic LV dysfunction may have substantial viable myocardium and can be candidates for revascularization.[14-17]

In addition, it has become clear that a substantial amount of viable myocardium (at least 25% of the left

TABLE I.—*Techniques to assess myocardial viability.*

Characteristics	Imaging modality	Markers of viability
Perfusion/intact cell membrane	Thallium-201 SPECT	Tracer activity >50% Redistribution >10%
Perfusion/intact mitochondria	Technetium-99m TF/MIBI SPECT	Tracer activity >50% Improved tracer uptake after nitrates
Perfusion/intact microcirculation	Myocardial contrast-echo	Preserved perfusion
Glucose metabolism	FDG imaging (PET or SPECT)	Preserved perfusion/FDG uptake Perfusion-metabolism mismatch Tracer activity >50%
Free fatty acid metabolism	BMIPP SPECT	Perfusion-BMIPP mismatch
Contractile reserve	Dobutamine echo/MRI Dobutamine gated SPECT	Improved contraction during low-dose dobutamine infusion

BMIPP: β-methyliodophenyl pentadecanoic acid; FDG: F18-fluorodeoxyglucose; MIBI: sestamibi; MRI: magnetic resonance imaging; PET: positron emission tomography; SPECT: single photon emission computed tomography; TF: tetrofosmin.

ventricle) is necessary to result in improvement of LVEF after revascularization.[5] Hence, both identification and quantification of the extent of viable myocardium are required for a careful selection of patients who have a higher likelihood of benefit from revascularization. Only in patients with a substantial amount of viable myocardium, the benefit of revascularization may outweigh the risk of surgical procedures.[18] As of now, numerous diagnostic techniques are available to distinguish viable myocardium from scar tissue, and they rely on detection of various characteristics of viable myocardium (Table I). Positron emission tomography (PET), myocardial perfusion imaging with thallium-201 (Tl-201) or technetium-99m (Tc-99m) labelled agents, and stress echocardiography have been widely used and are considered the traditional techniques to evaluate myocardial viability. Recently, newer techniques including cardiac magnetic resonance (CMR), myocardial contrast echocardiography (MCE) and electromechanical mapping have been introduced. In particular the use of CMR with contrast-enhanced imaging is of interest due to the extremely high resolution enabling detection of subendocardial scar tissue. In this manuscript, the status of the currently available techniques to assess viability and their relative merits for the prediction of functional recovery after revascularization will be discussed.

Nuclear imaging

Positron emission tomography

PET is considered the gold standard to assess myocardial viability. To achieve the maximum accuracy for the detection of viability, integrated assessment of function, perfusion and metabolism is needed.[19] The assessment of function is needed to identify the regions with contractile dysfunction, since in these regions viability assessment is an issue. For assessment of perfusion, various tracers are available, including N-13 ammonia, O-15 labelled water, or Rubidium-82. For assessment of metabolism, F-18-fluorodeoxyglucose (FDG) is mainly used. FDG is a glucose analogue that is accumulated in the myocardium after initial phosphorylation, and provides a clear signal for imaging. Viable myocardium can either show normal perfusion and metabolism (repetitively stunned myocardium) or reduced perfusion with (relatively) increased metabolism (perfusion-FDG mismatch pattern, reflecting hibernating myocardium).[19] In the clinical setting, the majority of the dysfunctional regions show normal perfusion and metabolism, and only a minority shows reduced perfusion with increased FDG uptake.[20] Indeed, hibernating myocardium is likely to represent an unstable substrate and may easily progress to cell death. Scar tissue shows a matched reduction in myocardial perfusion and FDG uptake.

A large number of studies (n=20, 598 patients) have used FDG PET to predict recovery of regional contractile function after revascularization, showing a sensitivity ranging from 71% to 100% (weighted mean 93%) with a specificity ranging from 33% to 91% (weighted mean 58%) (Table II).[21] Moreover, the number of viable segments on FDG PET was directly related to the magnitude of improvement in LVEF after revascularization.[22] Subsequent studies demonstrated the value of FDG PET in the prediction of improvement in LVEF after revascularization.[23] In particular,

TABLE II.—*Diagnostic accuracy of DSE and nuclear technique to assess viability.*[21]

Technique	No. of studies	No. of patients	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
DSE	32	1 090	81	80	77	85
Tl-201 RR	22	557	88	59	69	80
Tl-201 RI	11	301	86	50	57	83
MIBI	20	488	81	66	71	77
FDG PET	20	598	93	58	71	86

DSE: dobutamine stress echocardiography; FDG PET: F18-fluorodeoxyglucose positron emission tomography; MIBI: technetium-99m sestamibi; NPV: negative predictive value; PPV: positive predictive value; Tl-201 RI: Thallium-201 stress-reinjection; Tl-201 RR: Thallium-201 rest-redistribution.

data from the European Multicenter Trial on FDG PET demonstrated a sensitivity and specificity of 79% and 55% for the prediction of improvement in LVEF.[23] Also significant improvement in heart failure symptoms after revascularization was observed in patients with viability.[6] The prognostic value of FDG PET is shown in various studies. Haas *et al.* demonstrated that patients with viability had less perioperative events and a superior one-year survival after revascularization as compared to patients without viable tissue.[24] Additional studies, focusing on long-term survival, demonstrated that patients with viable tissue who underwent revascularization had a low event-rate, in sharp contrast to the high event-rate observed in patients with viable tissue who were treated medically.[13] When 7 prognostic studies (619 patients) on FDG PET were pooled [7, 9, 25-29] the event-rate was 42% in the viable patients who were treated medically, and 10% in the viable patients who underwent revascularization (Figure 1).

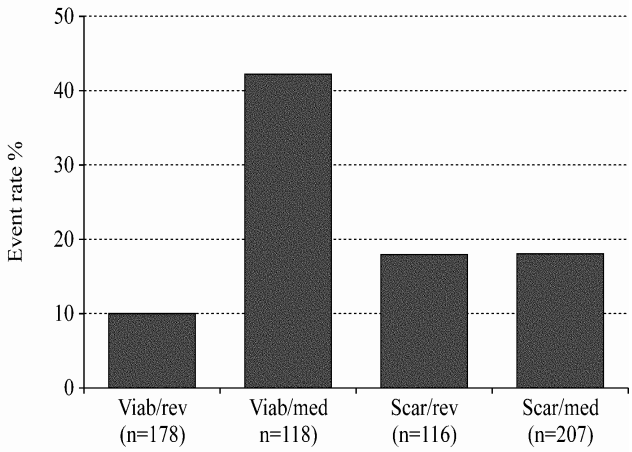

Figure 1.—Prognosis of patients with and without viability on FDG PET and mode of treatment (rev: revascularization; med: medical therapy; viab: viable).[7, 9, 25-29] The lowest event-rate is observed in patients with viable myocardium who undergo revascularization, as compared to the high event-rate in patients with viable myocardium who are treated medically.

Single photon imaging: thallium-201

Single photon emission computed tomography (SPECT) with Tl-201 relies on the principle that myocardial perfusion and cell membrane integrity need to be preserved for Tl-201 to accumulate in the myocyte. Tl-201 is a potassium analogue that is actively transported by the Na+/K+ ATPase pump trough the intact cell membrane of the myocyte.[30] The initial uptake of Tl-201 is mainly determined by perfusion whereas delayed retention is dependent on cell membrane integrity. Various protocols have been proposed with Tl-201, however the most frequently used are stress-redistribution-reinjection and rest-redistribution.

STRESS-REDISTRIBUTION-REINJECTION

With this protocol the images are acquired immediately after stress and at 3-4 hours after stress. Reversible perfusion defects indicate ischemic areas, whereas fixed defects may consist of scar tissue or severely hypoperfused but viable myocardium. To differentiate between scar tissue and hypoperfused but viable tissue, immediately after acquisition of the 3-4 hour images, a 2nd dose of Tl-201 chloride is injected (reinjection) and images are obtained again. Viability on the reinjection images is then considered present when the defects exhibit significant fill-in on the reinjection images (frequently defined as a >10% increase in tracer uptake) or in the absence of fill-in but with a tracer uptake >50% in the persistent defects. The advantage of this protocol is that it allows for a comprehensive assessment of patients with ischemic cardiomyopathy and provides information on both stress-inducible ischemia and viability. The stress-redistribution-reinjection protocol is time-consuming and to shorten the procedure, the reinjection may be performed immediately after the stress imaging and 1 hour later a new image acquisition may be obtained.[31]

A careful reanalysis of the 11 studies (with 301 patients) that used Tl-201 stress-redistribution-reinjection to predict improvement in regional function after revascularization showed that this technique has high sensitivity (weighted mean 86%, range 33-

100%), but a relatively low specificity (weighted mean 50%, range 16-80%) (Table II).[21] This observation suggests that Tl-201 stress-redistribution-reinjection may overestimate the potential for functional recovery.[32] Similarly, a low specificity has been reported for the prediction of improvement in global LV function.[33, 34] In particular, Tl-201 stress-redistribution-reinjection imaging showed a sensitivity of 83% with a specificity of 54% to predict recovery of LVEF after revascularization.[33] The prognostic value of Tl-201 stress-redistribution-reinjection has been demonstrated in several studies.[35-37] For example, Petretta *et al.* studied 104 patients with a previous infarction and demonstrated that Tl-201 reinjection added significantly to clinical and other data for prognostification.[35]

Rest-redistribution

In this protocol the injection of Tl-201 is performed only at rest. Resting perfusion is assessed from the images acquired 5 min after tracer injection. The 2nd set of images is obtained 3-4 hours later (the redistribution images) and tracer accumulation is only possible in myocytes when the cellmembrane is intact. Viability is considered present when segments on the delayed images exhibit significant fill-in of defects on the initial images (>10% increase in tracer uptake, or redistribution) or when the defects are "fixed" but have an activity >50%. A pooled analysis of the 22 studies (n=557 patients) using Tl-201 rest-redistribution showed an average sensitivity and specificity of 88% (range 44-100%) and 59% (range 22-92%) respectively, for the prediction of recovery of regional function (Table II).[21] Few studies focused on the prediction of improvement in global function; Iskandrian *et al.*[38] showed that 86% of patients with substantial viability of Tl-201 rest-redistribution improved in global function, whereas 67% of patients without viability did not improve in global LV function. Comparable results were reported by Mori *et al.*[39] and Ragosta *et al.*[40] In addition, the prognostic value of Tl-201 rest-redistribution imaging has been shown by Pagley *et al.*[8] The authors evaluated 70 patients with severely depressed LVEF and multi-vessel coronary artery disease; all patients underwent surgical revascularization. In patients with viability, the cardiac death-rate was 18% as compared to 41% in the patients without viability.

Single photon imaging: technetium-99m labelled agents

Myocardial uptake and retention of Tc-99m sestamibi/tetrofosmin is dependent on regional perfusion and also requires the integrity of the cellular and mitochondrial membranes, and thus reflects cellular viability.[41] Since Tc-99m labelled agents do not redistribute after initial myocardial uptake, only 1 set of images is obtained when the goal is to assess viability. When information on both ischemia and viability is needed, separate images are needed: 1 set of images following stress, and 1 set of images obtained under resting conditions. Viability is determined from the resting images; segments with tracer activity >50% are considered viable.

The majority of the studies focusing on viability assessment and prediction of functional recovery have used Tc-99m sestamibi. Reanalysis of the 13 available studies with Tc-99m sestamibi (n=308 patients) showed high sensitivity (average 79%, range 62-100%), but a relatively low specificity (average 58%, range 30-86%) for the prediction of functional recovery (Table II).[21] More recently, intravenous/sublingual administration of nitrates prior/during Tc-99m sestamibi injection has been proven to improve the accuracy in detection of viable myocardium and prediction of functional recovery.[42, 43] Nitrates are thought to increase blood flow to severely hypoperfused regions, thereby increasing tracer delivery and uptake in these severely hypoperfused but viable regions. Pooling of 7 studies (n=180 patients) with nitrate-enhanced Tc-99m sestamibi imaging, resulted in a sensitivity and specificity of 86% and 83% to predict improvement in regional function after revascularization.[21] Besides nitrate-enhanced imaging, the development of ECG-gated SPECT, enabling the simultaneous assessment of perfusion and function,[44, 45] has further improved the accuracy to assess viability. Levine *et al.*[46] have shown that gated SPECT improved sensitivity to predict functional recovery, although specificity was somewhat reduced. Another advantage of gated SPECT is that the functional data can be obtained at rest and following infusion of low-dose dobutamine; this approach makes a comprehensive evaluation possible, including assessment of perfusion and contractile reserve.[47] Leoncini *et al.* showed that an increase in LVEF of 5% or more during dobutamine gated SPECT, was highly accurate for the prediction of improvement in LVEF after revascularization (sensitivity 79%, specificity 78%).[48]

TABLE III.—*Comparative studies between FDG SPECT and FDG PET.*

Author	Patients (no.)	LVEF (%)	Agreement (%)
Burt [53]	20	NA	93
Martin [54]	9	NA	100
Bax [55]	20	39±16	76
Chen [56]	36	NA	90
Srinivasan [57]	28	33±15	94

LVEF: left ventricular ejection fraction. NA: not available.

Besides the use of Tc-99m sestamibi, more recent studies have used Tc-99m tetrofosmin. The available data showed an excellent agreement between the 2 tracers for assessment of viability and prediction of recovery of function after revascularization.[49-52]

Single photon imaging: F18-fluorodeoxyglucose

The recent introduction of SPECT systems equipped with 511-keV collimators has allowed the assessment of cardiac FDG uptake with SPECT.[19] Since SPECT cameras are widely available and less costly than PET systems, this approach has resulted in a more widespread use of FDG for the assessment of myocardial viability. A total of 5 studies,[53-57] with 113 patients, have performed a direct comparison between FDG imaging with PET and SPECT (Table III). These studies consistently showed a good agreement between PET and SPECT for the assessment of viability. Martin *et al.*[54] was the first to report on this issue and showed, using visual analysis, in 9 patients a perfect agreement for the detection of viability. Bax *et al.*[55] performed a similar study and showed, using quantitative analysis, a somewhat less perfect agreement (76%). A good relation between normalized FDG PET and SPECT activities was also shown. The most recent comparative study was performed by the NIH-group;[57] these authors evaluated 28 patients with chronic coronary artery disease and a severely depressed LVEF (33±15%), and showed an agreement of 94% for the assessment of viability.

An example of a patient with a perfusion-FDG mismatch on SPECT imaging is shown in Figure 2.

Few studies have evaluated the use of FDG SPECT for prediction of improvement of regional function postrevascularization. The largest study contained 55 patients with chronic coronary artery disease with a mean LVEF of 39±14%.[58] At baseline, 281 dysfunctional segments were identified and recovery of function was observed in 94 (33%). Of the segments with recovery of function, 80 were classified as viable on FDG SPECT, whereas 141 of the 187 segments without recovery of function were classified as nonviable. Accordingly, a sensitivity of 85% and specificity of 75% were obtained. These values are in line with the data obtained in a pooled analysis of 20 FDG PET studies (Table II).[21] Also, a recent work with FDG SPECT showed that the patients with an improved LVEF had on average 5.1±2.1 dysfunctional but viable segments, whereas the patients without an improvement in LVEF had 1.6±1.5 viable segments ($p<0.001$).[59] The sensitivity and specificity to predict improvement in LVEF were 86% and 92% respectively. Currently, not many data are available on FDG SPECT for prognostication. Two centers have reported initial data. Wijffels *et al.*[60] have evaluated 41 consecutive patients with chronic coronary artery disease and depressed LVEF (<35%); the patients with viable myocardium who underwent revascularization had no events, whereas a 42% event-rate was observed in the patients who

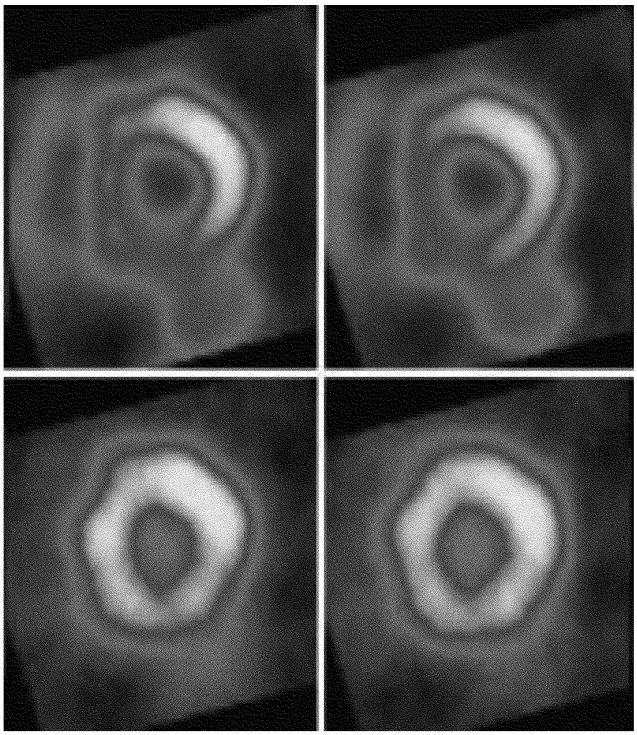

Figure 2.—FDG-SPECT imaging to assess viability. The Tc-99m tetrofosmin SPECT study (upper panel) reveals reduced perfusion in the septum and inferior wall, whereas the FDG uptake (lower panel) is preserved in these regions (perfusion-metabolism mismatch).

were treated medically with viable myocardium. Bax *et al.*[61] showed comparable results in 135 patients, with a mean follow-up of 28±11 months, namely a high event-rate in the viable, non-revascularized group (60%), as compared to 4% in viable, revascularized group. Intermediate event-rates were seen in the non-viable patients treated medically (9%) or revascularized (16%). Thus, the available prognostic FDG SPECT data confirm the high event rate in patients with viable myocardium who are treated medically.

Single photon imaging: free fatty acids

Several radiolabelled fatty acid analogues have been developed to evaluate myocardial viability.[62] The most frequently applied tracer is β-methyl-iodo-pentadecanoic acid (BMIPP) labelled with iodine-123; this tracer can be imaged successfully with SPECT.[53] For the detection of ischemia and/or viability, BMIPP is used in conjunction with a perfusion tracer (e.g. Tl-201 or Tc-99m sestamibi). In segments with reduced resting perfusion, BMIPP uptake can be concordantly reduced (perfusion-BMIPP match), more severely reduced (perfusion-BMIPP mismatch) or relatively increased (reversed perfusion-BMIPP mismatch). Matsunari *et al.*[63] reported that areas with a perfusion-BMIPP mismatch correlated with ischemia on stress-redistribution Tl-201 imaging. Moreover, Franken *et al.*[64] demonstrated that the presence of a perfusion-BMIPP mismatch was also associated with the presence of contractile reserve during low-dose dobutamine echocardiography. Finally, Tamaki *et al.*[65] showed that the regions with perfusion-BMIPP mismatch had persistent metabolic activity on PET imaging. All these comparative studies support the concept that regions with perfusion-BMIPP mismatch represent areas of jeopardized, but viable myocardium. Not many studies have focused on the prediction of improvement of function after revascularization. Two studies [66, 67] addressed this topic; on a regional basis, the sensitivity was 94% whereas the specificity was 50% for the prediction of improvement of function. In addition, these 2 studies [66, 67] also addressed the prediction of improvement of global function and showed a sensitivity of 81% with a specificity of 56% to predict improvement in LVEF after revascularization. Only 1 study evaluated the prognostic value of BMIPP imaging. Tamaki *et al.* [68] studied 50 patients with a mean follow-up of 23 months and showed that the number of segments with a perfusion-BMIPP mismatch was the single best predictor of future cardiac events.

Echocardiography

Initial information about myocardial viability may be obtained from resting 2-dimensional echocardiography. Severe thinning, *i.e.* a reduction in end-diastolic wall thickness ≤6 mm, is a marker of non-viability. Schinkel *et al.*[69] evaluated 150 patients and demonstrated that almost none of the severely thinned segments had contractile reserve during dobutamine infusion. Additional studies demonstrated that severely thinned segments virtually never recovered in contractile function after revascularization.[70-72]

Also, the presence of advanced LV remodeling, as indicated by large LV volumes and a spherical shape of the left ventricle, is associated with a low likelihood of functional recovery after revascularization.[73-75] However, although resting echocardiography may help to identify patients in whom functional recovery is extremely unlikely to occur, more advanced and elaborated features of echocardiography are applied to accurately evaluate the presence of myocardial viability. Stress echocardiography has been traditionally used to assess viability.

Stress echocardiography

Stress echocardiography may be performed using physiological exercise or pharmacological stress. Since the evaluation of myocardial viability may be difficult using exercise echocardiography, the application of pharmacological stress has become popular. Dobutamine and dipyridamole are generally used as stressors. The hallmark of myocardial viability on stress echocardiography is the recruitment of contractile reserve and/or the development of ischemia. Dipyridamole is a vasodilator that transiently increases coronary flow and recruits contractile reserve, whereas dobutamine is an inotropic agent that elicits contractile reserve through stimulation of the myocardial β_1-receptors. The infusion of high dosages of dipyridamole and dobutamine may induce ischemia. Although both dobutamine and dipyridamole stress echocardiography allow the assessment of viability and ischemia, dobutamine stress echocardiography (DSE) is more widely used. The recruitment of contractile reserve during low-dose dobutamine infusion

(5-15 µg/kg/min) has been shown to accurately predict recovery of function after revascularization.[33, 34, 76-83] Pooled analysis of the studies using low-dose DSE (32 studies, 1 090 patients, Table II) to predict recovery of segmental function showed an average sensitivity and specificity of 81% and 80%, respectively.[21] More recently, a low-high dose protocol of dobutamine infusion (up to 40 mg/kg/min plus atropine, if necessary) has been introduced to better identify viable myocardium and predict recovery of function.[5, 84] During low-high dose DSE, the viable myocardium may show a sustained improvement in the wall motion or an ischemic response (when a flow limiting coronary artery is present).[84] In particular, the biphasic response (improvement of contractility at low-dose followed by deterioration at higher dose) has been shown to be the best predictor of recovery in both regional and global function.[85-88]

In addition, various studies demonstrated that LVEF improved only in patients with substantial viability on DSE.[5, 33, 34, 71, 74, 89, 90] A linear relation was present between the number of viable segments and the improvement in LVEF after revascularization.[5] When ROC curve analysis was applied, the cutoff value of 4 segments (in a 16-segment model) yielded the highest sensitivity and specificity to predict improvement in LVEF;[5] this observation suggests that at least 25% of the left ventricle needs to be viable to result in improvement in LVEF. Moreover, in that same study, patients with 4 dysfunctional but viable segments not only improved in LVEF, but also exhibited a significant improvement in heart failure symptoms and had a favourable prognosis after revascularization (event-rate 17% *versus* 47% in patients with <4 viable segments). Similar results have been reported by Senior *et al.*[12]

Assessment of myocardial viability by DSE may be difficult in patients with poor echocardiographic windows (estimated 10-15% of patients referred for DSE).[91, 92] However, recent innovations, such as tissue harmonic and contrast-enhanced imaging, enable a better visualization of the endocardial border and a more reliable assessment of contractile function even in patients difficult to image with fundamental imaging only.[93-97] In addition, a further improvement in the assessment of myocardial viability during DSE has been provided by the introduction of Tissue Doppler Imaging (TDI), a modification of conventional Doppler. TDI measures amplitude, velocity and timing of myocardial function, providing an objective quantification of the contractile performance and overcoming the subjective interpretation of echocardiographic studies. TDI information may be displayed in spectral or color-coded mode showing the increase of the peak velocity during dobutamine infusion in dysfunctional but viable areas. Pulsed wave TDI allows the measurement of the longitudinal velocities of the left ventricle with high temporal resolution.[98] In the study by Rambaldi *et al.*,[99] the addition of pulsed-wave TDI to standard DSE significantly improved the sensitivity of DSE to detect viability (87% *vs* 75%, $p<0.05$). An increase in the peak systolic velocity of 1±0.5 cm/s during low-dose DSE was the best predictor of viability.[99] An example of increased peak systolic velocity during low-dose DSE is shown in Figure 3. Several studies have recently confirmed these findings.[100-102] Color-coded TDI provides higher spatial resolution as compared to pulsed-wave TDI and dedicated off-line analysis allows the quantification of the myocardial velocity gradient from the epicardium to the endocardium. This parameter has been shown very sensitive for detection of viable myocardium during DSE.[103, 104] Also, the postprocessing of TDI datasets allows the quantification of the myocardial deformation by measuring strain and strain rate.[105, 106] These parameters are important because they are not dependent on the rotation and translation of the left ventricle and may distinguish between passive wall motion (tethering) and true myocardial thickening.[105, 106] Preliminary studies suggest that assessment of strain and strain rate analysis may be properly integrated in the DSE studies to obtain a quantitative estimate of myocardial viability and/or ischemia.[107-110] Further studies are however needed to support these preliminary findings.

Myocardial contrast echocardiography

The improved technical properties of the myocardial contrast agents now allow for assessment of myocardial perfusion.[111, 112] Whereas in the early studies intracoronary injection of contrast was still needed, the more recently developed contrast agents allow intravenous administration. The recent contrast agents are composed of high molecular weight inert gases. The microbubbles stay in the vascular space, and do not enter the extravascular space; within the vascular space, microbubbles behave like red cells in terms of rheology and can be used in combination with

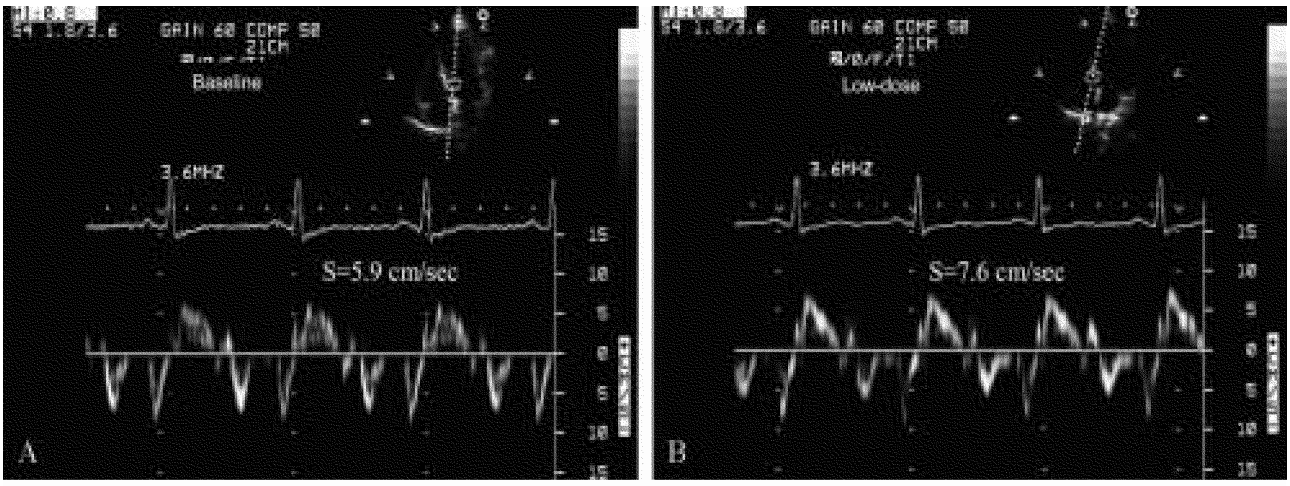

Figure 3.—Assessment of myocardial velocities using tissue Doppler imaging. An increase in the systolic velocity (S, from 5.9 cm/s to 7.6 cm/s) during dobutamine infusion indicates the presence of myocardial viability.

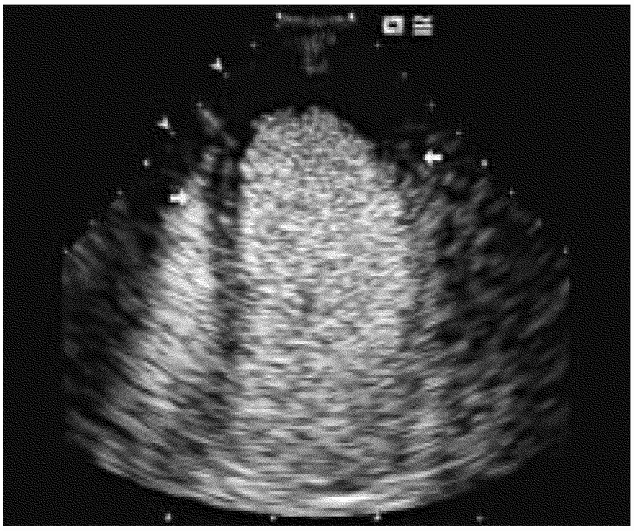

Figure 4.—Myocardial contrast echocardiography showing (arrows) absent perfusion in the apex, indicating scar tissue.

echocardiography to visualize directly the myocardial perfusion. Since myocardial perfusion is a prerequisite for myocardial viability, MCE has been used to assess tissue viability. For example, Shimoni *et al.*[113] showed that MCE parameters of myocardial perfusion correlate positively with the microvascular density and the capillary area and inversely with the extent of fibrosis.

In the clinical setting, myocardial perfusion by MCE is evaluated qualitatively, and segments are visually classified as having normal, patchy or absent perfusion.[88, 114, 115] A patient example of the technique is shown in Figure 4.

Nagueh *et al.*[88] performed a direct comparison between DSE, Tl-201 rest-redistribution imaging and MCE in 18 patients undergoing revascularization. Both Tl-201 imaging and MCE had a high sensitivity with a lower specificity, whereas DSE had a lower sensitivity with a relatively high specificity for the prediction of improvement after revascularization. In that study, MCE had a sensitivity of 89% and a specificity of 51%. Additional studies using MCE confirmed this observation and consistently showed a high sensitivity with a lower specificity.[116] The lower specificity is in part related to the presence of non-transmural infarction, similar to nuclear imaging; these regions contain some (epicardial) viable myocardium with intact perfusion, but will not improve in function post revascularization. The lower specificity can be improved by integrating MCE and DSE; the integration of information on perfusion and contractile reserve will allow more precise assessment of jeopardized myocardium with a high likelihood to improve in function after revascularization.

Cardiac magnetic resonance

Cardiac magnetic resonance (CMR) has the unique capability to assess different features of myocardial viability including the presence of contractile reserve (using low-dose dobutamine CMR) and the trans-

mural extent of scar tissue (using contrast-enhanced CMR), with an extremely high resolution.

Dobutamine CMR

Cine-CMR allows assessment of wall motion, similarly to echocardiography but with a higher spatial resolution (1-2 mm), resulting in a superior definition of the endocardial border with a highly accurate morphological and functional evaluation. Currently, CMR is considered the gold standard for the assessment of myocardial morphology and function.[117-119] Baer *et al.* showed that the measurement of the end-diastolic wall thickness during resting cine-CMR provides initial information about viability, similar to echocardiography.[120] The authors showed that dysfunctional segments with an end-diastolic wall thickness ≤5.5 mm contained predominantly scar tissue and the sensitivity of this criterium was 94% to predict absence of improvement of function after revascularization. The specificity of this marker was rather low (52%), indicating that when end-diastolic wall thickness is preserved additional testing is required to predict functional outcome.[120] The additional assessment of contractile reserve by low dose dobutamine CMR is needed to accurately identify the segments that will improve in function postrevascularization.[121] The accuracy of dobutamine CMR to predict improvement of regional function after revascularization is high, with a sensitivity of 89% and specificity of 94%.[120] A recent refinement in the evaluation of the response to dobutamine infusion is myocardial tagging; tagging allows to discriminate between passive movement (tethering) or active contraction.[122-124] Initial studies with dobutamine-tagged CMR showed a high accuracy (with a sensitivity of 89% and specificity of 93%) to predict improvement of function after revascularization in patients with chronic LV dysfunction.[122] Currently, dobutamine-tagged CMR is not widely implemented in the clinical setting, since analysis of the data remains a time-consuming process.

Besides prediction of improvement in regional LV function after revascularization, only few studies have focused on prediction of improvement in LVEF. Baer *et al.*[125] demonstrated a direct relation between the number of segments exhibiting contractile reserve during the infusion of low dose dobutamine and improvement in LVEF. At present, no prognostic studies with dobutamine CMR in patients with chronic ischemic LV dysfunction are available.

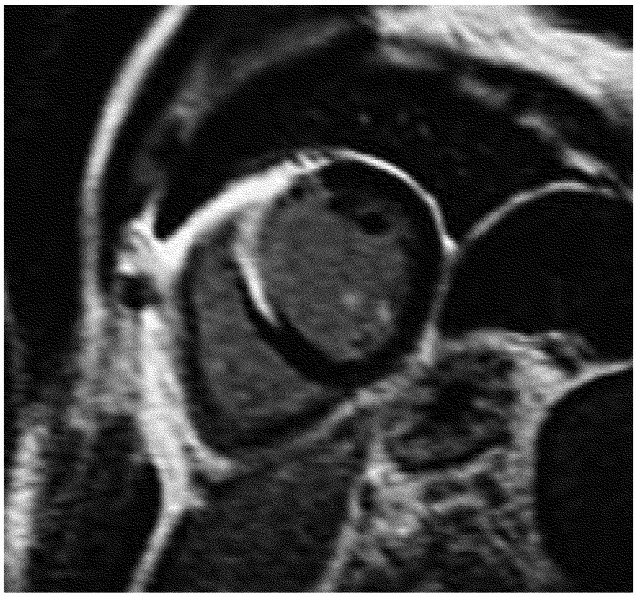

Figure 5.—Contrast-enhanced CMR study. A large area of transmural infarction in the anterior wall and septum can be observed (white, hyper-enhanced area).

Contrast-enhanced CMR

Contrast-enhanced CMR has become extremely popular to evaluate patients with chronic ischemic LV dysfunction. The administration of gadolinium-based contrast agents allows precise visualization of scar tissue and the excellent spatial resolution of CMR makes accurate assessment of the transmural extent of scar tissue possible. Currently, this is the only imaging technique that allows identification and separation of subendocardial and transmural damage. On imaging (images are obtained within 30 min after administration of contrast agents), the scar tissue appears white (hyperenhanced); an example of a patient with an anterior myocardial infarction is shown in Figure 5.

Early animal studies showed a perfect agreement between hyperenhancement on CMR and necrosis on histological examination.[126-128] Various studies have compared contrast-enhanced CMR to nuclear imaging techniques. Ramani *et al.*[129] compared contrast-enhanced CMR with Tl-201 rest-redistribution and DSE. The agreement between CMR and DSE was 75% and with Tl-201 rest-redistribution 83%. Two studies compared contrast-enhanced CMR with FDG PET and also showed a close agreement between the 2 techniques.[130, 131] Lee *et al.*[132] compared Tc-99m sestamibi SPECT with contrast-enhanced CMR and concluded that agreement was good for transmural infarcts, but

that small subendocardial infarcts on contrast-enhanced CMR were not noted on SPECT, and that these segments frequently had normal wall motion. Interestingly, Mahrholdt *et al.*[133] recently demonstrated that the majority of segments with subendocardial infarcts <25% of the LV wall frequently had normal contraction.

Clinical studies have shown that the transmurality of hyperenhancement is critical in determining the recovery of function after revascularization. The more transmural the extent of hyperenhancement, the lower the likelihood of recovery in function. Kim *et al.*[134] studied 41 patients with ischemic cardiomyopathy undergoing revascularization. The likelihood of functional recovery was 60% in segments with ≤25% hyperenhancement, 42% in segments with 26-50% hyperenhancement, 10% in segments with 51-75% and only 1.7% in segments with >75% hyperenhancement.[134]

Accordingly, when segments with transmurality ≤50% are considered viable, the sensitivity and specificity to predict improvement of function were 97% and 44%, percentages very comparable to those obtained with Tl-201 imaging.[21] Hence, additional information is needed in the segments with an intermediate transmurality of scar tissue to optimally predict improvement of function after revascularization. Kaandorp *et al.*[135] have recently suggested that integration of contrast-enhanced CMR and dobutamine CMR may provide optimal information on viability. Clearly, more studies on this topic are needed, in particular on the value of contrast-enhanced CMR for prediction of improvement in LVEF postrevascularization, and also on the prognostic value of the technique.

Electromechanical mapping

Electromechanical endocardial mapping using a non-fluoroscopic catheter-based system (the NOGA™ system) is a new technique to assess myocardial viability that has been studied recently in the experimental as well as in the clinical setting. This is an invasive procedure (generally performed during angiography or percutaneous intervention) that allows simultaneous assessment of electrical activity, anatomy and contractility of the left ventricle, on a 3D basis. Several studies have shown that electromechanical parameters such as local shortening and unipolar voltages accurately define viable myocardium, showing a good agreement with SPECT, PET and echocardiography.[136-142] In particular, the local shortening was reduced in relation to the severity of wall motion abnormalities on echocardiography. Viable myocardium has been shown to have preserved electrical activity despite reduced contraction (electromechanical mismatch). Accordingly, local shortening, unipolar voltages and electromechanical mismatch have all been used to predict functional recovery after revascularization.[142] However, electromechanical mapping is an invasive technique and will thus not be of clinical importance for the assessment of viability. However, the technique may appear very useful in combination with newer therapies such as gene and cell therapy.

What is currently clear and unclear in viability assessment?

At present, assessment of myocardial viability is part of the diagnostic and prognostic work-up of patients with chronic coronary artery disease and severely depressed LV function. The findings help in the guidance of therapeutic management of this difficult patient group. In the presence of extensive dysfunctional but viable myocardium, revascularization should be considered, but in the presence of predominantly scar tissue conservative management is indicated. Over the years, many different techniques have been developed to assess viability, and these different techniques rely upon the detection of different characteristics of viable myocardium (Table I). The techniques have been extensively tested in the clinical arena and it became evident that in general all techniques, with the exception of DSE and dobutamine CMR, have a somewhat lower specificity. When 105 viability studies (n=3 034 patients) were pooled, the sensitivity was 84% and the specificity was 69%.[143] One important main reason for the lower specificity is that many segments contain a mixture of viable myocardium and scar tissue. The most important question is whether the viable myocardium contains "normal, viable tissue" or "jeopardized (ischemic, stunned or hibernating) viable tissue"; in the presence of the latter group, functional recovery postrevascularization may be anticipated, whereas in the former group, no recovery will occur. Still, revascularization of viable myocardium may be worthwhile even in the absence of recovery of function, as it may prevent ongoing

remodeling, prevent lethal arrhythmias, and/or improve prognosis.

A total of 29 studies focused on the prediction of improvement in LVEF after revascularization; these studies were consistent in demonstrating improvement in LVEF in viable patients, whereas no improvement occurred in nonviable patients.[143] The precise amount of dysfunctional but viable myocardium needed to result in improvement in LVEF varied among the studies, but in general 25-30% of the myocardium needs to be viable to results in a meaningful improvement in LVEF (defined as ≥5%).

Besides improvement of function, other end points have been evaluated. Some studies demonstrated that patients with viable myocardium exhibited an improvement in symptoms and exercise capacity, although the data are scarce.[5, 6] Recently, it has been demonstrated that the presence of viability was also associated to a prevention of remodeling. Rizzello *et al.*[144] evaluated 100 patients with DSE before revascularization, and LV volumes were assessed late (4.5 years) after revascularization. The authors demonstrated that the number of viable segments was the only predictor of LV remodeling. Moreover, the likelihood of ongoing LV remodeling increased as the number of viable segments decreased (Figure 6). During the follow-up, reverse remodeling was observed in viable patients, whereas nonviable patients showed ongoing LV dilatation, associated with a worsening in heart failure symptoms. This landmark study indicates that the presence of viable myocardium has clinical implications beyond improvement in contractile function.

Finally, assessment of viable myocardium is important for prognosis. Allman *et al.*[13] have performed a careful meta-analysis of the available data and emphasized the high event-rate in viable patients who are treated medically, as compared to the low event-rate in viable patients who undergo revascularization. The major shortcoming of these studies is the retrospective, non randomized character of all studies. Currently no prospective data are available, but 2 randomized trials are ongoing (STICH and UK HEART). These studies are needed to clearly define the prognostic value of viability assessment.

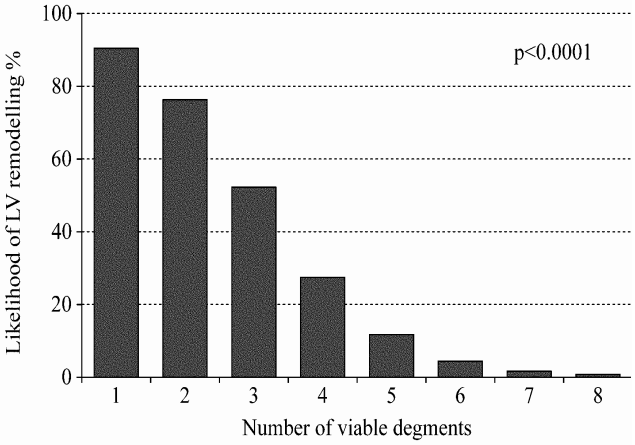

Figure 6.—Bar graph showing that the likelihood of ongoing LV remodeling after revascularization increases as the number of viable segments decreases.[144]

Conclusions

The available data support the clinical use of viability assessment. Patients with chronic coronary artery disease and severely depressed LV function should undergo viability testing to determine therapeutic strategy. Patients with viable myocardium benefit from revascularization. These patients have a high likelihood to improve in regional/global function, symptoms and exercise capacity after revascularization. LV reverse remodeling occurs also in viable patients after revascularization. Finally, the retrospective, non randomized studies suggest that patients with viable myocardium need to undergo revascularization.

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Outline of the Thesis

OUTLINE OF THE THESIS

Part I

In patients with ischemic cardiomyopathy, the presence of a substantial amount of viable myocardium is associated with a high likelihood of improvement in left ventricular ejection fraction (LVEF) after coronary revascularization. However, in the daily practice not all patients with viable myocardium do improve in LVEF after revascularization. The mechanisms that may play a role in preventing the improvement in LVEF after revascularization are unclear and have been investigated in the Part I of this thesis.

First, in chapter 2, it was evaluated whether the presence of subendocardial scars (showing sustained improvement of function during dobutamine stress echocardiography) may prevent the improvement of regional function after revascularization.

Next, in chapter 3, it has been assessed the role of the extent of scar tissue (showing no change in contraction during dobutamine infusion) in prohibiting improvement of LVEF in 108 patients with ischemic cardiomyopathy. The aim of the study was to evaluate whether the extent of scars may limit the effect of viable myocardium on improvement of LVEF after revascularization. A model was developed considering the interaction between scarred myocardium and viable myocardium in the prediction of improvement in LVEF (scar-to-biphasic model).

In chapter 4, the importance of the timing of revascularization was considered. The study population (85 patients) was divided in 2 groups according to the waiting time for revascularization: the early revascularization group consisted of 40 patients who underwent revascularization within 30 days from assessment of viability; the late revascularization group consisted of 45 patients with a waiting time >30 days. The outcome of revascularization was compared in the two groups.

Next step was to evaluate the role of LV dilatation in prohibiting improvement in LVEF. In chapter 5, the relation between the end-systolic volume before revascularization and the LVEF after revascularization was assessed in 118 patients with ischemic cardiomyopathy.

Finally, as described in chapter 6, the combined effect of viable myocardium and LV dilatation on the outcome of revascularization was studied in a population of 79 patients who were referred for surgical revascularization. In this study, the assessment of myocardial viability was performed by 18F-deoxyglucose single photon emission computed tomography.

Part II

Besides improvement of LVEF, alternative end-points of revascularization may be of clinical interest. Thus, Part II of the thesis deals with the additional benefits of revascularization of viable myocardium beyond improvement of LVEF.

In chapter 7, we evaluated whether in patients with ischemic cardiomyopathy and viable myocardium, coronary revascularization may result in prevention of ongoing LV remodeling even though LVEF does not improve. In this study, myocardial viability was assessed by dobutamine stress echocardiography in 106 patients who were referred for revascularization. LVEF and LV volumes were assessed before and serially after revascularization at 1 and 5 years in order to evaluate the occurrence of LV remodeling.

In chapter 8, the improvement of stress LVEF rather than rest LVEF after coronary revascularization was investigated in a population of 50 patients with ischemic cardiomyopathy and a substantial amount of viable myocardium. The study population was divided in 2 groups according to the presence of a significant improvement in rest LVEF after revascularization. Improvement of stress function during low-high dose dobutamine stress echocardiograpy after revascularization was compared in the 2 groups.

Next, whether improvement of LVEF does persist during the long-term follow-up was evaluated in chapter 9. Also in this study the occurrence of improvement of LVEF late after revascularization in patients without early improvement in LVEF was investigated.

The next issue addressed in this thesis was the occurrence of improvement of heart failure symptoms after revascularization. In particular, it was evaluated whether improvement in heart failure symptoms may occur in those patients with viable myocardium who do not improve in LVEF after revascularization (chapter 10).

Subsequently, the effect of coronary revascularization on prognosis of patients with ischemic cardiomyopathy was prospectively investigated. In particular the long-term prognosis (up to 5 years) of 129 patients with ischemic cardiomyopathy undergoing coronary revascularization and the relation to viability and ischemia during dobutamine stress echocardiography was evaluated in chapter 11.

In addition, to evaluate whether improvement in LVEF after revascularization does affect long-term prognosis, in chapter 12, we prospectively studied a population of 97 patients with ischemic cardiomyopathy already scheduled to revascularization. All patients underwent dobutamine stress echocardiography before revascularization to assess myocardial viability. The study population was divided in 3 groups according to the presence of myocardial viability and improvement of LVEF after revascularization. Cardiac events were evaluated during a 4 years follow-up in the 3 groups.

Finally, the interaction between myocardial viability and diabetes mellitus (a well established risk factor for poor prognosis) on long-term prognosis after revascularization was evaluated in chapter 13.

PART I

CHAPTER 2

Comparison of functional recovery of mildly hypokinetic--vs--severely dysfunctional left ventricular segments after revascularization in patients with ischemic cardiomyopathy

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Comparison of Functional Recovery of Mildly Hypokinetic Versus Severely Dysfunctional Left Ventricular Segments After Revascularization in Patients With Ischemic Cardiomyopathy

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Dysfunctional left ventricular (LV) segments showing contractile reserve during dobutamine stress echocardiography (DSE) are considered viable myocardium; functional recovery is expected after revascularization. Many segments, however, particularly mildly hypokinetic segments, do not recover. The reason for this failure is unknown. Two-dimensional echocardiography at rest and low–high-dose DSE were performed before revascularization in 114 consecutive patients with ischemic cardiomyopathy. Two-dimensional echocardiography at rest was repeated after 9 to 12 months. Segmental function was scored by a 5-point grading score. Functional recovery after revascularization was assessed in mildly hypokinetic (score 2, group I) and severely dysfunctional segments (score 3 to 5, group II). For each segment, functional recovery was defined as an improvement in functional score of ≥1 grade compared with the baseline score at rest. During low-dose DSE (up to 10 μg/kg/min), 183 group I segments (68%) and 438 group II (39%) segments had contractile reserve (p <0.0001). However, functional recovery was observed less frequently in group I segments (41%) than in group II segments (55%) with contractile reserve (p <0.005). During high-dose DSE (up to 40 μg/kg/min), in the group I segments with contractile reserve at the low dose, the sustained improvement pattern (indicating subendocardial scar) was prevalent (73%). After revascularization, 73% of segments with sustained improvement did not recover. Conversely, the biphasic response (indicating ischemically jeopardized myocardium) was observed only in 27% of group I segments. Functional recovery occurred in 39 of these segments (78%) (p <0.001 vs sustained improvement). Hence, mildly hypokinetic segments probably indicate the presence of subendocardial scars, and may explain the failure in functional recovery after revascularization. ©2004 by Excerpta Medica, Inc.

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In patients with ischemic cardiomyopathy, left ventricular (LV) dysfunction may be due to irreversibly damaged myocardium (scar), hibernating myocardium, or repetitive stunning.[1–8] However, previous studies showed that many segments with contractile reserve during low-dose dobutamine stress echocardiography (DSE) do not recover after revascularization.[9,10] Particularly, in hypokinetic segments, the presence of contractile reserve overestimates functional recovery.[11] This failure of functional recovery may be due to the presence of subendocardial scar, with the viable (nonjeopardized) epicardial tissue being responsible for the observed contractile reserve. During low-dose DSE, both regions of subendocardial scar with viable epicardial tissue and truly hibernating myocardium exhibit contractile reserve. Additional infusion of high doses of dobutamine may allow differentiation between these 2 entities. In this study, combined low–high-dose DSE was used to differentiate between possible subendocardial scars and hibernating myocardium in patients with heart failure symptoms due to coronary artery disease. Recovery of function after revascularization was the gold standard to verify the predicted outcome.

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METHODS

Patient population and study protocol: The study population consisted of 114 consecutive patients with coronary artery disease and LV dysfunction who were scheduled for revascularization. All patients had heart failure symptoms. The LV ejection fraction was assessed by radionuclide ventriculography. The decision to revascularize was based on clinical criteria. Two-dimensional echocardiography at rest was performed to identify baseline regional wall motion abnormalities in all patients, followed by low–high-dose DSE to

assess myocardial viability in dysfunctional regions. Radionuclide ventriculography, resting and DSE studies were performed within 1 month before revascularization. All patients were clinically stable during this interval and during follow-up. Nine to 12 months after revascularization, 2-dimensional echocardiography at rest was repeated to assess recovery of regional function. The local ethics committee approved the protocol and all patients gave informed consent.

Resting and low–high-dose dobutamine stress echocardiography: Resting and DSE studies were performed using a Sonos-5500 imaging system (Philips Medical Systems, Eindhoven, The Netherlands) equipped with a 1.8-MHz transducer using second harmonic imaging to optimize endocardial border visualization. Standard parasternal and apical views of the left ventricle were obtained as described by the American Society of Echocardiography.[12]

Dobutamine was administered intravenously, starting at a dose of 5 μg/kg/min for 5 minutes, followed by 10 μg/kg/min for 5 minutes (low-dose challenge). Subsequently, incremental dobutamine doses of 10 μg/kg/min were given at 3-minute intervals, up to a maximum dose of 40 μg/kg/min. If the test end point was not reached at the maximum dose of dobutamine, atropine (up to 2 mg) was administrated intravenously (high-dose challenge).[13] Blood pressure, cardiac rhythm, and ST segments were continuously monitored. Test end points were achievement of target heart rate (85% of the age-predicted maximum heart rate[14]), extensive new wall motion abnormalities, horizontal or downsloping ST-segment depression (≥2 mm compared with baseline), severe angina, a decrease in systolic blood pressure of ≥40 mm Hg, blood pressure >240/120 mm Hg, and significant supraventricular and ventricular arrhythmias. Metoprolol (1 to 5 mg intravenously) was used to reverse side effects. The images were recorded on videotape at the last minute of every stage and digitized on optical disk.

Assessment of wall motion abnormalities at rest: From the baseline and follow-up echocardiographic images, regional wall motion and systolic wall thickening were scored using a 5-point grading scale: 1 = normal, 2 = mildly hypokinetic, 3 = severely hypokinetic, 4 = akinetic, and 5 = dyskinetic.[15] Follow-up echocardiograms were compared with the corresponding images at rest obtained before revascularization, by 2 experienced observers without knowledge of the DSE study results. For each segment, recovery of function at follow-up was defined as an improvement in the wall motion score of ≥1 grade, with the exception of dyskinesia becoming akinesia. The occurrence of functional recovery was assessed in 2 different groups of dysfunctional segments: group I: mildly hypokinetic segments (score 2), and group II: severely dysfunctional segments (score 3 to 5). A high inter- and intraobserver agreement (92% and 90%, respectively) for the classification of wall motion has been previously reported.[4]

Assessment of myocardial viability: Off-line interpretation was performed using cineloops, displayed side-by-side in a quad-screen format. Two experienced reviewers, who were blinded to the clinical data and echocardiographic data at rest at follow-up, analyzed the DSE images using the 16-segment model, according to American Society of Echocardiography recommendations.[12] The presence of myocardial viability was evaluated in both mildly (score 2) and severely dysfunctional segments (score 3 to 5). In each dysfunctional segment, myocardial viability was judged present when contractile reserve was elicited by low-dose dobutamine infusion (improvement by ≥1 point of the wall motion score, with the exception of dyskinesia becoming akinesia). Segments without contractile reserve during low-dose dobutamine infusion were considered nonviable myocardium.[10,11,16]

During high-dose dobutamine infusion, the segments with contractile reserve were further classified as showing either sustained improvement (improvement in wall motion at low dose that persisted or further improved at high dose) or a biphasic response (improvement in wall motion at low dose with worsening at high dose). Segments with sustained improvement were considered subendocardial scars (viable without superimposed ischemia),[17–19] whereas segments with a biphasic response were considered viable and ischemically jeopardized myocardium.[17–19]

Statistical analysis: Data are expressed as mean ± SD or median and range, as indicated. Percentages are rounded. Continuous variables were compared using the unpaired Student's *t* test when appropriate. Univariate analysis for categorical variables was performed using the chi-square test. A p value <0.05 was considered statistically significant.

TABLE 1 Clinical Characteristics of the Study Population

Clinical Characteristics	No. of Patients (%)
Age (yrs), median (range)	61 (40–78)
Men	96 (84%)
Smoking	64 (56%)
Hypertension	99 (87%)
Hypercholesterolemia	63 (55%)
Familial ischemic heart disease	69 (60%)
Previous myocardial infarction	105 (92%)
Previous coronary bypass	22 (19%)
Previous coronary angioplasty	19 (17%)
Symptoms of heart failure	114 (100%)
New York Heart Association functional class, mean ± SD	2.8 ± 1.2
Left ventricular ejection fraction, median (range)	27 (16–44%)
Angiotensin-converting enzyme inhibitors	81 (71%)
β blockers	71 (62%)
Diuretics	82 (72%)
Nitrates	95 (83%)
Digoxin	23 (20%)
Aspirin or anticoagulants	114 (100)

RESULTS

Study population: Clinical characteristics of the study population are listed in Table 1. Sixty-nine patients (60%) had 3-vessel disease, 32 (28%) had 2-vessel disease, and 13 (11%) had 1-vessel disease. Ninety-four patients (82%) underwent coronary by-

TABLE 2 Contractile Reserve During Low-dose Dobutamine Challenge

	Segments With Contractile Reserve	Segments Without Contractile Reserve
All segments	621 (44%)	773 (53%)
Group I (mildly hypokinetic segments)	183 (68%)*	87 (32%)
Group II (severely dysfunctional segments)	438 (39%)*	686 (61%)

*p <0.001.

pass and 20 (18%) underwent coronary angioplasty. The descending anterior coronary artery was revascularized using the left internal mammary artery in 99 patients (87%), the circumflex artery in 85 patients (75%), and the right coronary artery in 89 patients (78%, with the use of the right internal mammary artery in 25% of these patients). After revascularization, significant improvement of heart failure symptoms was observed in the entire population (New York Heart Association functional class from 2.8 ± 1.2 to 1.8 ± 0.8, p <0.001).

Wall motion abnormalities at rest: The analysis of the acquired images showed that 1,437 of 1,824 segments (79%) were dysfunctional. Of these segments, 43 were excluded because of inadequate revascularization. Hence, the analysis was performed in 1,394 segments; 270 segments (20%) were mildly hypokinetic (group I segments) and 1,124 (80%) were severely dysfunctional (group II segments) (642 severely hypokinetic and 482 akinetic and/or dyskinetic segments). After revascularization, 452 segments (32%) showed functional recovery, whereas 942 segments (68%) did not recover. Of the 270 group I segments, 97 (36%) had functional recovery and 173 (64%) did not. Similarly, of the 1,124 group II segments, 355 (32%) improved in function and 769 (68%) did not.

Dobutamine stress echocardiography: HEMODYNAMIC RESPONSE: During low-dose DSE, heart rate increased from 70 ± 16 to 82 ± 21 beats/min (p <0.001). Systolic blood pressure did not change significantly, whereas diastolic blood pressure significantly decreased (76 ± 13 to 71 ± 13 mm Hg, p <0.001). During the high-dose dobutamine challenge, heart rate increased to 126 ± 27 beats/min (p <0.001 vs baseline). All patients achieved the target heart rate during the high-dose dobutamine challenge. Fifty patients (44%) received atropine. Both systolic and diastolic blood pressure decreased during the high-dose dobutamine challenge (both p <0.001 vs baseline).

Side effects: No serious side effects occurred during low–high-dose DSE; therefore the test was not discontinued before the achievement of target heart rate. In 3 patients (3%), an asymptomatic decrease in systolic blood pressure (≥40 mm Hg) was observed at peak of the study. Seven patients (6%) had ventricular extrasystolic beats and 5 patients (4%) had short runs (<10 beats) of (supra-)ventricular tachycardia.

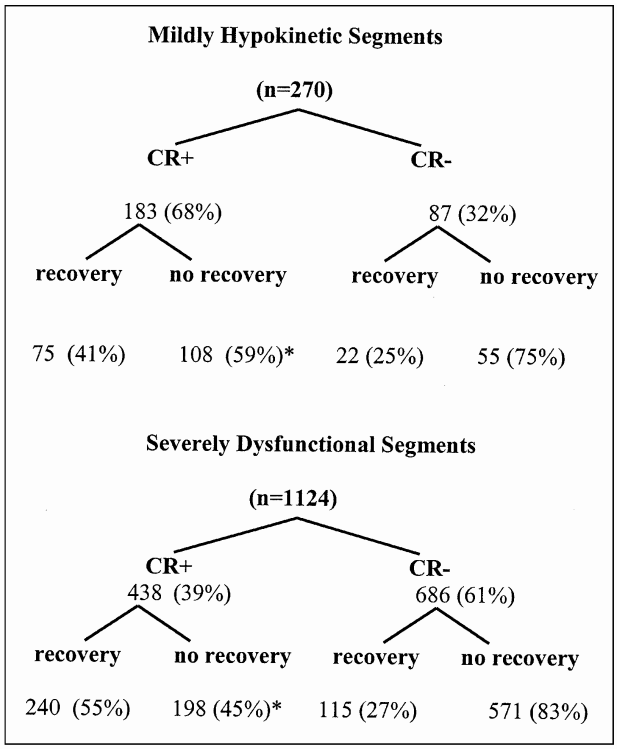

FIGURE 1. Flowchart showing the presence/absence of contractile reserve (CR+/CR−) and the recovery/no recovery of contractile function after revascularization in mildly hypokinetic and severely dysfunctional segments. *p <0.005.

Response to low-dose dobutamine challenge and functional outcome after revascularization: The presence of contractile reserve during low-dose dobutamine challenge (up to 10 μg/kg/min) is presented in Table 2. Contractile reserve during low-dose DSE was observed more frequently in group I than in group II (p <0.001). Overall, after revascularization, functional recovery occurred in 315 segments (51%) with contractile reserve, whereas 306 segments (49%) did not recover. Functional recovery failed to occur in 636 segments without contractile reserve (82%, p <0.001 vs segments with contractile reserve).

After revascularization, only 75 segments (41%) with contractile reserve in group I and 240 segments (55%) with contractile reserve in group II had functional recovery. Thus, a relatively high percentage of segments did not recover function after revascularization. The lack of functional recovery, despite apparently viable myocardium, was observed more frequently in group I compared with group II (59% vs 45%, respectively, p <0.005; see Figure 1). Functional recovery after revascularization did not occur in most of the segments without contractile reserve during dobutamine challenge, both in groups I and II (75% and 83%, respectively).

Response to high-dose dobutamine challenge and functional outcome after revascularization: During high-dose dobutamine infusion, 133 of the 183 group I segments (73%) with contractile reserve showed sustained improvement in wall motion, whereas 50 (27%) showed a biphasic response. After revascular-

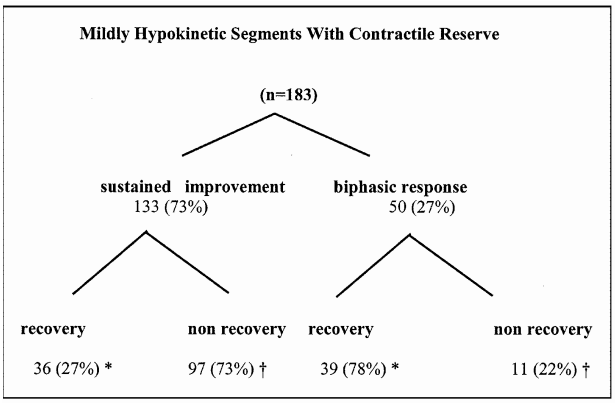

FIGURE 2. Flowchart showing recovery/no recovery of function and pattern of response to high-doses of dobutamine in mildly hypokinetic segments with contractile reserve during low-dose DSE. *p <0.001; †p <0.001.

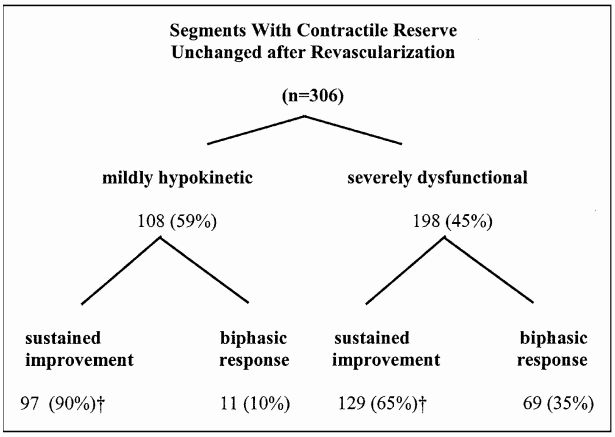

FIGURE 3. Flowchart showing the pattern of response to high-dose dobutamine in segments with contractile reserve without recovery of function after revascularization. †p <0.001

ization, in group I, 36 segments (27%) with a sustained improvement pattern recovered in function compared with 39 segments (78%) with a biphasic response. Hence, most of the segments (73%) with sustained improvement did not recover after revascularization compared with only 11 segments (22%) with a biphasic response ($p < 0.001$; see Figure 2). The sustained improvement pattern (indicating subendocardial scar) was present in 90% of group I segments with contractile reserve that did not recover function after revascularization. Conversely, a biphasic response (indicating hibernating myocardium) was present in only 10% of the unchanged segments (see Figure 3).

In group II, sustained improvement was observed in 212 of the 438 segments (48%) with contractile reserve during low-dose DSE; a biphasic response was seen in 226 segments (52%). After revascularization, 157 segments (70%) with a biphasic response improved compared with 83 segments (39%) that had a sustained improvement pattern ($p < 0.001$). A sustained improvement pattern was observed in 65% of group II segments with contractile reserve that did not recover after revascularization.

DISCUSSION

In segments with wall motion abnormalities at rest, the presence of contractile reserve during low-dose DSE indicates viable myocardium that is expected to recover function after revascularization. However, previous studies have shown that after revascularization, many segments with contractile reserve do not recover.[9–11] This is particularly true in mildly hypokinetic segments.[11]

Accordingly, in the present study, contractile function did not recover in the most of the mildly hypokinetic segments (59%) that had contractile reserve at low-dose dobutamine. Functional recovery failed to occur more frequently in mildly hypokinetic segments compared with severely dysfunctional segments (59% vs 45%, respectively; $p < 0.005$) (see Figure 1). The infusion of low–high doses of dobutamine was used to test the hypothesis that many mildly hypokinetic segments may represent subendocardial scar that do not recover function after revascularization. Improved contraction during low-dose dobutamine infusion may reflect both a mixture of subendocardial scar and normal contracting myocardium or the induction of contraction in chronic dysfunctional myocardium supplied by a critically stenotic coronary artery (hibernating myocardium). During the infusion of high doses of dobutamine, a subendocardial scar shows a sustained improvement pattern, because the surrounding viable nonischemic myocardium maintains contraction during the infusion.[17–19] Conversely, hibernating myocardium shows a biphasic response (induction of contraction followed by reworsening of wall motion due to development of ischemia).[17–19] In the present study, mildly hypokinetic segments frequently showed a sustained improvement pattern (73%) during high-dose DSE. Functional recovery did not occur in most of these segments (73%). Moreover, 90% of mildly hypokinetic segments with contractile reserve at low-dose dobutamine that remained unchanged after revascularization showed a sustained improvement pattern at high doses of dobutamine. Although these findings do not directly show the transmural extention of scarred myocardium, they suggest that many mildly hypokinetic segments may represent subendocardial scars, and this may also explain the recovery failure in contractile function after revascularization. Recently, magnetic resonance imaging has been used to detect myocardial viability.[20] With the enhanced resolution of magnetic resonance imaging, direct detection of subendocardial scars[20] and more accurate testing of our hypothesis may become possible.

The findings in the present study underline the need to differentiate between myocardial viability and functional recovery. Hypokinetic segments are considered viable myocardium. However, our results showed that myocardial viability is not a synonym of functional recovery and that functional recovery even in mildly hypokinetic segments is dependent on the specific pattern of response to dobutamine infusion. Low–high-dose DSE may discriminate between viable, nonischemic (nonjeopardized) myocardium and hibernating, ischemically jeopardized myocardi-

um.[17–19] However, DSE has been shown to be less sensitive than nuclear techniques to predict functional recovery after revascularization.[21] Even in this study, 18% of the segments without contractile reserve recovered function after revascularization. A sequential approach based on nuclear and echocardiographic methods may more accurately predict functional recovery.[22] This issue is clinically relevant because recovery of function has been associated with increased long-term survival.[23]

Study limitations: Alternative benefits for prevention of LV remodeling and/or improvement of prognosis were not assessed in the present study. Revascularization of viable, nonischemic myocardium may affect LV remodeling and prognosis.[24] This issue needs further evaluation. Moreover, coronary angiography was not repeated after revascularization. Graft closure or restenosis may represent an alternative mechanism responsible for the lack of recovery in many viable segments. Also, LV remodeling and myocardial wall stress may have hampered functional recovery. Finally, independent diagnostic techniques, such as nuclear or magnetic resonance imaging, were not performed to verify our hypothesis. Because nuclear techniques often overestimate functional recovery and hardly detect subendocardial scars,[21] magnetic resonance imaging would have been a better technique to directly assess the transmural extent of scars.[20]

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CHAPTER 3

Individual prediction of functional improvement after revascularization in patients with ischemic cardiomyopathy: the scar-to-biphasic model

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Individual Prediction of Functional Recovery After Coronary Revascularization in Patients With Ischemic Cardiomyopathy: The Scar-to-Biphasic Model

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Currently, the prediction of improvement of left ventricular (LV) ejection fraction (EF) after revascularization in patients with ischemic cardiomyopathy relies only on viable myocardium extent, whereas both the amount of viable and scar tissue may be important. A model was developed, based on the amount of viable and nonviable myocardium, to predict functional recovery. Viable and scarred myocardium was defined by dobutamine stress echocardiography (DSE) in 108 consecutive patients. LVEF before and 9 to 12 months after revascularization was assessed by radionuclide ventriculography; an improvement of >5% was considered significant. In the 1,089 dysfunctional segments (63%), DSE elicited biphasic response in 216 segments (20%), sustained improvement in 205 (19%), worsening in 43 (4%), and no change in 625 (57%). LVEF improved in 39 patients (36%). Only the numbers of biphasic and scar segments were predictors of improvement or no improvement of LVEF (odds ratio 1.5, 95% confidence interval 1.2 to 1.7, p < 0.0001 for biphasic segments; odds ratio 0.8, 95% confidence interval 0.7 to 0.9, p <0.0005 for scarred segments). The sustained improvement and worsening pattern were not predictive of improvement or no improvement. A regression function, based on the number of scar and biphasic segments, showed that the likelihood of recovery was 85% in patients with extensive biphasic tissue and no scars and 11% in patients with extensive scars and no biphasic myocardium. Patients with a mixture of scar and biphasic tissue had an intermediate likelihood of improvement (50%). In patients with ischemic cardiomyopathy and a mixture of viable and nonviable tissue, both numbers of viable and nonviable segments should be considered to accurately predict functional recovery after revascularization. ©2003 by Excerpta Medica, Inc.

(Am J Cardiol 2003;91:1406-1409)

Chronic coronary artery disease is the cause of left ventricular (LV) dysfunction in most patients with heart failure. Morbidity and mortality in these patients is high, and the prognosis is related to the degree of LV dysfunction.[1-3] Patients with a substantial amount of dysfunctional but viable myocardium may benefit from revascularization.[3-11] Dobutamine stress echocardiography (DSE) is a clinically useful method to identify dysfunctional but viable myocardium.[10,12,13] Previous studies showed that the biphasic response is the strongest predictor of improvement after revascularization, whereas patients with only scar tissue will probably not benefit from revascularization.[13-16] Most patients referred to DSE for the assessment of viability have a mixture of viable and nonviable myocardium. Currently, the individual likelihood of LV ejection fraction (LVEF) recovery after revascularization, according to the proportions of both viable and nonviable tissue, is unknown. In the present study, we developed a model based on the individual number of scar and biphasic segments during DSE to predict the potential of functional recovery in patients with ischemic cardiomyopathy who underwent revascularization.

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METHODS

Patient population and study protocol: The study population consisted of 108 consecutive patients with chronic coronary artery disease and LV dysfunction (LVEF <40%) already scheduled for revascularization. Patients with idiopathic cardiomyopathy or significant valvular heart disease were excluded. The LVEF was assessed by radionuclide ventriculography. All patients underwent 2-dimensional echocardiography at rest to identify regional dysfunction, followed by DSE to assess myocardial viability in dysfunctional regions. Nine to 12 months after revascularization, radionuclide ventriculography was repeated to evaluate changes in LVEF. The local ethics committee approved

the protocol and all patients gave informed consent.

Two-dimensional echocardiography at rest: All 2-dimensional echocardiograms were performed using a Sonos-5500 imaging system (Hewlett-Packard, An-dover, Massachusetts) equipped with a 1.8-MHz transducer using second harmonic imaging to optimize endocardial border visualization. Standard parasternal and apical views of the left ventricle were obtained as described by the American Society of Echocardiography.[17]

Dobutamine stress test: Dobutamine was adminis-tered intravenously, starting at a dose of 5 µg/kg/min for 5 minutes, followed by 10 µg/kg/min for 5 minutes. Subsequently, incremental dobutamine doses of 10 µg/kg/min were given at 3-minute intervals up to a maximum dose of 40 µg/kg/min. If the test end point was not reached at the maximum dose of dobutamine, atropine (up to 2 mg) was administrated intravenously. Blood pressure, cardiac rhythm, and ST segment were continuously monitored. Test end points were: achievement of target heart rate, extensive new wall motion abnormalities (involving multiple locations),[18] horizontal or downsloping ST-segment depression ($\geq$2 mm compared with baseline), severe angina, systolic blood pressure decrease >40 mm Hg, blood pressure >240/120 mm Hg, or significant (supra)ventricular arrhythmia. Metoprolol (1 to 5 mg intravenously) was available to reverse the effects of dobutamine or atropine.

Assessment of myocardial viability: Off-line interpretation was performed using cine loops that were displayed side-by-side in a quad-screen format. Two experienced reviewers, blinded to the clinical data, analyzed the images using the 16-segment model according to the American Society of Echocardiography recommendations.[17] Regional wall motion and systolic wall thickening were scored using a 5-point grading scale: 1 = normal, 2 = mildly hypokinetic, 3 = severely hypokinetic, 4 = akinetic, and 5 = dyskinetic.[10] Only severely dysfunctional segments (score 3 to 5) were subsequently evaluated for myocardial viability. Four patterns of wall motion responses were observed during DSE: 1 = sustained improvement, 2 = worsening, 3 = biphasic response, and 4 = no change.[13] Segments with biphasic, sustained improvement or worsening wall motion response during DSE were considered viable, with the exception of akinesia becoming dyskinesia. This was considered a mechanical phenomenon.[19] Segments with unchanged wall motion were considered nonviable (scar) tissue.[10,12,13]

Assessment of LVEF: LVEF was assessed by radio-nuclide ventriculography at rest before and 9 to 12 months after revascularization. A small field-of-view γcamera system (Orbiter; Siemens, Erlangen, Ger-many) was used and oriented in a 45° left anterior oblique position with a 5° to 10° caudal tilt. After the injection of technetium-99m (740 MBq), radionuclide ventriculography was performed at rest with the patient in the supine position. LVEF was calculated by standard methods (Odyssey VP; Picker, Cleveland, Ohio). An improvement in LVEF$\geq$5% after revascularization was considered significant.[10]

Statistical analysis: All continuous data are expressed as mean ± SD and dichotomous data as percentage differences. Continuous variables were compared using Student's *t* test for paired and un-paired samples, as indicated. Logistic uni- and multivariate analyses were performed to evaluate the pre-dictive value of the echo patterns for improvement of LVEF after coronary revascularization. A regression function was elaborated, including the variables that were significant during multivariate analysis, to determine the likelihood of LVEF improvement in individual patients. The predictive value of each echo pattern and of our model was determined by the C-index, which indicates how well a model can predict functional recovery (C-index of 0.5 = not predictive at all; C-index of 1.0 = optimal predictive value).[20] A p value <0.05 was considered statistically significant.

RESULTS

Patient characteristics and global LV function: The clinical characteristics of the 108 patients are listed in Table 1. All patients were stable during the study, and no cardiac events occurred during the follow-up pe-riod. LVEF improved modestly but significantly 9 to 12 months after revascularization (34 ± 10% vs 36 ± 10%, p <0.05). Thirty-nine patients (36%) improved $\geq$5% in LVEF (from 31 ± 9% to 41 ± 10%, p <0.0001), whereas in the remaining 69 patients (64 %) LVEF decreased from 35 ± 10% to 33 ± 10% (p <0.05).

Regional LV dysfunction: Two-dimensional echocardiography at rest demonstrated severe regional dysfunction in 1,089 of 1,728 segments (63%). Six hun-dred twenty-nine segments (58%) exhibited severe hypokinesia, 456 segments (42%) were akinetic, and 4 segments were dyskinetic (<1%).

TABLE 1 Patients' Clinical Characteristics

Clinical Characteristics	(n = 108)
Age (yrs)	60 ± 9.2
Men	91 (84%)
Diabetes mellitus	12 (11%)
Smoker	34 (31%)
Systemic hypertension	94 (87%)
Hypercholesterolemia*	61 (56%)
Previous coronary bypass	20 (18%)
Previous coronary angioplasty	18 (17%)
Heart failuret	108 (100%)
New York Heart Association functional class†	2.8 ± 0.5
LVEF	34 ± 10%
ACE-inhibitors	77 (71%)
β- blockers	66 (61%)
Diuretics	82 (76%)
Nitrates	78 (72%)
Digoxin	19 (18%)
Aspirin or anticoagulants	108 (100%)

*Defined as a total cholesterol $\geq$6.4 mmol/L or treatment with lipid-lowering medications.

†Defined according to Framingham criteria.[21]

ACE = angiotensin-converting enzyme.

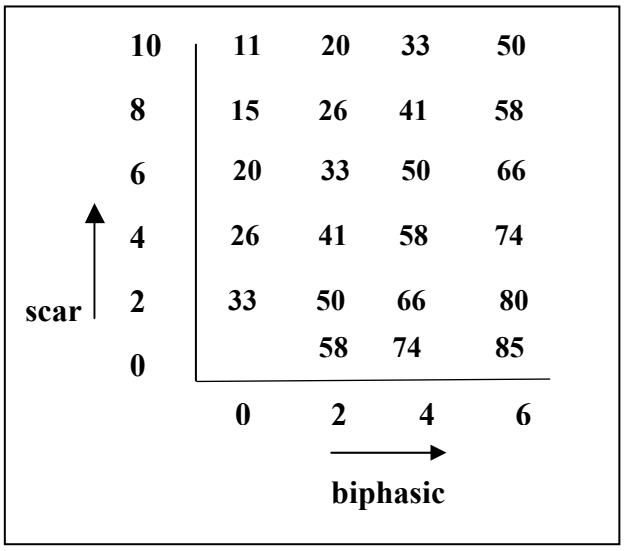

FIGURE 1. Likelihood of LVEF recovery after revascularization according to the number of scar and biphasic segments. The logistic regression formula applied was: likelihood of LVEF improvement = $1/1 + e^{-x}$, where x is -0.36 + 0.34 X number of biphasic segments - 0.17 X number of scars.

Hemodynamic response during dobutamine stress testing: During DSE, there was a significant increase in heart rate during high-dose dobutamine infusion compared with baseline (71 ± 13 vs 129 ±14 beats/ min, p <0.0001). Overall, diastolic blood pressure decreased (80 ± 15 vs 74 ± 15 mm Hg, p <0.005) and systolic blood pressure did not significantly change (125 ± 15 vs 127 ± 15 mm Hg, p = NS).

Assessment of myocardial viability: In dysfunctional segments, DSE showed a biphasic response in 216 segments (20%), a sustained improvement in 205 segments (19%), and a worsening in wall motion in 43 segments (4%). These 464 segments (43%) were considered viable. No change in wall motion and thickening (scar tissue) during DSE was observed in 625 segments (57%). Univariate analyses showed that the number of segments with a biphasic response was predictive of improvement in LVEF after revascularization (odds ratio 1.5 per segment, 95% confidence interval 1.2 to 1.8, p <0.0001, C-index 0.76), whereas the number of segments with the scar pattern was predictive of no recovery (odds ratio 0.8 per segment, 95% confidence interval 0.7 to 0.9, p <0.0005, C-index 0.72). The sustained improvement and the worsening pattern were not predictive of improvement or no improvement (C-index 0.58 and 0.50, respectively). At multivariate analysis the number of biphasic and scarred segments were predictors of recovery or a lack of recovery, respectively (odds ratio 1.5, 95% confidence interval 1.2 to 1.7 for biphasic pattern; odds ratio 0.8, 95% confidence interval 0.7 to 0.9 for scar pattern, C-index 0.84). The likelihood of improvement in LVEF is shown in Figure 1 ; this is from the predictive model that is based on number of scar and biphasic segments. The likelihood of recovery of LVEF ranged from 11% (lowest likelihood) in the patients with 10 scarred segments and 0 biphasic segments to 85% (highest likelihood) in the patients with 0 scars and 6 biphasic segments. Patients with a small number of scarred and biphasic segments, as well as patients with extensive scar and biphasic tissue, had an intermediate likelihood of improvement.

DISCUSSION

In this study, a logistic model was developed to predict recovery in LVEF after revascularization in patients with ischemic cardiomyopathy. Patients with a large number of biphasic segments without scars had the highest likelihood of functional improvement, whereas those with extensive scar and no biphasic response had the lowest likelihood. Limited number of scar and biphasic segments, as well as extensive scar and biphasic tissue, had an intermediate likelihood of improvement. An additional value over the usual prediction by the number of biphasic segments was present. The relation of this model to other predictors (wall thickness, LV volumes, and deceleration time) may deserve further studies.

During DSE, the biphasic pattern may indicate dysfunctional, viable segments in which the relatively impaired coronary reserve results in mild ultrastructural alterations.[22] Relief of ischemia by revascularization may allow the recovery of contraction. The scar pattern may reflect severe ultrastructural damage as loss of cardiomyocytes and fibrosis.[23, 24] Accordingly, in this study, the biphasic and scar patterns anticipated improvement or no improvement. Sustained improvement and worsening patterns were not predictive of functional recovery. This may be due to several issues: sustained improvement during DSE may indicate the presence of subendocardial scar tissue,[25] which cannot recover function after revascularization; worsening pattern may be due to a severely decreased coronary reserve [14, 15, 23] ; these segments may also not improve in function at rest. It remains of interest to determine whether stress function in these segments will improve after revascularization.[16]

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CHAPTER 4

Early versus delayed revascularization in patients with ischemic cardiomyopathy and substantial viability: impact on outcome

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Early Versus Delayed Revascularization in Patients With Ischemic Cardiomyopathy and Substantial Viability: Impact on Outcome

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Background—Patients with ischemic cardiomyopathy and viable myocardium may improve in function and prognosis following revascularization. Delayed revascularization may result in less favorable outcome, and therefore the impact of timing of revascularization on long-term outcome was evaluated.

Methods and Results—Patients (n=85) with ischemic cardiomyopathy and substantial viability (≥25% of the left ventricle) on dobutamine stress echocardiography underwent surgical revascularization. Based on the waiting time for revascularization, patients were divided into 2 groups: early (≤1 month) and late (>1 month) revascularization. Left ventricular ejection fraction (LVEF) was assessed before and 9 to 12 months after revascularization; follow-up data were acquired up to 2 years after revascularization. Hence, 40 patients underwent early (20±12 days) and 45 late (85±47 days) revascularization. Baseline characteristics of the two groups were comparable. Preoperative deaths were 0 in the early and 2 in the late group. Patients with early revascularization remained shorter time in the intensive care unit (2.4±1.5 days versus 5.9±2.1 days for the late group, $P<0.05$). Low output syndrome was observed more frequently in the late group (8% versus 22%, $P=0.06$). On long-term follow-up, mortality (5% versus 20%, $P<0.05$) and re-hospitalization for heart failure (10% versus 24%, NS) were higher in the late group. LVEF improved from 28±9% to 40±12% ($P<0.05$) in the early group and remained unchanged in the late group (27±10% versus 25±7%, NS).

Conclusion—Patients with ischemic cardiomyopathy and viable myocardium benefit from early revascularization (with improvement in LVEF and favorable prognosis), whereas delayed revascularization of these patients is associated with worse outcome. **(*Circulation*. 2003;108[suppl II]:II-39-II-42.)**

Key Words: myocardial viability ■ hibernating myocardium ■ heart failure ■ surgical revascularization

Patients with ischemic cardiomyopathy and a substantial amount of dysfunctional but viable (hibernating) myocardium have a high likelihood to improve in function after revascularization.[1–6] Moreover, in these patients, an improvement in symptoms was observed, with a superior long-term survival.[1–6] Accordingly, assessment of viability (hibernation) is used to guide therapy in patients with ischemic cardiomyopathy, and patients with viable myocardium should be considered for revascularization. It has also been demonstrated that patients with viable myocardium who are treated medically are at high risk for future cardiac events.[7] In daily practice, revascularization can frequently not be performed immediately and waiting times exist. Retrospective studies have indicated that patients with viable myocardium who are treated medically had a high event (and death) rate. A meta-analysis performed by Allman and colleagues,[7] including 24 studies with 3088 patients, demonstrated that the cardiac death rate was 16% in patients with viable myocardium who were treated medically as compared with 3% in patients with viable myocardium who underwent revascularization. Based on these observations, it has been suggested that dysfunctional but viable myocardium is an unstable substrate which may progress to cell death unless adequate restoration of blood flow is obtained.

Accordingly, prolonged time before revascularization may unfavourably influence outcome in patients with ischemic cardiomyopathy and viable myocardium.[8,9]

In the current study, the influence of waiting time for revascularization in patients with ischemic cardiomyopathy and viable myocardium on outcome was evaluated in a large group of patients.

Patients and Methods

Patients and Study Protocol

The study population existed of 85 patients with ischemic cardiomyopathy and substantial viable myocardium who were already

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scheduled for surgical revascularization. The patients presented with heart failure and 24% had accompanying angina pectoris. The decision for revascularization was based on clinical grounds (symptoms, presence/absence of ischemia/viability, and angiographic findings). All patients were stable during the study. Patients with severe mitral regurgitation were excluded. The patients were divided into two groups according to the waiting time for revascularization; the waiting time was dictated by the discretion of the referring physician and the availability of resources. The waiting time was considered the time interval between assessment of viability by dobutamine stress echocardiography (DSE) and the date of surgical revascularization. Group I (early revascularization group) consisted of 40 patients who underwent revascularization within 30 days (1 month) from DSE and group II (late revascularization group) consisted of 45 patients with a waiting time >30 days.

The study protocol included DSE, and assessment of left ventricular (LV) ejection fraction (EF) using radionuclide ventriculography (before and 9 to 12 months after revascularization). Follow-up was performed up to 2 years after revascularization. Each patient gave informed consent to the study protocol that was approved by the local Ethics Committee.

Assessment of Viability

Beta-adrenergic blocking agents were withdrawn 36 hours before DSE; other cardiac medications were continued. Low-high dose DSE (up to 40 μg/kg/min with addition of 2 mg atropine if necessary) was performed as described previously.[10] Interpretation of the DSE studies was performed by two experienced observers blinded to the clinical data. Inter- and intra-observer agreement for analysis of DSE studies were reported previously (92% and 94%, respectively).[10] The echocardiograms were analyzed according to the 16-segment model.[11] Segmental wall motion and thickening were scored according to a 5-point scale: 1=normal, 2=mildly hypokinetic, 3=severely hypokinetic, 4=akinetic, and 5=dyskinetic. Severely dysfunctional segments (score 3 or more) were evaluated for viability. The four patterns that were observed in dysfunctional segments during DSE included: (1) biphasic response (improvement of wall motion during low dose (5 and 10 μg/kg/min), followed by worsening of wall motion during high dose dobutamine); (2) sustained improvement (improvement during low and/or high dose dobutamine without subsequent deterioration of wall motion); (3) worsening (immediate deterioration of wall motion during dobutamine infusion); and (4) no change (no change in wall motion during DSE).

Dysfunctional segments were classified viable when they exhibited any of the patterns except for the "no change" pattern.[10] A patient was considered to have substantial viability in the presence of 4 or more dysfunctional but viable segments (≥25% of the LV).[10]

Assessment of Left Ventricular Ejection Fraction Before and After Revascularization

LVEF was assessed before and 9 to 12 months after surgical revascularization, using radionuclide ventriculography.[10] Radionuclide ventriculography was performed at rest with the patient in the supine position after the administration of 740 MBq of ^{99m}technetium. Images were acquired with a small-field-of-view gamma camera (Orbiter, Siemens Corp, Iselin, NJ), oriented in the 45-degree left anterior oblique position with a 5 to 10° caudal tilt. The LVEF was calculated from the 45-degree left anterior oblique view by an automated technique.

Assessment of Functional Status and Long-term Follow-up

Functional status was assessed according to the New York Heart Association (NYHA) criteria (for symptoms of heart failure) and the Canadian Cardiovascular Society (CCS) classification (for angina pectoris). Symptoms were evaluated before revascularization and at 2-year follow-up. The long-term follow-up was performed by chart review and telephone contact. Follow-up data (events) were acquired up to 2 years. Events included cardiac death, myocardial infarction, and hospitalization for heart failure. Moreover, the number of days

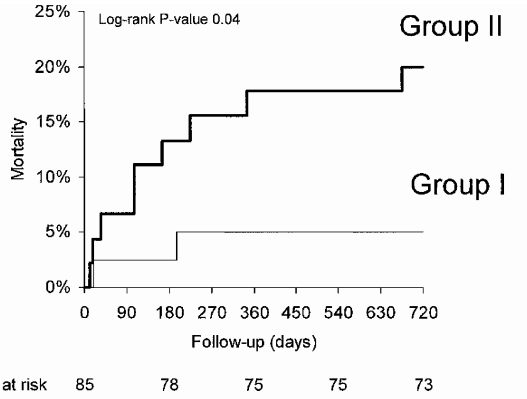

Figure 1. Mortality curves of the patients in the two groups; patients with early revascularization had significantly lower mortality as compared with patients with late revascularization. The curves start at the time of surgery. Group I, early revascularization; group II, late revascularization.

the patient stayed in the intensive care unit were noted, and the number of patients experiencing low-output syndrome (defined as the need for high dosages of inotropic medication, and/or intra-aortic balloon pumping to sustain adequate hemodynamic status[12]).

Statistical Analysis

Continuous data were expressed as mean ± SD and compared using the Student's *t* test for paired and unpaired data when appropriate. Comparison of proportions was performed using chi-square analysis. Survival of the two groups (early versus late revascularization) was compared using Kaplan-Meier curves. Differences between survival curves were tested with the log-rank chi-square statistic. For all tests, a probability value <0.05 was considered significant.

Results

According to the waiting time, the patients were divided into two groups. Group I, the early revascularization group, consisted of 40 patients; the mean waiting time was 20±12 days, and group II, the late revascularization group, consisted of 45 patients with a mean waiting time of 85±47 days. Complete revascularization was attempted in all patients; arterial grafts were used in 92% of patients.

Baseline characteristics of the two groups were comparable (Table 1). In particular, the extent (and distribution) of viable tissue and the extent of scar tissue were comparable between the two groups. Moreover, baseline LVEF was also comparable (28±9%, range 14% to 33%, in group I and 27±10%, range 12% to 35%, in group II, NS). The time from first infarction to the study was 4.8±1.4 years in group I and 5.9±2.1 years in group II ($P<0.05$), and the time from diagnosis of heart failure to the study was 1.4±0.7 years in group I as compared with 1.9±1.2 years in group II ($P<0.05$).

There were no preoperative deaths in group I and there were two preoperative deaths (4%) in group II (1 sudden cardiac death, 1 ongoing heart failure). One patient in group I and two patients in group II experienced an intraoperative myocardial infarction. Group I patients stayed significantly shorter in the intensive care unit (2.4±1.5 days versus 5.9±2.1 days, $P<0.05$). Also, more group II patients exhibited low-output syndrome in the intensive care unit, although the difference was not significant (22% versus 8%, $P=0.06$).

Patient Characteristics

	Group I (early revasc, n=40 pts)	Group II (late revasc, n=45 pts)	*P*-value
Age (yrs)	59±11	61±7	NS
Gender (M/F)	36/4	42/3	NS
DM	6 (15%)	5 (11%)	NS
HT	8 (20%)	6 (13%)	NS
Severe COPD	3 (8%)	5 (11%)	NS
Renal failure	4 (10%)	3 (7%)	NS
Previous CVA	1 (3%)	3 (7%)	NS
Previous MI	40 (100%)	43 (96%)	NS
Previous CABG	5 (13%)	7 (16%)	NS
NYHA	3.3±0.6	3.4±0.3	NS
CCS	2.6±0.8	2.4±0.5	NS
VD	2.5±0.7	2.7±0.4	NS
LVEF (%)	28±9	27±10	NS
Nr viable segs	5.1±3.8	4.9±3.5	NS
Nr scar segs	3.9±3.4	3.7±2.6	NS

CABG indicates coronary artery bypass grafting; CCS, Canadian Cardiovascular Score; DM, diabetes mellitus; HT, hypertension; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NYHA, New York Heart Association; revasc, revascularization; segs, segments; VD, vessel disease.

Long-term follow-up was obtained up to 2 years after revascularization (median follow-up 720 days, range 12 to 720 days; ie, the follow-up was completed until first hard event or otherwise until 2 years).

On long-term follow-up (up to 2 years after revascularization), two patients died (*cause: heart failure*) in group I as compared with 9 in group II (1 sudden cardiac death, 8 heart failure).

Accordingly, mortality after revascularization was significantly higher in group II (5% versus 20%, $P<0.05$, 1). Early mortality (<30 days of surgery) occurred in two patients of group II (persistent heart failure) and in one patient of group I (heart failure following infarction). Four patients who died post-operatively had a previous CABG, as compared with one patient in group I. Two patients had a left ventricular aneurysm, 1 died post-operatively (heart failure).

Hospitalization for heart failure occurred in 4 (10%) patients in group I, as compared with 11 (24%) patients in group II (NS).

LVEF had improved significantly in group I (from 28±9% to 40±12%, $P<0.05$) and remained unchanged in group II (27±10% versus 25±7%, NS).

Finally, NYHA class had improved in both groups: from 3.3±0.6 to 2.0±0.8 ($P<0.05$) in group I and from 3.4±0.3 to 2.3±0.7 ($P<0.05$) in group II. CCS score had improved from 2.6±0.8 to 1.1±0.4 ($P<0.05$) in group I and from 2.4±0.5 to 1.3±0.2 ($P<0.05$) in group II.

Discussion

Assessment of myocardial viability is important to guide management of patients with ischemic cardiomyopathy.[1–6] Patients with substantial viable myocardium have a high likelihood to improve in LV function, symptoms, and long-term prognosis.[1–7]

The findings in the current study indicate that early revascularization in patients with viable myocardium is warranted and that delayed revascularization has an adverse effect on improvement of function and long-term outcome.

Beneficial Effect of Revascularization of Viable Myocardium and the Influence of Delayed Revascularization

Various studies have demonstrated the beneficial effect of viable myocardium on outcome after revascularization, in terms of improvement of regional and global LV function.[13–15] In the current study, an improvement in global LV function was confirmed, but only in the patients with short waiting time. Besides improvement of function, the presence of viable myocardium is also linked to a favorable prognosis in patients undergoing revascularization.[7] In contrast, a high event-rate was demonstrated in patients with viable myocardium who were treated medically.[7] Based on these observations, it has been proposed that dysfunctional but viable myocardium provides an unstable substrate placing patients at high risk for future cardiac events.[7] In line with this hypothesis is the current observation that two patients (with extensive viable myocardium) died during the waiting time for revascularization.

Various studies have provided insight in the morphology of dysfunctional but viable myocardium.[16–18] In these studies, biopsies of viable myocardium were obtained during surgery. The structural findings included a loss of contractile material (sarcomeres, but also proteins including myosin, titin, and α-actinin), accumulation of glycogen, collagen, and formation of fibrosis.[16] Studies have indicated that ultrastructural damage may vary extensively, and that the severity of damage was related to the time needed for (complete) recovery of function.[16,19]

Additional studies have indicated that the longer the duration of hibernation (viability), the more severe the ultrastructural damage will be.[8] In particular, Schwarz and colleagues[8] have demonstrated that hibernation exhibited a time-dependent deterioration because of progressive structural degeneration with enhanced fibrosis. Elsässer et al[20] have illustrated the presence of apoptosis in patients with hibernating myocardium. Based on these observations, Schelbert[21] has suggested recently that ongoing hibernation may eventually result in cell death and early revascularization should be attempted to allow maximal recovery of function after revascularization.

In the current study, patients with ischemic cardiomyopathy and substantial dysfunctional but viable myocardium who underwent delayed revascularization had a less favorable postoperative course as evidenced by longer stay in the intensive care unit, more often low-output syndrome with the need for high dosages of inotropes and/or intraaortic balloon pumps, in line with previous observations.[8] Moreover, recovery of function was less in patients with delayed revascularization, and these patients showed more events during 2-year follow-up, comparable with previous data.[8] In addition, these patients had a longer history of disease before revascularize-

tion, as evidenced by the longer time interval from first infarction and diagnosis of heart failure to revascularization.

Altogether, the available evidence from the two previous studies on the topic of delayed versus early revascularization[8,9] and the findings in the current study suggest that longer duration of hibernation results in more severe structural damage on the myocyte level, clinically translating in absence of recovery of function with a less favorable long-term prognosis.

Limitations

The number of patients in the 2 groups is relatively small. Moreover, biopsies were not obtained in the current study, and, therefore, the relation between the severity of ultrastructural damage and the waiting time for revascularization cannot be explored.

In addition, the time interval between assessment of viability by DSE and the time of surgery was used to separate patients with early and late revascularization; information on duration of hibernation before entrance in the study is not available, although the time interval from first infarction and diagnosis of heart failure was longer in group II, indicating longer duration of disease.

Finally, graft patency was not assessed, and graft occlusion may have affected the results.

Conclusion

The waiting time for revascularization significantly affects outcome after revascularization of patients with ischemic cardiomyopathy and viable myocardium. Early revascularization resulted in improvement of LV function associated with a favorable long-term survival; in contrast, late revascularization did not result in improvement of LV function and was associated with a significantly higher mortality during 2-year follow-up.

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CHAPTER 5

Why do patients with ischemic cardiomyopathy and a substantial amount of viable myocardium not always recover in function after revascularization?

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Why do patients with ischemic cardiomyopathy and a substantial amount of viable myocardium not always recover in function after revascularization?

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Objective: In patients with ischemic cardiomyopathy and a substantial amount of dysfunctional but viable myocardium, myocardial revascularization may improve left ventricular ejection fraction. The aim of this study was to evaluate why not all patients with a substantial amount of viable tissue recover in function after revascularization.

Methods: A total of 118 consecutive patients with a depressed left ventricular ejection fraction (on average 29% ± 6%) due to chronic coronary artery disease underwent myocardial revascularization. Before revascularization all patients underwent dobutamine stress echocardiography to assess regional dysfunction, left ventricular volumes, and myocardial viability as well as radionuclide ventriculography to determine the left ventricular ejection fraction. Next, 3 to 6 months after revascularization, the left ventricular ejection fraction and regional contractile function were reassessed. Improvement of left ventricular ejection fraction ≥ 5% following revascularization was considered clinically significant.

Results: Dobutamine stress echocardiography revealed that 489 (37%) of the 1329 dysfunctional segments were viable. A total of 61 (52%) patients had a substantial amount of viable myocardium (≥4 viable segments). In these 61 patients the global function was expected to recover ≥ 5% after revascularization. However, left ventricular ejection fraction did not improve in 20 (33%) of 61 patients despite the presence of substantial viability. Clinical characteristics and echocardiographic data were comparable between patients with and without improvement. However, patients without improvement had considerably larger end systolic volumes (153 ± 41 mL vs 133 ± 46 mL, $P = .007$). The likelihood of recovery of global function decreased proportionally with the increase of end systolic volume ($P < .001$, $R = 0.43$, n = 61). Receiver operating characteristic curve analysis demonstrated that an end systolic volume ≥ 140 mL had the highest sensitivity/specificity to predict the absence of global recovery.

Conclusions: In patients with ischemic cardiomyopathy not only the amount of dysfunctional but viable myocardium but also the extent of left ventricular remod-

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eling determines the improvement in function following myocardial revascularization. Patients with a high end systolic volume due to left ventricular remodeling have a decreased likelihood of improvement of global function.

Treatment of patients with heart failure and ischemic left ventricular (LV) dysfunction remains challenging; the prognosis of these patients is poor and proportionally decreases with the severity of LV dysfunction.[1,2] Cardiac transplantation may substantially improve clinical outcome; however, its clinical application is limited by a shortage of donors.[3] Myocardial revascularization can be an alternative therapeutic option. Because of advances in surgical techniques, and optimization of perioperative metabolic and mechanical support, coronary artery bypass grafting (CABG) is now more realistic in the patients with the most severe LV dysfunction.[4-7]

It has become clear that approximately 50% of the patients with ischemic cardiomyopathy have a substantial amount of hibernating myocardium.[8,9] Myocardial contractility in this dysfunctional but viable tissue can be restored by myocardial revascularization. In patients with a substantial amount of dysfunctional but viable myocardium, CABG may improve or even normalize LV ejection fraction (LVEF).[10,11] Moreover, revascularization may substantially improve heart failure symptoms and prognosis.[10,11] However, in daily clinical practice not all patients with ischemic LV dysfunction recover in function after revascularization despite the presence of substantial viable myocardium. Currently, the reasons for this absence of improvement after CABG are not clear. Failure of recovery in patients with considerable viable tissue may be related to an increased LV volume due to extensive ventricular remodeling.[12,13] To test this hypothesis, patients with ischemic cardiomyopathy were studied before and 3 to 6 months after myocardial revascularization.

Methods

Patient Population, Study Protocol

The study population comprised 118 consecutive patients with a depressed LVEF due to chronic coronary artery disease (confirmed by angiography). All patients were already scheduled for myocardial revascularization based on clinical grounds. Patients were in clinically cardiac stable condition and were studied at least 6 months from previous myocardial infarction. Patients with primary cardiomyopathy, significant valvular heart disease, or an inadequate acoustic window were not included in the study. Patients who died perioperatively or during the follow-up were not included in the study. A total of 5 patients died perioperatively (4 cardiac death, 1 sepsis); these patients had on average 9.8 ± 2.2 dysfunctional segments and 3.8 ± 3.0 dysfunctional but viable segments. In these patients the LVEF was 23% ± 6%, the LV end diastolic volume averaged 191 ± 60 mL, and the LV end systolic volume was 148 ± 41 mL. The decision to perform surgical revascularization was based on clinical grounds and coronary angiography. Coronary artery bypass grafting was performed with use of cardiopulmonary bypass in all patients. All patients were operated on by standard techniques and optimization of perioperative support. All patients underwent isolated CABG procedures and patients having concomitant valve surgery were not included.

The study protocol was as follows. Before myocardial revascularization all patients underwent rest and dobutamine stress echocardiography to assess regional dysfunction, LV volumes, and myocardial viability. Radionuclide ventriculography was used to determine the exact LVEF before and 3 to 6 months after revascularization. Before revascularization and at follow-up a structured clinical interview was performed including assessment of the New York Heart Association (NYHA) functional class. The Hospital Ethics Committee approved the protocol and all patients gave informed consent before the study.

Evaluation of Regional Function and Volumes

All echocardiograms were performed with a Sonos-5500 imaging system (Andover, Mass) with a 1.8-MHz transducer using second harmonic imaging to optimize endocardial border visualization. Four standard views (apical 2- and 4-chamber views and parasternal short- and long-axis views) were digitized on optical disks and also stored on videotape. The end diastolic and end systolic LV volumes were measured using the standard biplane Simpson method.

Assessment of Myocardial Viability

After baseline echocardiography, dobutamine was administered, starting at a dose of 5 μg/kg body weight per minute for 5 minutes, followed by a 10 μg/kg/min dose for 5 minutes (low-dose). Incremental dobutamine doses of 10 μg/kg/min were then given at 3-minute intervals up to a dose of 40 μg/kg/min; atropine was added if necessary. Test end points were: target heart rate, extensive new wall motion abnormalities, ST-segment depression ≥ 2 mm, severe angina, systolic blood pressure fall >40 mm Hg, blood pressure > 240/120 mm Hg, significant (supra)ventricular arrhythmia. The echocardiograms were scored by 2 experienced reviewers using a 16-segment model.[14]. Regional wall motion and systolic wall thickening were scored on a 5-point scale: 1 = normal, 2 = mild hypokinetic, 3 = severe hypokinetic, 4 = akinetic, 5 = dyskinetic. Myocardial segments were considered normal if the regional wall motion was normal or mildly hypokinetic. Only dysfunctional segments (severe hypokinesia, akinesia, or dyskinesia at resting echocardiography) were evaluated for myocardial viability. Segments with an improvement, worsening, or a biphasic wall motion response during stress echocardiography were considered viable. Segments with unchanged wall motion were con-

TABLE 1. Baseline characteristics (n = 118)

Clinical features	
Age (y)	60 ± 10
Male gender	95 (81%)
Previous infarction	109 (92%)
Number of stenosed arteries	2.7 ± 0.6
NYHA functional class	2.8 ± 1.2
Baseline LVEF	29% ± 6%
Number of viable segments	4.1 ± 3.2
End diastolic volume (mL)	190 ± 57
End systolic volume (mL)	133 ± 46

LVEF, Left ventricular ejection fraction; *NYHA,* New York Heart Association. Data are presented as mean ± SD, or as numbers (%).

sidered nonviable. A patient was classified as viable in the presence of ≥4 dysfunctional viable segments.[8,10,15]

Assessment of LVEF

LVEF was assessed by radionuclide ventriculography before and 3 to 6 months after revascularization. A small field-of-view gamma camera system (Orbiter, Siemens, Erlangen, Germany) was used, oriented in a 45° left anterior oblique position with a 5° to 10° caudal tilt. After injection of technetium Tc 99m-pertechnate–labeled autologous erythrocytes (550 MBq), radionuclide ventriculography was performed at rest with the patient in supine position. LVEF was calculated by standard methods (Odyssey VP, Picker, Cleveland, Ohio). Improvement of LVEF ≥5% following revascularization was considered clinically significant, as described previously.[10]

Statistical Analysis

All continuous data were expressed as mean ± SD and percentages were rounded. Statistical analysis was performed with the BMDP statistical software package (BMDP Statistical Software Inc, Los Angeles, Calif). Continuous variables were compared using the Student *t* test for unpaired samples. Differences between proportions were compared using the chi-square test. Linear regression analysis was used to determine the relation between end systolic volume and change in LVEF. The LV volume that was related to a low likelihood of improvement of LVEF postrevascularization was determined by receiver operating characteristic (ROC) curve analysis. The optimal cutoff value was the number of segments that yielded the highest sum of sensitivity and specificity. Multivariate analysis was performed to identify the relative contributions of ventricular size and viability on the change in LVEF after coronary bypass surgery. Dependent variable was change in LVEF; independent variables were number of viable segments, end systolic volume, and the end diastolic volume.

Results

Patient Characteristics

The clinical and echocardiographic characteristics of the study population are presented in Table 1. The study group consisted of 118 patients with ischemic cardiomyopathy (95 men, mean age 60 ± 10 years). The majority of the patients had a previous myocardial infarction, and all patients had heart failure symptoms; the NYHA functional class was on average 2.8 ± 1.2. The range of preoperative ejection fraction was 9% to 35%. A total of 73 (62%) patients had angina. A total of 17 (14%) patients had previous coronary artery bypass operations. A total of 3 patients had perioperative myocardial infarctions (by enzymatic criteria). Thirty-eight patients needed inotropic support postoperatively. An intra-aortic balloon pump was placed in 2 patients. Ventricular assist devices were not used.

TABLE 2. Comparison of patients with a substantial amount of viable myocardium with and without improvement in function after revascularization

Clinical features	Patients with improvement (n = 41)	Patients without improvement (n = 20)	*P* value
Age (y)	61 ± 10	60 ± 9	.84
Male gender	33 (80%)	16 (80%)	1
Previous infarction	35 (85%)	20 (100%)	.18
Number of stenosed arteries	2.7 ± 0.6	2.7 ± 0.5	.54
NYHA functional class	2.8 ± 1.2	3.1 ± 1.2	.29
Baseline LVEF	28% ± 7%	28% ± 6%	.78
Number of viable segments	6.7 ± 2.5	6.7 ± 2.0	.96
End diastolic volume (mL)	174 ± 49	194 ± 65	.18
End systolic volume (mL)	121 ± 43	153 ± 41	.007

LVEF, Left ventricular ejection fraction; *NYHA,* New York Heart Association. Data are presented as mean ± SD, or as numbers (%).

Contractile Function

Two-dimensional echocardiography was performed in 1888 segments, of which 559 (30%) had a normal contraction and 1329 (70%) segments had an abnormal contractile function. Of the 1329 dysfunctional segments, 638 showed severe hypokinesia, 690 akinesia, and 1 dyskinesia. Global function was severely depressed; the LVEF was on average 29% ± 6%.

Myocardial Viability and Functional Outcome

Dobutamine stress echocardiography revealed that 489 (37%) of the dysfunctional segments were viable. Of the 489 dysfunctional but viable segments, 293 segments showed a sustained improvement pattern during dobutamine stimulation and the remaining 196 segments had an ischemic pattern. In the remaining 840 (63%) dysfunctional segments, no myocardial viability was present. A total of 61 patients had a substantial amount of viable myocardium (≥4 dysfunctional but viable segments). In these 61 patients the global function was expected to recover (improvement of LVEF ≥ 5%) after revascularization. However, although 41 (67%) of these patients had an improved LVEF following revascularization, the LVEF did not improve in 20 patients despite the presence of a substantial amount of viable myocardium. A total of 57 patients had <4 viable segments and were considered nonviable.

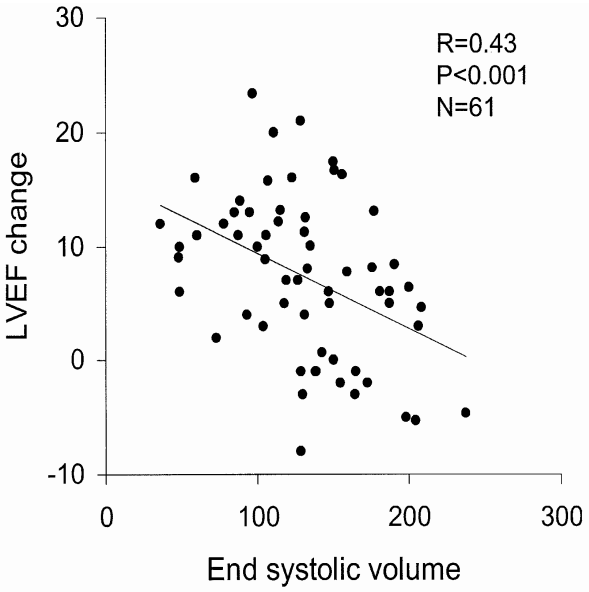

Figure 1. Scatter plot indicating the relation between the end systolic volume (in mL) and the LVEF change following myocardial revascularization in the 61 patients with a substantial amount of viability ($R = 0.43$, $P < .001$).

Comparison of Viable Patients With and Without Improvement

The patients with a substantial amount of viability were divided into 2 groups: patients with and patients without improvement in LVEF. Table 2 compares these 2 groups. Clinical characteristics and echocardiographic data were comparable between the 2 groups. However, improvement of global function following revascularization was related to the end systolic volume. Patients without improvement of LVEF had considerably larger end systolic volumes compared with the patients with recovery of global function (153 ± 41 ml vs 133 ± 46 mL, $P = .007$). Patients with improvement had after revascularization had on average 2.7 ± 0.6 stenosed coronary arteries, and patients without improvement had 2.7 ± 0.5 stenosed vessels ($P = .54$). Coronary artery target vessels were comparable in patients with and without improvement following revascularization. A total of 4 (7%) of the 61 patients with substantial viability had a decrease ≥ 5% in LVEF. This was related to a perioperative myocardial infarction in 3 patients and progression of LV dysfunction in 1 patient.

Of the total study population of 118 patients, 20 had LV aneurysms or akinetic anterior walls that could have potentially been treated with surgical ventricular remodeling in an attempt to improve myocardial function. Of the 20 patients with substantial viable myocardium but without improvement in function following revascularization, 13 (65%) patients had a large anterior myocardial infarction that may have derived benefit from ventricular remodeling procedures. Overall, coronary bypass surgery markedly improved symptoms; the angina scores (Canadian Cardiovascular Score) improved from 2.9 ± 0.8 before to 1.3 ± 0.6 after revascularization ($P < .01$). Heart failure symptoms also improved: NYHA functional class changed from 2.8 ± 1.2 before to 2.1 ± 1.0 after surgery ($P < .01$). Of the total study population of 118 patients (including the 57 patients without viable myocardium), 63 patients did not improve in LVEF and heart failure symptoms following revascularization. However, angina symptoms improved significantly in this patient subset; Canadian Cardiovascular Score decreased from 2.9 ± 1.0 to 1.3 ± 0.7 ($P < .01$).

Of the 57 patients with <4 viable segments, 7 (12%) patients had an improved LVEF after revascularization. These 7 patients all had 3 dysfunctional but viable segments and a preserved end systolic volume (81 ± 8 mL).

End Systolic Volume Versus Improvement of LVEF

Figure 1 demonstrates the relation between the end systolic volume and the change in LVEF after revascularization in the patients with a substantial amount of viable myocardium. The likelihood of recovery of global function decreased proportionally with the increase of end systolic volume ($P < .001$, $R = 0.43$, n = 61). ROC curve analysis demonstrated that an end systolic volume ≥ 140 mL was related to a low likelihood of improvement of LVEF postrevascularization; the C-index was 0.75. This value of ≥140 mL had the highest sensitivity/specificity (68% and 65%, respectively) to predict the absence of global recovery. Multivariate analysis showed the relative contributions of ventricular size and viability on the LVEF after coronary bypass surgery. Predictors of change in LVEF were number of viable segments, hazard ratio 1.4, 95% confidence interval [1.0-1.8] and end systolic volume (per mL), hazard ratio −0.038, 95% confidence interval [0.010-0.066]. The end diastolic volume was not predictive. The best model to predict LVEF was: *LVEF change = 2.15 + 1.4 · number of viable segments − 0.038 · end systolic volume.*

Discussion

Medical therapy is still associated with a poor prognosis in patients with ischemic cardiomyopathy.[1,2] Cardiac transplantation offers a good therapeutic option; however, many patients who are eligible for transplantation will never receive a donor heart and die awaiting transplantation. Myocardial revascularization can be a good alternative treatment for patients with ischemic cardiomyopathy. Clearly, a careful case selection by cardiac surgeons, anesthetists, and cardiologists is mandatory. Several noninvasive techniques have been developed to identify dysfunctional but viable tissue (hibernating myocardium).[16]. Patients with a substantial amount of dysfunctional but viable myocardium may considerably improve in LVEF and prognosis following

revascularization.[10,11] However, in clinical practice not all patients with a substantial amount of dysfunctional but viable myocardium improve after revascularization. The absence of recovery in patients with a considerable amount of viable tissue may be related to an increased LV volume due to extensive ventricular remodeling. To elucidate this issue, a large group of patients with ischemic cardiomyopathy already scheduled for revascularization were evaluated before and 3 to 6 months after revascularization. A total of 61 patients had a substantial amount of viable myocardium; in these patients the global function was expected to recover following revascularization. However, although the majority of these patients had an improved LVEF following revascularization, LVEF did not improve in 33% of these patients. Comparison of the patients with and without improvement showed that clinical characteristics and echocardiographic data were comparable. Only the end systolic volume was different between both groups; patients who did not improve had significantly higher end systolic volumes. An end systolic volume ≥ 140 mL had the highest sensitivity/specificity to predict the absence of global recovery. Multivariate analysis demonstrated that the number of viable segments and end systolic volume were predictors of change in LVEF after coronary bypass surgery. This may be related to expansion of the infarcted area and adverse remodeling of the LV in patients with ischemic LV dysfunction.[12,13]

Previous Studies

The current results are in line with previous observations by Louie and colleagues.[12] In that study 22 patients with ischemic cardiomyopathy underwent myocardial revascularization. In patients with a successful revascularization, the end diastolic dimension was smaller than in patients with failed revascularization (68 ± 3 mm vs 81 ± 4 mm, $P < .05$). Yamaguchi and colleagues[13] studied 20 patients with ischemic cardiomyopathy. Patients were divided into 2 groups on the basis of the end systolic volume index. The mean LVEF improved significantly after revascularization in patients with an end systolic volume index < 100 mL/m^2. However, myocardial viability was not in this study.[13] In the present study, the preoperative end systolic volume dictated the postoperative LV function, even in patients with a substantial amount of dysfunctional but viable myocardium. This may be caused by an increased wall stress and adverse LV geometry. Restoration of myocardial blood flow may not be capable of reversing myocardial function in these segments. Nevertheless, Kim and colleagues[17] have suggested that patients with ischemic cardiomyopathy and LV dilation should not be excluded from surgical revascularization based on ventricular size alone. Due to revascularization of viable myocardium, the remodeling process may be stopped, resulting in an improved long-term survival, even in the absence of improvement of function. In addition, resection of nonviable scar tissue may also favorably influence survival. Randomized clinical trials, like the Surgical Treatment for IsChemic Heart failure (STICH) trial, are needed to assess the optimal treatment in these patients.[18]

Clinical Implications

Previous studies have demonstrated that a certain amount of dysfunctional but viable tissue is needed for an improvement of global function following revascularization.[10,11,15] Usually a level of ≥4 viable segments is advised as a cutoff value to predict improvement of LVEF.[10,15] This cutoff value represents approximately 25% of the LV and can be used to identify patients who may benefit from revascularization.[10,15] The present study confirms the findings from these previous studies. An enlarged end systolic volume prevented global recovery, even in patients with substantial viability. In these patients CABG could be combined with resection of nonviable scar tissue. Traditionally, only dyskinetic regions (cardiac aneurysms) were excised and closed. However, it was recognized that surgical reduction of akinetic regions may reduce wall stress and improve the geometry and LV function in selected patients.[19,20] In patients with a previous anterior infarction, surgical anterior ventricular endocardial restoration is a safe and effective operation to restore geometry and reverse LV remodeling.[20] Further studies are needed to determine the value of these additional surgical procedures in patients with a substantial amount of viable tissue.

The present data suggest that improvement may also occur in patients with <4 viable segments. A total of 57 patients had <4 viable segments and were considered nonviable. Interestingly, 7 of the nonviable patients had an improved LVEF after revascularization. This was probably related to the combination of 3 dysfunctional but viable segments and a preserved end systolic volume in these patients. Hence, the cutoff value of 4 viable segments is to some extent arbitrary, because not only myocardial viability but also remodeling and enlargement of the LV should be considered. This may further improve case selection before revascularization procedures in patients with ischemic cardiomyopathy.

Techniques to Assess Viability

In the present study, dobutamine stress echocardiography was used to assess myocardial viability. Although positron emission tomography may be slightly more accurate for the prediction of functional recovery after revascularization, both techniques provide similar prognostic information and accurately identify high-risk patients who may benefit from revascularization.[21] In particular, Allman and colleagues[22] have demonstrated in a meta-analysis that no significant difference in prognostic value between stress echocardiog-

raphy and positron emission tomography existed. Recently, magnetic resonance imaging combined with gadolinium-based contrast agents was proposed to evaluate myocardial viability.[23] Importantly, LV volumes and the transmural extent of viable/nonviable myocardium can be determined with the high spatial resolution of magnetic resonance imaging. This may have important clinical implications as the extent of transmural injury is related to functional improvement after revascularization.

Study Limitations

Several limitations of this study have to be mentioned. First, during bypass surgery an attempt was made to revascularize all vessels with a significant stenosis; however, angiography was not repeated at follow-up, and therefore graft occlusion may have prevented functional recovery of viable segments. Second, improvement in global function was assessed before and 3 to 6 months after revascularization. A longer follow-up time may be needed for complete recovery of contractile function in all dysfunctional but viable segments.[24] Third, beta-blockers and angiotensin-converting enzyme inhibition were used based on clinical grounds. This may have influenced LV function; however, this reflects daily clinical practice. Finally, magnetic resonance imaging may be more accurate than 2-dimensional echocardiography to assess LV volumes.

Conclusions

In patients with ischemic cardiomyopathy not only the amount of dysfunctional but viable myocardium but also the extent also LV remodeling and enlargement determines the improvement in function following myocardial revascularization. Patients with a high end systolic volume due to LV remodeling have a decreased likelihood of improvement of global function. Additional surgical procedures may be needed to improve LV function in these patients.

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CHAPTER 6

Extensive LV remodeling does not allow viable myocardium to improve in LVEF after revascularization and is associated with worse long-term prognosis

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Extensive Left Ventricular Remodeling Does Not Allow Viable Myocardium to Improve in Left Ventricular Ejection Fraction After Revascularization and Is Associated With Worse Long-Term Prognosis

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Background—Extensive left ventricular (LV) remodeling may not allow functional recovery after revascularization, despite the presence of viable myocardium.

Methods and Results—Seventy-nine consecutive patients with ischemic cardiomyopathy (left ventricle ejection fraction [LVEF] 29±7%) underwent surgical revascularization. Before revascularization, viability was assessed by metabolic imaging with F18-fluorodeoxyglucose and SPECT. LV volumes and LVEF were assessed by resting echocardiography. LVEF was re-assessed by echocardiography 8 to 12 months after revascularization. Three-year clinical follow-up (events: cardiac death, infarction, and hospitalization for heart failure) was also obtained. Forty-nine patients had substantial viability; 5 died before re-assessment of LVEF. Of the remaining 44 patients, 24 improved ≥5% in LVEF after revascularization, whereas 20 did not improve in LVEF. LV end-systolic volume was the only parameter that was significantly different between the groups (109±46 mL for the improvers versus 141±31 mL for the nonimprovers; $P<0.05$). The change in LVEF after revascularization was linearly related to the baseline LV end-systolic volume, with a higher LV end-systolic volume associated with a low likelihood of improvement in LVEF after revascularization. During the 3-year follow-up, the highest event-rate (67%) was observed in patients without viable myocardium with a large LV size, whereas the lowest event rate (5%) was observed in patients with viable myocardium and a small LV size. Intermediate event rates were observed in patients with viable myocardium and a large LV size (38%), and in patients without viable myocardium and a small LV size (24%).

Conclusion—Extensive LV remodeling prohibits improvement in LVEF after revascularization and affects long-term prognosis negatively, despite the presence of viability. **(*Circulation.* 2004;110[suppl II]:II-18–II-22.)**

Key Words: myocardial viability ■ hibernating myocardium ■ heart failure ■ left ventricle remodeling ■ surgical revascularization

Patients with chronic ischemic left ventricular (LV) dysfunction and substantial viability (extending to ≥25% of the LV) are likely to improve in function after revascularization.[1–3] Still, a subset of patients with substantial viability does not improve in function after revascularization. Meta-analysis of 20 studies with 598 patients focusing on assessment of viability with metabolic imaging (with F18-fluorodeoxyglucose [FDG]) before revascularization demonstrated that the specificity of viability testing was lower than the sensitivity (93% versus 58%).[4] A lower specificity is partially related to the fact that patients with viable myocardium do not improve in function after revascularization. It has been suggested that a severely dilated LV (extensive remodeling) may not allow functional recovery after revascularization.[5,6] Currently, not much information is available on this issue. In particular, the relation between LV size and viability, in some cases, and improvement of function after revascularization, in other cases, is not known. Moreover, the prognostic value of viability in combination with LV size is unknown.

Accordingly, we have studied 79 consecutive patients who were referred for surgical revascularization; in these patients, LV dimensions, LV ejection fraction, and viability were assessed preoperatively and outcome (improvement in LV ejection fraction, long-term prognosis) were assessed.

Methods

Patients and Study Protocol

The study population consisted of 79 patients with ischemic cardiomyopathy who were already scheduled for surgical revascularia-

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tion. The patients presented with heart failure and 34% had accompanying angina pectoris. The decision for revascularization was based on clinical grounds (symptoms, presence of ischemia, and angiographic findings). None of the patients experienced acute infarction or decompensated heart failure in the period between imaging and surgery. All patients were stable during the study. Patients with severe (grade 3 to 4+) mitral regurgitation were excluded. The study protocol was as follows. Within 1 week before surgery, resting perfusion was assessed by technetium-99m tetrofosmin SPECT, glucose use was assessed by FDG SPECT, and regional contractile (dys)function was assessed by 2-dimensional echocardiography. In addition, the LV ejection fraction and LV volumes (end-systolic, end-diastolic) were assessed from 2-dimensional echocardiography. Eight to 12 months after surgery, 2-dimensional echocardiography was repeated to assess LV ejection fraction. Follow-up was performed up to 3 years after revascularization. Each patient gave informed consent to the study protocol that was approved by the local Ethics Committee.

2-Dimensional Echocardiography

All echocardiograms were acquired with a HP Sonos-5500 imaging system with a 1.8-MHz transducer using second harmonic imaging to optimize endocardial border visualization. Four standard views (apical 2-chamber and 4-chamber views, parasternal short-axis and long-axis views) were digitized on optical disks and also stored on videotape. Two experienced reviewers scored the regional contractile function. The left ventricle was divided according to the standard 16-segment model suggested by the American Society of Echocardiography.[7] Regional wall motion and systolic wall thickening were scored using a 5-point grading scale: 1, normal; 2, mild hypokinetic; 3, severe hypokinetic; 4, akinetic; and 5, dyskinetic. Segments with severe hypokinesia, akinesia, or dyskinesia were considered dysfunctional and evaluated for myocardial viability.

The LV volumes (end-systolic, end-diastolic) and LV ejection fraction were calculated from the conventional apical 2-chamber and 4-chamber images using the biplane Simpson technique. The first echocardiogram was performed within 1 week before surgery and the follow-up echocardiogram was performed 8 to 12 months after revascularization. An improvement LV ejection fraction $\geq$5% after revascularization was considered clinically significant, as described previously.[8]

Assessment of Viability by SPECT

Patients received, after a light breakfast, an intravenous injection of technetium-99m tetrofosmin (600 MBq) to evaluate resting perfusion. FDG imaging, to evaluate myocardial glucose use, was performed after Acipimox administration (500 mg, oral dose) in all patients. Acipimox (a nicotinic acid derivative) enhances myocardial FDG uptake by reducing the plasma level of free fatty acids.[9,10] In addition, a light meal was provided to stimulate endogenous insulin release to further enhance cardiac FDG uptake.[10] Sixty minutes after the meal, FDG (185 MBq) was injected, and after an additional 45 minutes to allow cardiac FDG uptake,[10] dual-isotope simultaneous acquisition SPECT was performed. A triple-head gamma camera system (Picker Prism 3000XP) was used, equipped with commercially available high-energy 511-keV collimators. The energies were centered on the 140-keV photon peak of technetium-99m tetrofosmin with a 15% window (on each side of the peak) and on the 511-keV photon peak of FDG with a 15% window. Data acquisition was performed over 360° (120 sectors of 3°), with a total imaging time of 32 minutes. Data were stored in a 64×64, 16-bit matrix.

Data Reconstruction and Analysis

From the raw scintigraphic data, 6-mm-thick (1-pixel) transaxial slices were reconstructed by filtered back-projection using a Butterworth filter (cutoff frequency at 0.17 cycle/pixel of order 3.5). No attenuation correction was used. Further reconstruction yielded standard short-axis and long-axis projections perpendicular to the heart axis. The technetium-99m tetrofosmin and FDG data were reconstructed simultaneously to obtain exact alignment of the perfusion and metabolic images.[10] The perfusion and FDG short-axis slices were displayed in polar maps, which were normalized to maximum activity (set at 100%); the polar maps were divided into 16 segments matching the echocardiographic segments. Segments with normal tracer uptake (activity >75%), and segments with a perfusion defect (activity $\leq$75%) with a relatively increased FDG uptake (>10% as compared with perfusion activity, perfusion–metabolism mismatch) were considered viable. Segments with concordantly reduced perfusion and FDG uptake (perfusion–metabolism match) were considered nonviable. A patient was considered to have substantial viability in the presence of 4 or more dysfunctional but viable segments ($\geq$25% of the LV).[8]

Assessment of Functional Status and Long-Term Follow-Up

Functional status was assessed before revascularization according to the New York Heart Association (NYHA) criteria (for symptoms of heart failure) and the Canadian Cardiovascular Society (CCS) classification (for angina pectoris). The long-term follow-up was performed by chart review and telephone contact. Follow-up data (events) were acquired up to 3 years. Events included cardiac death, myocardial infarction, and hospitalization for heart failure.

Statistical Analysis

Continuous data were expressed as mean±SD and compared using the Student *t* test for paired and unpaired data when appropriate. Comparison of proportions was performed using χ^2 analysis. Differences in cardiac event rates (cardiac death, myocardial infarction, and hospitalization for heart failure) over time were analyzed by the method of Kaplan–Meier and log-rank test. For all tests, $P<0.05$ was considered significant.

Results

Baseline Characteristics

A total of 79 patients were prospectively studied, including 72 men with a mean age of 70±8 years. Seventy-four (94%) patients had a previous infarction >3 months before inclusion in the study. The average time of infarction to the study was 2.4±3.7 years.

Seventeen (22%) patients had hypertension, 14 (18%) had diabetes, 9 (11%) had severe pulmonary disease, 9 (11%) had impaired renal function, and 12 (15%) had peripheral vascular disease. Nine (11%) patients had a history of a previous CABG. They had, on average, 2.4±0.8 stenosed coronary arteries. Complete revascularization of all stenosed lesions was obtained.

The mean LV ejection fraction was 29±7% (range 10% to 35%). The mean NYHA class score was 3.2±0.8 and the CCS score was 2.8±0.6.

Viability, LV Size, and Improvement in LV Ejection Fraction

Based on the SPECT findings, the patients were divided into viable (n =49) and nonviable (n =30) patients. There were no differences between the viable and the nonviable patients, except for the number of viable segments (by definition): 6.9±2.8 versus 2.2±1.7 dysfunctional but viable segments. In the viable patients, 5 patients died before reassessment of LV ejection fraction had occurred (3 heart failure deaths, 1 fatal infarction, and 1 sudden cardiac death). In the nonviable patients, 3 patients died before reassessment of LV ejection fraction (2 heart failure deaths, 1 multi-organ failure 3 days after surgery).

Patient Characteristics

	Patients with improved LVEF (n=24)	Patients without improved LVEF (n=20)	P
Age, y	68±8	69±6	NS
Gender, M/F	22/2	20/0	NS
DM (%)	1 (4)	2 (10)	NS
HT (%)	4 (17)	4 (20)	NS
Severe COPD (%)	2 (8)	2 (10)	NS
Renal failure (%)	2 (8)	1 (5)	NS
Previous MI (%)	22 (92)	20 (100)	NS
Previous CABG (%)	1 (4)	1 (5)	NS
NYHA	3.2±0.7	3.4±0.8	NS
CCS	2.5±0.8	2.7±0.7	NS
VD	2.4±0.7	2.6±0.8	NS
LVEF, %	27±9	30±6	NS
LV ESV, mL	109±46	141±31	<0.05
LV EDV, mL	159±52	183±51	NS
LV EDD, mm	52±8	63±7	<0.05
No. viable segs	7.4±3.1	6.7±2.5	NS
No. transmural scar segs	2.5±2.1	2.8±1.7	NS

Only viable patients with LVEF reassessment, n=44.

CABG indicates coronary artery bypass grafting; CCS, Canadian Cardiovascular Score; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; HT, hypertension; LVEF, left ventricular ejection fraction; LV EDD, left ventricular end-diastolic dimension; LV EDV, left ventricular end-diastolic volume; LV ESV, left ventricular end-systolic volume; MI, myocardial infarction; NYHA, New York Heart Association; segs, segments; VD, vessel disease.

In the remaining 44 viable patients, the LV ejection fraction improved modestly from 27±8% to 32±5% ($P<0.05$), whereas the LV ejection fraction remained unchanged in the remaining 27 nonviable patients (28±9% versus 27±11%; NS). On an individual basis, only 11% of the nonviable patients demonstrated an improvement ≥5% in LV ejection fraction, as compared with 55% of the viable patients ($P<0.05$).

When the viable patients were divided according to the presence or absence of improvement in LV ejection fraction after revascularization, no significant differences were noted, except that the viable patients without improvement in LV ejection had a higher LV end-systolic volume, a larger end-diastolic LV diameter, and a trend toward a higher LV end-diastolic volume; resting LVEF in particular was not different (Table). In the improvers, the mean improvement in LVEF was 10±4%.

Mild mitral regurgitation was present in 2 (10%) patients without improvement in LVEF as compared with 3 (12.5%) patients with improvement in LVEF.

The number of grafts was comparable between patients with and without improvement in LVEF and medication (beta-blockers, ACE inhibitors, diuretics, and anticoagulants) was also not different between the 2 groups.

Figure 1 demonstrates the relation between the LV end-systolic volume at baseline and the change in LV ejection fraction after revascularization. When the LV end-systolic volume increased, the likelihood of improvement in LV ejection fraction decreased.

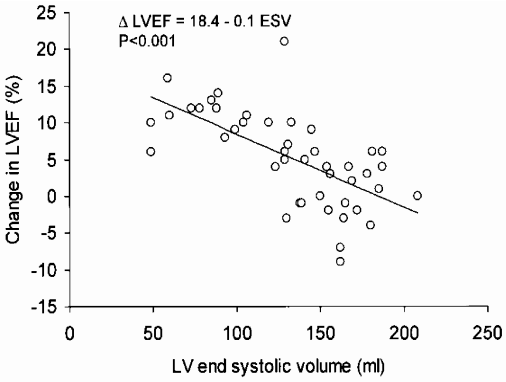

Figure 1. Scatter plot demonstrating the relation between the left ventricular (LV) end-systolic volume at baseline and the change in LV ejection fraction after revascularization. When the LV end-systolic volume increased, the likelihood of improvement in LV ejection fraction decreased. ESV indicates end-systolic volume; LVEF, left ventricular ejection fraction.

Viability, LV Size, and Prognosis

A total of 23 (29%) events occurred in the 79 patients during 3 years of follow-up. There were 12 (15%) cardiac deaths, including 5 early (within 30 days of surgery) and 7 late deaths; there were 4 nonfatal infarctions (1 early and 3 late after revascularization) and 7 rehospitalizations for heart failure (all late after revascularization). There were 12 events in 49 patients with an improved LV ejection fraction, as compared with 11 events in 30 nonimprovers (NS).

Based on the median LV end-systolic volume (130 mL), the patients were divided into 4 groups: with substantial viability (≥4 dysfunctional but viable segments), without substantial viability (<4 dysfunctional but viable segments), with a relatively large LV size (LV end-systolic volume ≥130 mL), and with a relatively small LV size (LV end-systolic volume <130 mL). The highest event rate (67%) was observed in the patients without viable myocardium with a large LV size (6 of 9 patients); the lowest event-rate (5%) was observed in the patients with viable myocardium with a small LV size (1 of 20 patients). Intermediate event rates were observed in the patients with viable myocardium and a large LV size (38%, 11 of 29 patients) and in the patients without viable myocardium and a small LV size (24%, 5 of 21 patients).

Despite the presence of viability, the event rate increased in parallel to the LV end-systolic volume: in viable patients with an LV end-systolic volume ≥130 mL, the event rate was 37%, as compared with 53% in patients with an LV end-systolic volume ≥160 mL and 63% in patients with a volume ≥180 mL.

The cardiac event curves according to viability and LV size are shown in Figure 2.

Discussion

Assessment of viability has become important in the management of patients with ischemic cardiomyopathy.[1–3,11–14] Different techniques are available and FDG imaging is considered the most sensitive technique for the detection of

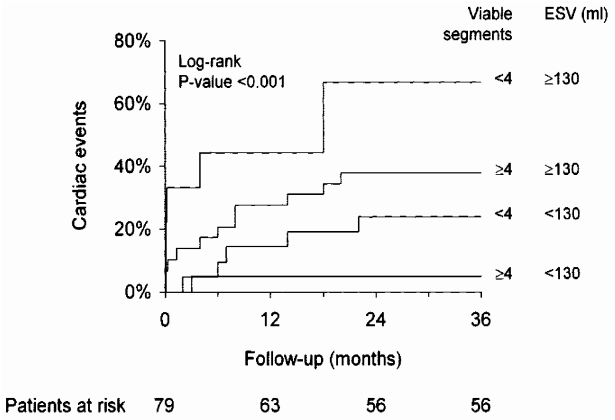

Figure 2. Cardiac events (cardiac death, myocardial infarction, and hospitalization for heart failure) during 3-year follow-up of the 4 different groups according to the presence of substantial viable myocardium (≥4 segments) and the left ventricular end-systolic volume (ESV). Patients with a small LV (ESV <130 mL) and viable myocardium had the best prognosis (5% event rate during 3-year follow-up), whereas patients without viable myocardium and a large LV had the worst prognosis (67% event rate during 3-year follow-up).

dysfunctional but viable myocardium.[15] Meta-analysis of 20 studies with 598 patients has shown a sensitivity of 93%.[4] The problem, however, is the lower specificity. Data from the meta-analysis demonstrated a specificity of 58%. The lower specificity has been of concern and has also been encountered in clinical practice when some patients with viable myocardium do not improve in function after revascularization. This lower specificity is observed not only with FDG imaging but also with other forms of radionuclide imaging.[4] The failure of viable myocardium to recover in function after revascularization may be related to various issues. One important issue, suggested recently by Yamaguchi et al,[5] is the presence of extensive LV remodeling. The authors evaluated 41 patients undergoing surgical revascularization and demonstrated that 10 of 16 (63%) patients with extensive remodeling had heart failure after surgery and that in these patients, the LV ejection fraction did not improve after revascularization (24±6% versus 25±6%, NS). In this study, preoperative viability testing was not performed. In the current study, we have evaluated the relation between viability and LV size and improvement in LV ejection fraction after revascularization. In line with the literature, we observed that patients without viable myocardium had a low likelihood of recovery of function. In addition, we observed that a substantial number of patients (55%) with viable myocardium improved in LV ejection fraction after revascularization, but at the same time, the 45% of patients with viable myocardium did not improve after revascularization. Careful analysis of these patients revealed that only the LV volumes were different between the 2 groups, with only the LV end-systolic volume being *significantly* larger in the patients with viable myocardium without improvement in LV ejection fraction after revascularization. This finding is not surprising, because LV end-systolic volume has been identified several years ago as a strong prognostic marker in patients after myocardial infarction.[16] To further explore the relation interaction between LV remodeling and the likelihood of recovery of viable patients, we evaluated the change in LV ejection fraction as a function of the baseline LV end-systolic volume (Figure 1). The patients with a lower LV end-systolic volume had a higher likelihood of improvement in LV ejection fraction after revascularization. These observations extend the results from Yamaguchi et al[5] and suggest that extensive remodeling of the LV may indeed prevent improvement in LV ejection fraction after revascularization, despite the presence of substantial (≥25% of the LV) viable myocardium.

The next important issue is the prognostic value of the presence/absence of viability in relation to LV size. In particular, do the patients with viable myocardium, with a larger LV size, without improvement in LV ejection fraction benefit from surgical revascularization? Louie et al[6] have shown that patients with an LV end-diastolic dimension ≥70 mm had a poor survival after surgical revascularization, but a specific analysis on the relation between viability, LV size, change in LV ejection fraction, and long-term survival was not performed. In the current study, we have used the median LV end-systolic volume (130 mL) to divide the patients into patients with a (relatively) large LV and a smaller LV. Combination of the LV size and presence/absence of viability allowed separation of high-risk and low-risk patients, as demonstrated in Figure 2. Patients without viable myocardium and a large LV had the highest event rate (67%) as compared with the lowest event rate (5%) observed in patients with viable myocardium and a small LV. These findings indicate that combination of these 2 parameters may allow superior risk stratification before surgical revascularization as compared with viability assessment alone.

Limitations

Echocardiography was used to assess recovery of function after revascularization. This technique may not be the most accurate technique to assess LVEF, although it has been used in most studies.[4] Improvement in LVEF ≥ 5% was considered significant. This is the value used most frequently in studies as a measure of improvement in LVEF,[8,14] although it can be debated whether it is clinically meaningful. However, the mean change in LVEF was 10±4% in the viable patients who exhibited improvement in LVEF, and this value is probably clinically important.

Graft occlusion may prevent recovery of function after revascularization, and this was not systematically evaluated in our patients. However, none of the patients experienced new symptoms of angina during the follow-up period.

Conclusion

LV end-systolic volume substantially influences outcome after revascularization. Despite the presence of viable myocardium, patients with a large LV may not improve in LV ejection fraction after revascularization. In addition, patients with a large LV end-systolic volume have a worse long-term prognosis as compared with patients with a smaller LV end-systolic volume. The combination of viability testing and assessment of LV end-systolic volume may allow superior risk stratification of patients with ischemic cardiomyopathy undergoing surgical revascularization.

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PART II

CHAPTER 7

Opposite patterns of LV remodeling after coronary revascularization in patients with ischemic cardiomyopathy: role of myocardial viability

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Opposite Patterns of Left Ventricular Remodeling After Coronary Revascularization in Patients With Ischemic Cardiomyopathy

Role of Myocardial Viability

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Background—In patients with ischemic cardiomyopathy, left ventricular (LV) remodeling is an important prognostic indicator. The precise relation between viable myocardium, revascularization, and ongoing or reversed remodeling is unknown and was evaluated in the present study.

Methods and Results—A total of 100 patients with ischemic cardiomyopathy underwent dobutamine stress echocardiography to assess myocardial viability and LV geometry (volumes and shape). At a mean of 10.2 months and 4.5 years after revascularization, resting echocardiography was repeated to evaluate LV remodeling. Long-term follow-up (mean 5±2 years) data were obtained. According to dobutamine stress echocardiography, 44 patients (44%) were defined as viable (≥4 viable segments) and 56 as nonviable. After revascularization, 40 patients (43%) had ongoing LV remodeling and 53 (57%) did not (in 7 patients who died early after revascularization, postoperative echocardiographic evaluation was not available). On multivariable analysis, the number of viable segments was the only predictor of ongoing LV remodeling (OR 0.60, 95% CI 0.48 to 0.75; $P<0.0001$). The likelihood of LV remodeling decreased as the number of viable segments increased. During the follow-up, reverse remodeling was present in viable patients, whereas in nonviable patients, LV volumes significantly increased, which indicates ongoing LV remodeling. At follow-up, viable patients also showed a persistent improvement of heart failure symptoms and fewer cardiac events than nonviable patients ($P<0.05$).

Conclusions—In patients with ischemic cardiomyopathy, a substantial amount of viable myocardium prevents ongoing LV remodeling after revascularization and is associated with persistent improvement of symptoms and better outcome. **(*Circulation*. 2004;110:2383-2388.)**

Key Words: remodeling ■ revascularization ■ cardiomyopathy

In patients with ischemic cardiomyopathy coronary revascularization is a therapeutic option that may improve left ventricular (LV) function and prognosis.[1–10] A substantial amount of viable myocardium is necessary to obtain improvement of LV ejection fraction (LVEF), symptoms and prognosis.[2–10] It has been suggested that the preservation of LV geometry in patients with ischemic cardiomyopathy may also be an important end point after revascularization.[11] The restoration of adequate flow to viable myocardium may prevent LV distortion and ongoing LV remodeling, and thus prevent progressive heart failure and death. Some studies showed that revascularization can prevent the LV remodeling process in patients with recent myocardial infarction and residual viability.[12,13] Information on the effect of viability and revascularization on LV remodeling in patients with chronic LV dysfunction is scarce.[14,15] Accordingly, in the present study, the role of myocardial viability in the LV remodeling process after revascularization has been evaluated in a large cohort of patients with ischemic cardiomyopathy. In addition, long-term clinical follow-up has been obtained.

Methods

Study Population

The study population existed of 106 patients (89 men, age 61±10 years) with ischemic cardiomyopathy and heart failure symptoms already scheduled for revascularization according to clinical criteria (symptoms, presence/absence of ischemia, and angiographic findings). Sinus rhythm was present in all patients. Ninety-eight patients (93%) had a history of myocardial infarction that had occurred >6 months before study entrance (median 3 years, range 0.8 to 23 years). Patients with moderate to severe valvular disease were excluded.

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Study Protocol

Patients with ischemic cardiomyopathy were studied prospectively to evaluate LV remodeling, LV ejection fraction (LVEF), and cardiac events during a long-term follow-up after revascularization and their relation to myocardial viability. Before revascularization (study 1, baseline) resting 2D echocardiography was performed to assess regional wall-motion abnormalities and LV geometry, followed by dobutamine stress echocardiography (DSE) to evaluate myocardial viability. After revascularization, resting 2D echocardiography was repeated at a mean of 10.2 months (study 2) and 4.5 years (study 3) to assess changes in LV geometry. Within 2 weeks of each echocardiographic study, radionuclide ventriculography (RNV) was performed to assess LVEF by an independent technique. Before and sequentially after revascularization, functional status was evaluated by structured clinical interviews. Cardiac events were obtained during a 5±2-year follow-up. The local ethics committee approved the protocol, and all patients gave informed consent.

Echocardiographic Studies

All echocardiograms were performed with a Sonos-5500 device (Hewlett-Packard, PMS) equipped with a second-harmonic 1.8- to 3.6-MHz transducer. Standard views of the LV were obtained.[14]

Myocardial Viability

Low- to high-dose DSE (up to 40 $\mu g \cdot kg^{-1} \cdot min^{-1}$ plus 2 mg of atropine, if necessary) was performed as described previously.[6] Interpretation of DSE studies was performed offline from cine loops by 2 experienced observers blinded to the clinical data. Interobserver and intraobserver agreement for analysis of DSE studies was 92% and 94%, respectively.[16] Regional function was scored with a 16-segment, 5-point scoring model as follows: 1=normal, 2=mildly hypokinetic, 3=severely hypokinetic, 4=akinetic, and 5=dyskinetic.[6] The wall-motion score index (WMSI) was calculated by dividing the summed wall-motion score by the number of segments. Myocardial viability was evaluated only in severely dysfunctional segments (score 3 to 5). Segments showing a sustained improvement in wall motion up to the high dose and segments with an ischemic pattern (biphasic response or worsening of the wall motion) during DSE were considered viable.[4,6,11] Segments with unchanged wall motion or with akinesia that became dyskinesia were considered nonviable.[4,6] A patient was defined as viable in the presence of ≥4 viable segments and as nonviable in the presence of <4 viable segments.[6] This definition is based on previous work with receiver operator characteristic curve analysis that showed that recovery of function may be predicted in the presence of ≥4 viable segments.[6]

LV Geometry (Volumes and Sphericity)

LV volumes and LV sphericity index (LVSI) were measured from the resting echocardiography (before and sequentially after revascularization). All measurements were performed offline in random order by 2 experienced readers blinded to patient data and study time. LV volumes were measured with the biplane Simpson's rule.[17] The end-diastolic and end-systolic volumes were indexed (LVEDVI and LVESVI, respectively) by the body surface area. LVEDVI ≤55.5±8.7 mL/m^2 and LVESVI ≤22.1±4.9 mL/m^2 were considered normal values.[18,19] Interobserver and intraobserver variability for the measurement of LV volumes was 5% and 7%, respectively. An increase >15% in the LVEDVI or LVESVI after revascularization defined ongoing LV remodeling. Absolute changes in LVEDVI and LVESVI were expressed as the change (Δ) between the volume late after revascularization (at 4.5 years) and the baseline volume. The LVSI was derived by the ratio of LV short- to long-axis dimensions in the end-systolic apical 4-chamber view.[16] The higher the LVSI, the more spherical the shape. Intraobserver and interobserver agreement for assessment of LVSI was 95% and 91%, respectively.

Assessment of Improvement in LVEF

RNV was performed at rest with the patient in the supine position after administration of 740 MBq of ^{99m}Tc. Images were acquired with a small-field-of-view gamma camera (Orbiter, Siemens Corp) oriented in the 45° left anterior oblique position with a 5° to 10° caudal tilt. LVEF was calculated from the 45° left anterior oblique view by an automated technique. An improvement in LVEF ≥5% at study 2 or 3 was considered clinically significant.[6]

Symptoms and Long-Term Follow-Up

At each study point, patients' New York Heart Association (NYHA; for heart failure symptoms) and Canadian Cardiovascular Society (CCS) class (for angina) were defined by an independent physician blinded to all data. Long-term follow-up was obtained by chart review and telephone contact. Events included cardiac death, myocardial infarction, hospitalization for heart failure, and major ventricular arrhythmias (ventricular tachycardia/fibrillation). Moreover, the duration of stay in the intensive care unit after surgery was noted, as was the presence of low-output syndrome (defined as the need for high dosages of inotropic medication and/or intra-aortic balloon pumping to sustain adequate hemodynamic status).

Statistical Analysis

Continuous data were expressed as mean±SD and compared with the Student's t test for (un)paired samples, as indicated. Proportions for dichotomous data were compared by χ^2 analysis. Repeated measurements were analyzed by 2-way ANOVA to evaluate differences across time and between different groups. Univariable and multivariable logistic regression analyses were performed to characterize predictors of ongoing LV remodeling. Categorical variables included diabetes, anterior/inferior Q-wave myocardial infarction, persistent ST-segment elevation, ACE inhibitor and/or β-blocker therapy, and mode and completeness of revascularization. Continuous variables included age, WMSI at rest, baseline LV volumes and LVEF, and number of viable and nonviable segments. To define the predictive value for LV remodeling of each DSE pattern that indicated viable myocardium, the numbers of segments with sustained improvement, biphasic response, or worsening of the wall motion were included in the analyses. All variables entered the multivariable stage, regardless of the results of univariable analyses. Multivariable regression was then performed by stepwise backward deletion. All variables with a probability value <0.25 remained in the final model. Linear regression analysis was performed to evaluate the relation between the amount of viable myocardium and the changes (Δs) in LV volumes. Cardiac event rate was evaluated by Kaplan-Meier analysis. Differences between curves were tested with log-rank χ^2 statistics. For all tests, a probability value <0.05 was considered significant.

Results

Study Population

CABG was performed in 85 patients (80%) and PTCA in 21 patients (20%). Revascularization procedures were performed within 1 month of the DSE and were complete in all but 1 patient, who had perioperative myocardial infarction (peak creatine kinase level of 2640 IU/L). Five patients who underwent associated procedures influencing LV remodeling (aneurysmectomy [n=3] and mitral valve repair [n=2]) were subsequently excluded. One patient was lost to follow-up. Cardiac death occurred early after revascularization in 6 patients, and 1 patient died of progressive heart failure at 6 months after revascularization. These patients were included in the follow-up analysis, but sequential evaluations after revascularization were not available in these 7 patients. One patient had an acute myocardial infarction 5 months after study 2. In this patient, ongoing LV remodeling was already present at study 2. Study 3 (at 4.5 years) was not performed in 8 patients who died (3 noncardiac deaths) during the follow-up period.

TABLE 1. WMSI, Systolic Blood Pressure/End-Systolic Volume Ratio, and LVEF at Different Study Points

	Group 1 (Remodeling)				Group 2 (No Remodeling)			
	Study 1	Study 2	Study 3	*P*	Study 1	Study 2	Study 3	*P*
WMSI*	2.7±0.6	2.7±0.7	2.8±0.61	NS	2.8±0.7	2.6±0.7	2.5±0.5	<0.01
SBP/ESV*	1.5±0.8	1.6±0.7	1.5±0.7	NS	1.6±0.6	2.6±1.6	2.7±0.6 1.4	<0.001
LVEF, % *	32±8	31±10	31±9	NS	32±9	38±11	41±11	<0.001

SBP/ESVI indicates systolic blood pressure/end-systolic volume ratio.
*$P<0.001$, group 1 vs group 2 by ANOVA.

Baseline Echocardiographic Data

All patients presented with moderate to severe LV dilatation. LVEDVI and LVESVI were on average 108±34 and 71±31 mL/m^2, respectively. Analysis of wall motion showed that 939 segments (59%) were severely dysfunctional. On average, patients had 9.3±4.7 severely dysfunctional segments. During DSE, 392 segments (42%) were viable: 176 (19%) had a biphasic response, 185 (20%) had sustained improvement, and 31 (3%) had worsening of wall motion. The remaining 597 segments (58%) were nonviable. Forty-four patients (44%) had ≥4 viable segments (viable patients), whereas 56 patients had <4 viable segments (nonviable patients).

LV Geometry After Revascularization

After revascularization, patients were divided into group 1 (40 patients [43%] with ongoing LV remodeling) and group 2 (53 patients [57%] without ongoing LV remodeling). Overall, WMSI and LVEF improved significantly after revascularization in group 2 but remained unchanged in group 1 (Table 1). Table 2 summarizes the baseline characteristics of the 2 groups. Q-wave anterior myocardial infarction was more frequent in group 1 ($P<0.04$). In addition, a trend toward a higher prevalence of persistent ST elevation was present in group 1. Finally, the number of viable and nonviable segments was significantly different between the 2 groups. At baseline, in groups 1 and 2, medications included ACE inhibitors in 67% and 64% of the patients, respectively (P=NS) and β-blockers in 48% and 66% of the patients, respectively (P=NS). At study 2 and 3, groups 1 and 2 were comparable for use of ACE inhibitors (82% versus 75% and 74% versus 79%, respectively, both P=NS) and β-blockers (25% versus 38% and 49% versus 52%, respectively,

TABLE 2. Baseline Characteristics

	Group 1 (Remodeling)	Group 2 (No Remodeling)	*P*
Age, y	60±11	61±10	NS
Male, n (%)	35 (87)	42 (80)	NS
CCS class	2.8±0.6	2.7±0.6	NS
NYHA class	2.6±1.2	2.9±0.9	NS
Hypertension, n (%)	29 (72)	38 (73)	NS
Hypercholesterolemia, n (%)	18 (45)	23 (43)	NS
Smoking, n (%)	20 (50)	23 (57)	NS
Family history of CAD, n (%)	24 (60)	28 (53)	NS
Diabetes, n (%)	4 (10)	4 (7)	NS
History of myocardial infarction, n (%)	39 (97)	51 (92)	NS
Q-wave myocardial infarction, n (%)	36 (90)	40 (75)	NS
Anterior	26 (65)	22 (41)	0.04
Septal	14 (35)	13 (24)	NS
Lateral	7 (17)	6 (11)	NS
Inferoposterior	16 (40)	28 (53)	NS
Persistent ST elevation, n (%)	21 (52)	17 (32)	0.08
Stenotic vessels, n	2.5±0.7	2.6±0.6	NS
LVEF, %	32±9	33±9	NS
Severely dysfunctional segments, n	8.6±4.2	9.6±5.1	NS
Viable segments, n	2.2±2.2	6.1±3.3	<0.001
Biphasic response, n	1±1.6	2.4±2.7	<0.01
Sustained improvement, n	0.9±1.7	2.7±2.4	<0.001
Worsening, n	0.3±0.7	0.4±0.9	NS
Unchanged, n	6.4±4.2	4.2±3.4	<0.01

CAD indicates coronary artery disease.
All values are presented as mean±SD or percentage (%).

TABLE 3. Predictors of LV Remodeling

	Univariable Analysis			Multivariable Analysis		
	OR	CI	*P*	OR	CI	*P*
LVEDVI	1.01	0.9–1.1	0.82	...	...	...
LVESVI	1.00	0.9–1.1	1	...	...	...
Viable segments, n	0.61	0.5–0.7	<0.0001	0.6	0.4–0.7	<0.0001
Nonviable segments, n	1.16	1.1–1.3	<0.05	1.11	0.9–1.3	0.13
Biphasic response, n	0.73	0.5–0.9	<0.01	...	...	...
Sustained improvement, n	0.66	0.5–0.8	<0.001	...	...	...
Worsening, n	0.86	0.5–1.5	0.6	...	...	...
LVEF	0.98	0.9–1.1	0.45	...	...	...
Inferior Q wave	0.61	0.2–1.4	0.26	...	...	...
Anterior Q wave	2.50	1.1–5.8	0.03	0.96	0.8–7.2	0.11
Persistent ST elevation	1.83	0.7–4.5	0.18	...	...	...
Mode of revascularization	1.99	0.6–6.2	0.23	...	...	...
Diabetes	2.88	0.5–16.6	0.28	...	...	...
WMSI	1.03	0.5–1.9	0.9	...	...	...
ACE inhibitors	1.12	0.4–2.6	0.78	...	...	...
β-Blockers	0.49	0.2–1.1	0.09	0.48	0.2–1.4	0.19
Age	0.99	0.9–1.1	0.78	...	...	...

both *P*=NS). In addition, 55% of patients in group 1 and 49% of patients in group 2 were taking lipid-lowering drugs at baseline (*P*=NS). The proportion of patients taking lipid-lowering drugs in the 2 groups was similar at study 2 (48% and 53%) and at study 3 (both 66%).

Predictors of Ongoing LV Remodeling After Revascularization

The presence of anterior Q-wave myocardial infarction and the number of scar segments were positively related to ongoing LV remodeling. The sustained improvement pattern was significantly more related to the occurrence of no remodeling (OR 0.66, 95% CI 0.5 to 0.8, χ^2=10.9, *P*<0.0001) than was the biphasic response (OR 0.73, 95% CI 0.5 to 0.9, χ^2=6.7, *P*<0.01). The worsening pattern was not related to LV remodeling. The total number of viable segments (showing sustained improvement, biphasic response, or worsening) was the strongest univariable predictor (OR 0.62, 95% CI 0.50 to 0.76, χ^2=20.3, *P*<0.0001) and the only multivariable predictor of ongoing LV remodeling (OR 0.60 for each additional viable segment, 95% CI 0.48 to 0.75, χ^2=18.7, *P*<0.0001; Table 3). The likelihood of ongoing LV remodeling decreased for each additional viable segment. When normal (not only dysfunctional) segments were included in the number of viable segments, this variable remained predictive of LV remodeling. Moreover, the Δs in LV volumes were inversely related to the number of viable segments (LVEDVI *P*<0.001; LVESVI *P*<0.001; Figure 1).

Myocardial Viability, Remodeling, and Long-Term Follow-Up

After revascularization, the duration of stay in the intensive care unit was 1.4±2 and 3.5±2 days for viable and nonviable patients, respectively (*P*<0.005). Low-output syndrome occurred in 12 viable (27%) and 29 (52%) nonviable patients (*P*<0.05). In 2 nonviable patients, an intra-aortic balloon pump was placed.

After revascularization, the majority of viable patients (88%) showed preserved LV volumes. Conversely, ongoing LV remodeling occurred in the majority of nonviable patients (72%, *P*<0.0001 versus viable patients). On average, in viable patients, LVEDVI did not change significantly during follow-up (from 105±37 to 102±35 up to 98±48 mL, *P*=NS by ANOVA), whereas LVESVI decreased significantly (from 70±34 to 65±31 up to 61±39 mL, *P*<0.05 by ANOVA). In nonviable

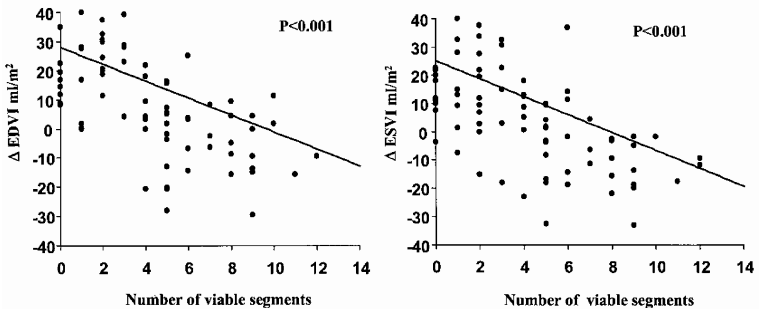

Figure 1. Relation between extent of viability and changes (Δs) in LV volumes after revascularization. Δs in LVEDVI (A) and LVESVI (B) decreased as number of viable segments increased.

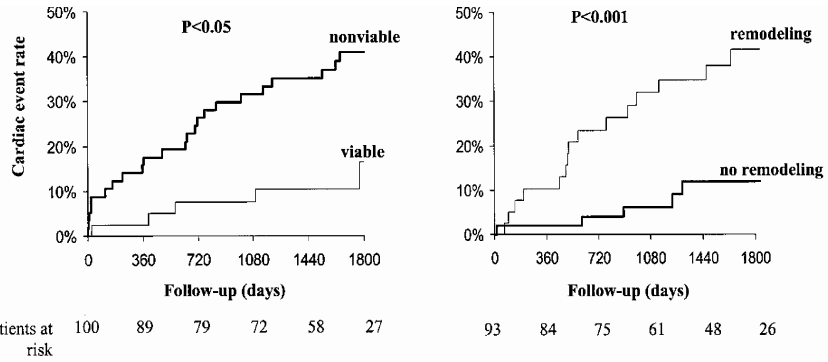

Figure 2. Kaplan-Meier curves showing cardiac event rate in viable and nonviable patients (A) and in patients with and without remodeling (B).

patients, LV volumes significantly increased over the follow-up period (ongoing LV remodeling; LVEDVI from 105±28 to 121±36 up to 131±50 mL/m^2, LVESVI from 65±24 to 80±32 up to 88±45 mL/m^2, both $P<0.001$ by ANOVA). Also, LVSI improved in viable patients (from 0.60±0.09 to 0.57±0.1, $P<0.01$ by ANOVA), whereas it worsened significantly in nonviable patients (from 0.59±0.09 to 0.65±0.1, $P<0.01$ by ANOVA). LVEF significantly improved in 65% of viable patients compared with 25% of nonviable patients ($P<0.001$). Changes in LVEF were inversely related to changes in LVEDVI ($P<0.01$). In addition, viable patients showed persistent improvement of symptoms during follow-up (CCS from 2.6±0.6 to 1.2±0.7 and NYHA from 3.1±0.8 to 1.5±0.5, both $P<0.001$ by ANOVA). In nonviable patients, although CCS class improved persistently (from 2.8±0.6 to 1.1±0.9, $P<0.001$ by ANOVA), NYHA class did not improve over the follow-up (from 2.9±0.9 to 2.9±0.7, P=NS by ANOVA). During the long-term follow-up, 1 nonviable patient underwent cardiac resynchronization therapy, and 2 patients (1 viable and 1 nonviable) received an intracardiac defibrillator.

Overall cardiac events were significantly less frequent in viable than in nonviable patients (16% versus 41%, $P<0.05$; Figure 2A). A trend toward a lower frequency of cardiac death was observed in viable patients (7% versus 21%, $P=0.08$). Also, cardiac events were less common in patients without LV remodeling than in those with ongoing LV remodeling (12% versus 42%, $P<0.001$; Figure 2B). Cardiac death occurred less frequently in patients without remodeling (4% versus 17%, $P=0.06$).

Discussion

Improvement in LV function, symptoms, and prognosis is likely to occur after revascularization in patients with ischemic cardiomyopathy and viable myocardium.[2,6–10] The findings in the present study indicate that in these patients, substantial myocardial viability prevents ongoing LV remodeling after revascularization and is associated with improvement of symptoms and favorable long-term prognosis.

Beneficial Effects of Revascularization in Patients With Viable Myocardium

Several studies have demonstrated that revascularization in patients with ischemic cardiomyopathy and viable myocardium improves regional and global LV function.[2,6, 20,21] A substantial amount (≥25% of the LV) of viable myocardium is necessary to result in improvement in LVEF.[6–10] However, it has been stated that the improvement in LV function may underestimate the benefit of revascularization and that improvement of symptoms and prognosis need to be considered.[11] In particular, a recent meta-analysis demonstrated that in patients with viable myocardium, revascularization is associated with a good prognosis.[22] Initial data suggested that in patients with ischemic cardiomyopathy, preservation of LV geometry and prevention of ongoing LV remodeling after revascularization can be an additional end point.[14,15] Accordingly, in the present study, coronary revascularization resulted in improvement in LVEF only in 65% of viable patients, whereas ongoing LV remodeling was prevented in 88% of viable patients. Hence, after revascularization, some viable patients did improve in terms of LV remodeling, although they failed to improve in LVEF. It is known that LV remodeling after acute myocardial infarction is a major determinant of poor prognosis.[23,24] In the present study, ongoing LV remodeling after revascularization of patients with ischemic cardiomyopathy was associated with a higher cardiac event rate (42%) than for patients with no remodeling (13%, $P<0.001$).

LV Remodeling After Revascularization

Senior and coworkers[14] demonstrated that coronary revascularization resulted in a significant reduction of LV volume in 32 patients with ischemic cardiomyopathy and viable myocardium. Conversely, ongoing LV remodeling occurred in viable patients treated medically.[14] Dalle Mule et al[15] showed a decrease in LV volumes 3 months after revascularization only in patients with substantial viability during ^{201}Tl imaging. Interestingly, an increase in LV volumes was observed in 24 nonviable patients undergone revascularization.[15] In the present study, a large number of patients were included, and more importantly, serial measurements of LV volumes were performed at different time points after revascularization. It appeared that LV volumes changed in different directions in relation to myocardial viability. In patients with minimal or absent viability, LV volumes continued to increase, which indicates ongoing LV remodeling, whereas in viable patients, attenuation or even reversion of LV dilatation occurred. Uniquely, the present study demonstrated that the extent of viable myocardium was related to the occurrence and extent of LV remodeling. In the individual patient, the likelihood of LV remodeling and the absolute changes in LV volumes decreased for each additional viable segment. Among the different patterns of response to dobutamine that indicated viable myocardium, the sustained-improvement pattern was a stronger univariable predictor of no LV remodeling

(χ^2=10.9) than the biphasic response (χ^2=6.7). It may well be that the duration of hibernation before study entrance affected the predictive power of the biphasic response. Also, the extent of nonviable myocardium was a univariable predictor of ongoing LV remodeling, whereas baseline volumes and resting WMSI failed to predict LV remodeling. The inclusion of only patients with moderate to severe LV dilatation and extensive wall-motion abnormalities at rest may explain this finding. Finally, β-blocker therapy before revascularization showed a trend toward a lower occurrence of LV remodeling, and the presence of anterior Q-wave myocardial infarction was a univariable predictor of ongoing LV remodeling. However, only the total number of viable segments remained predictive of LV remodeling in multivariable analysis. The beneficial effect of revascularization of viable myocardium on LV remodeling may have important prognostic implications. In the present study, patients with a substantial amount of viable myocardium, together with an improvement in LV geometry, had persistent improvement in heart failure symptoms and fewer cardiac events during the long-term follow-up. In addition, a trend toward a lower frequency of cardiac death was observed. Conversely, nonviable patients demonstrated ongoing LV remodeling without an improvement in heart failure symptoms after revascularization. Moreover, the cardiac event rate was higher in these patients (Figure 2A). Previous studies have already shown the beneficial effect of revascularization on early and mid-term prognosis.[6–10] These findings further extend previous observations to a long-term follow-up and demonstrate that the benefit of revascularization in patients with substantial myocardial viability may be due, at least in part, to prevention of ongoing LV remodeling.

Study Limitations

Angiographic follow-up was not performed after revascularization. Therefore, graft closure or restenosis may have occurred in some patients, affecting LV remodeling. Moreover, during follow-up, patients received different medications according to the attending physician. The possibility that medications influencing LV remodeling (ACE inhibitors and β-blockers) may have affected the results of the present study cannot be excluded. However, at each study point, medications used were comparable in the 2 groups.

Conclusions

In patients with ischemic cardiomyopathy, substantial myocardial viability prevents ongoing LV remodeling after revascularization and is associated with improvement of symptoms and favorable long-term outcome.

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CHAPTER 8

Improvement of stress LVEF rather than rest LVEF after coronary revascularization in patients with ischemic cardiomyopathy and viable myocardium

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Improvement of stress LVEF rather than rest LVEF after coronary revascularisation in patients with ischaemic cardiomyopathy and viable myocardium

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Objective: To evaluate prospectively the response of left ventricular ejection fraction (LVEF) to high dose dobutamine infusion in patients showing substantial viability, with and without improved resting LVEF after revascularisation.

Methods: Before and 9–12 months after revascularisation, 50 patients with ischaemic cardiomyopathy (LVEF 32 (8)%) and substantial myocardial viability (⩾ 4 viable segments) underwent radionuclide ventriculography and dobutamine stress echocardiography. Patients were divided into group 1, patients with, and group 2, patients without significant improvement in resting LVEF (⩾ 5% by radionuclide ventriculography) after revascularisation. The response of LVEF during dobutamine stress echocardiography was compared in these two groups.

Results: Groups 1 and 2 were comparable in baseline characteristics, resting LVEF, and number of viable segments (mean (SD) 7 (4) *v* 6 (2), not significant). After revascularisation, the LVEF response during dobutamine stress echocardiography improved significantly in both groups (group 1, 34 (10)% to 56 (8)%; group 2, 32 (10)% to 46 (11)%; both $p < 0.001$). Interestingly, although resting LVEF did not improve in group 2, peak stress LVEF after revascularisation did ($p < 0.001$). Group 1 patients had, however, a greater increase in peak stress LVEF (group 1, 22 (10)%; group 2, 13 (9)%; $p < 0.01$). New York Heart Association and Canadian Cardiovascular Society classes decreased in both groups.

Conclusions: Although patients with viable myocardium did not always have improved rest LVEF after revascularisation, peak stress LVEF improved. Assessment of improvement of resting function may not be the ideal end point to evaluate successful revascularisation.

Assessment of myocardial viability is important in the management of patients with ischaemic cardiomyopathy. In patients with a substantial amount of viable myocardium, left ventricular (LV) dysfunction is likely to improve after coronary revascularisation.[1] Improvement of resting LV ejection fraction (LVEF) has often been used to assess the success of coronary revascularisation of viable myocardium.[1–8] Previous studies have reported a variable proportion of patients with viable myocardium with improved LVEF after revascularisation, ranging from 36–88%.[3 5] Hence, resting LVEF does not always improve after revascularisation despite the presence of substantial myocardial viability. It has been suggested that contractile reserve may improve during inotropic stimulation after revascularisation even though resting function does not improve.[9 10] However, information about peak stress LVEF (as a marker of cardiac stress performance) after revascularisation is lacking. In particular, whether patients with viable myocardium who do not have improved resting LVEF may have improved peak stress LVEF after revascularisation is unknown. In the present study, combined low and high dose dobutamine stress echocardiography (DSE) was performed before and after revascularisation to evaluate postoperative changes in stress LVEF in patients with and without improvement in resting LVEF.

METHODS

Study population

The study population consisted of 56 patients (44 men, mean (SD) age 60 (11) years) with ischaemic cardiomyopathy (LVEF 32 (8)%) and a substantial amount of viable myocardium (⩾ 4 segments, ⩾ 25% of the LV) who were already scheduled for coronary revascularisation. Seven of these patients had taken part in a previous study.[11] All patients had heart failure symptoms (mean (SD) New York Heart Association (NYHA) class 3.1 (0.7)), and 70% had accompanying angina pectoris (Canadian Cardiovascular Society (CCS) class 2.5 (0.6)). A history of myocardial infarction was present in 54 patients (96%). In these patients, myocardial infarction had occurred ⩾ 6 months before the study (median three years, range 0.7–22 years). The decision for revascularisation was based on clinical grounds (symptoms, presence or absence of ischaemia, and angiographic findings). Patients with severe (grade 3 to 4) mitral regurgitation were not included. Revascularisation was performed by coronary artery bypass grafting in 45 patients (80%) and by angioplasty in 11 patients (20%). None of the patients had a perioperative myocardial infarction. Two patients (4%) died during the postoperative period (within 30 days) and four patients (one treated by angioplasty and three treated by bypass surgery) were excluded because of incomplete revascularisation according to the procedure report. Therefore, the final study population consisted of 50 patients (40 men, mean (SD) age 61 (11) years). These patients had complete revascularisation and were stable during the study period.

Abbreviations: CCS, Canadian Cardiovascular Society; DSE, dobutamine stress echocardiography; LV, left ventricular; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; RNV, radionuclide ventriculography

Table 1 Baseline characteristics

	Group 1: improvers (n = 26)	Group 2: non-improvers (n = 24)	p Value
Men	22 (85%)	18 (75%)	NS
Age (years)	62 (12)	60 (12)	NS
Previous MI	24 (92%)	24 (100%)	NS
Q wave MI	20 (83%)	21 (87)%	NS
Anterior MI	14 (54%)	15 (62%)	NS
NYHA class	3.15 (0.8)	2.96 (0.7)	NS
CCS class	2.57 (0.7)	2.67 (0.6)	NS
Stenotic vessels	2.4 (0.7)	2.7 (0.6)	NS
Smoking	12 (46%)	14 (58%)	NS
Hypertension	22 (85%)	21 (87%)	NS
Hypercholesterolaemia	16 (61%)	13 (54%)	NS
Family history of CAD	13 (50%)	16 (67%)	NS
Diabetes mellitus	1 (5%)	2 (8%)	NS
Lipid lowering drugs	13 (50%)	10 (42%)	NS
ACE inhibitors	17 (65%)	19 (79%)	NS
Nitrates	22 (85%)	19 (79%)	NS
β Blockers	16 (61%)	16 (67%)	NS
Diuretics	12 (46%)	16 (67%)	NS
Digoxin	4 (15%)	7 (29%)	NS
Aspirin/anticoagulant	26 (100%)	22 (92%)	NS
LVEF (%)*	33 (10)	32 (7)	NS
LV end diastolic volume (ml)	160 (59)	194 (39)	<0.05
LV end systolic volume (ml)	105 (49)	135 (37)	<0.05
LV sphericity index†	0.58 (0.09)	0.61 (0.11)	NS

Data are mean (SD) or number (%).
*Assessed by radionuclide ventriculography.
†Derived by the ratio of left ventricular (LV) short to long axis dimensions in the apical four chamber view.[15]
ACE, angiotensin converting enzyme; CAD, coronary artery disease; CCS, Canadian Cardiovascular Society; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NS, not significant; NYHA, New York Heart Association.

Study protocol

The study protocol was prospectively designed to evaluate the response of LVEF to dobutamine challenge before and after revascularisation. DSE was performed one week before and 9–12 months after revascularisation. Radionuclide ventriculography (RNV) was also performed before and 9–12 months after revascularisation to assess improvement of resting LVEF by an independent technique. β Blockers were not discontinued before DSE and RNV. An improvement in LVEF ⩾ 5% after revascularisation was considered clinically significant.[5] According to the presence or absence of significant improvement in resting LVEF after revascularisation, the patients were divided into two groups: group 1, patients with improved resting LVEF; and group 2, patients without improved resting LVEF. Next, the response of LVEF during dobutamine stress before and after revascularisation was compared in these two groups. In addition, heart failure symptoms and angina score were evaluated during the study period. The local ethics committee approved the protocol and all patients gave informed consent to participate in the study.

Assessment of LVEF

Before and 9–12 months after revascularisation, RNV was performed to assess LVEF improvement by an independent technique. RNV was performed at rest with the patient in the supine position after the administration of 740 MBq of ^{99m}technetium. Images were acquired with a small field of view gamma camera (Orbiter; Siemens Corp, Iselin, New Jersey, USA) oriented in the 45° left anterior oblique position with a 5–10° caudal tilt. LVEF was calculated from the 45° left anterior oblique view by an automated technique. An improvement in LVEF ⩾ 5% after revascularisation was considered clinically significant.[5]

Dobutamine stress echocardiography

All echocardiograms were recorded by commercially available equipment (Sonos 5500; Hewlett Packard, Philips Medical Systems, Eindhoven, the Netherlands) with a second harmonic 1.8–3.6 MHz transducer to optimise endocardial border visualisation. Standard parasternal and apical views of the LV were obtained[12] at rest and at the end of each step of dobutamine infusion. Dobutamine was administered intravenously as previously described,[13] starting at a dose of 5 μg/kg/min for five minutes, followed by 10 μg/kg/min for five minutes. Subsequently, incremental dobutamine doses of 10 μg/kg/min were given at three minute intervals up to a maximum dose of 40 μg/kg/min. Atropine (up to 2 mg) was administered intravenously if the test end point was not reached. Blood pressure, cardiac rhythm, and ST segment were continuously monitored.

Test end points were achievement of target heart rate, extensive new wall motion abnormalities, horizontal or down sloping ST segment depression (⩾ 2 mm compared with baseline), severe angina, systolic blood pressure fall > 40 mm Hg, blood pressure > 240/120 mm Hg, and significant supraventricular or ventricular arrhythmia. Metoprolol (1–5 mg intravenously) was available to reverse the effects of dobutamine. Severely dysfunctional segments (including severe hypokinesia, akinesia, and dyskinesia) were evaluated for the presence of viability. Segments with a sustained improvement in wall motion up to high dose dobutamine and segments with a biphasic response or worsening of wall motion during DSE were considered viable.[5] Segments with unchanged wall motion and segments with akinesia becoming dyskinesia were considered nonviable.[5] A substantial amount of viable myocardium was defined as the presence of ⩾ 4 viable segments.[5] This definition is based on previous work with receiver operating characteristic curve analysis showing that recovery of function may be predicted in the presence of ⩾ 4 viable segments.[5]

Assessment of response in LVEF to high dose dobutamine

The study results were analysed off line. LV volumes were measured at rest and during low and high dose dobutamine

infusion with the biplane disk method, a modification of Simpson's rule.[12] Subsequently, the LVEF at baseline and during low and high dose dobutamine were calculated by using the following equation: [end diastolic volume − end systolic volume]/end diastolic volume. All measurements were taken by an independent, experienced reader blinded to the clinical data and time of the study. Interobserver and intraobserver variability for LVEF calculation were reported previously (3.3% and 5.3% respectively).[14]

Assessment of functional status

Before and after revascularisation, an independent physician blinded to all data conducted structured clinical interviews to assess the functional status according to the NYHA (for symptoms of heart failure) and the CCS (for angina) criteria.

Statistical analysis

Continuous data are expressed as mean (SD) and dichotomous data as proportions. Continuous data were compared by Student's *t* test for paired and unpaired samples and two way analysis of variance to evaluate differences across time and between different groups, as indicated. Proportions was compared by χ^2 analysis. For all tests, $p < 0.05$ was considered significant.

RESULTS

Improvement of resting LVEF after revascularisation

After revascularisation, resting LVEF improved significantly (⩾ 5%) in 26 patients (group 1) whereas it failed to improve in 24 patients (group 2). In particular, resting LVEF increased on average from 33 (10)% to 43 (10)% ($p < 0.001$) in group 1, whereas a slight but significant decrease was observed in group 2 (from 32 (7)% to 30 (7)%, $p < 0.05$). Baseline clinical characteristics of patients with (group 1) and without (group 2) improved resting LVEF were comparable (table 1).[15] Resting LVEF by RNV and LV sphericity index were similar in the two groups (table 1), whereas LV end diastolic and end systolic volumes were significantly larger in group 2 (table 1). In addition, group 1 and group 2 were comparable in the extent of viable myocardium (7.4 (4) and 6.0 (2) segments, not significant) but group 2 patients had a larger extent of scar tissue (6.1 (2.3) *v* 3.7 (3.0), $p < 0.05$).

DSE before and after revascularisation

The haemodynamic response during DSE was similar before and after revascularisation in the two groups. In particular, the peak rate–pressure product was 16.270 (2.895) *v* 16.057 (2.902) (not significant) in group 1 and 16.897 (3.226) *v* 16.208 (3.225) (not significant) in group 2. The proportion of patients who reached 85% of the age predicted target heart rate was also similar before and after revascularisation (98% *v* 92%, respectively, not significant). Before and after revascularisation, medication (including β blockers) was comparable; only the use of nitrates was significantly reduced postoperatively (85% *v* 19%, $p < 0.001$, in group 1 and 79% *v* 25%, $p < 0.001$, in group 2). Table 2 shows the patterns of LVEF response during low and high dose DSE. Before revascularisation, LVEF had increased during low dose dobutamine infusion and deteriorated at peak DSE in both group 1 and group 2 ($p < 0.001$ by analysis of variance). The magnitude of change in LVEF during DSE was slightly higher in group 1 than in group 2 ($p = 0.03$ by analysis of variance). After revascularisation, LVEF increased during low dose dobutamine infusion and remained increased at peak DSE in the two groups (both $p < 0.001$ by analysis of variance). The improvement in LVEF response during DSE after revascularisation was significant in both groups ($p < 0.001$ by analysis of variance) (table 2). In group 1 peak stress LVEF after revascularisation improved significantly compared with peak stress LVEF before revascularisation ($p < 0.001$) (fig 1). Interestingly, after revascularisation, although resting LVEF had not improved in group 2, peak stress LVEF did also improve significantly in these patients ($p < 0.001$) (fig 1). In particular, 19 of 24 patients (79%) without improved resting LVEF had improved peak stress LVEF. The magnitude of improvement in LVEF at high dose dobutamine was higher in group 1 than in group 2 (22 (10)% *v* 13 (9)%, $p < 0.01$).

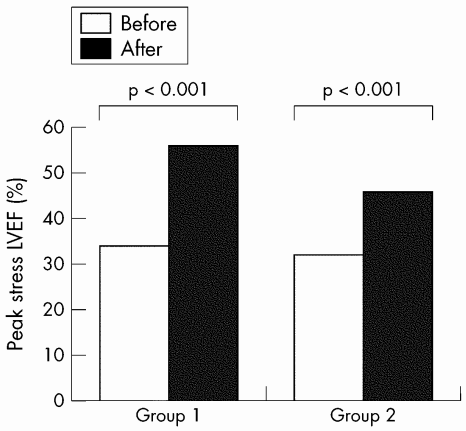

Figure 1 Bar graph showing the effect of revascularisation on peak stress left ventricular ejection fraction (LVEF) in viable patients with (group 1) and without (group 2) improvement of resting LVEF. After revascularisation, peak stress LVEF improved even in viable patients without improvement in resting LVEF.

Functional status

After revascularisation all patients had a significant improvement in heart failure and angina symptoms (fig 2). In particular, the mean (SD) NYHA functional class improved from 3.2 (0.8) to 1.8 (0.7) in group 1 ($p < 0.001$) and from 3.0 (0.7) to 2.2 (0.8) in group 2 ($p < 0.01$). Similarly, the CCS class improved from 2.6 (0.7) to 1.3 (0.7) in group 1 and from 2.7 (0.6) to 1.3 (0.6) in group 2 (both $p < 0.001$).

Table 2 LVEF (%) during dobutamine stress echocardiography

	Before revascularisation*				After revascularisation**				
	Rest	LD	Peak	p Value	Rest	LD	Peak	p Value	p Value†
Group 1	34 (8)	46 (11)	34 (10)	<0.001	43 (9)	54 (8)	56 (8)	<0.001	<0.001
Group 2	31 (8)	41 (9)	32 (10)	<0.001	31(7)	44 (10)	46 (11)	<0.001	<0.001

*p=0.03 group 1 *v* group 2; ** p<0.001 group 1 *v* group 2; †p value before versus after revascularisation for the pattern of response during dobutamine stress echocardiography.
LD, low dose.

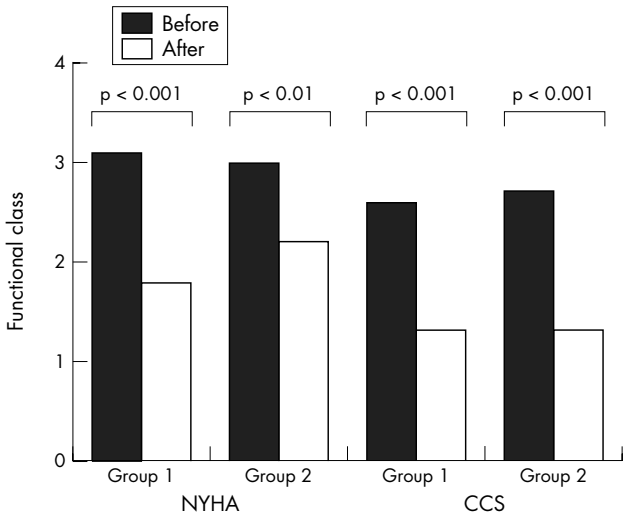

Figure 2 Bar graph showing the effect of revascularisation on heart failure and angina symptoms. After revascularisation, New York Heart Association (NYHA) and Canadian Cardiovascular Society (CCS) classes improved significantly both in patients with (group 1) and in patients without (group 2) improvement in resting LVEF.

DISCUSSION

Improvement of LVEF after coronary revascularisation has been described in variable proportions of patients with ischaemic cardiomyopathy and substantial myocardial viability. The findings in the present study showed that, although resting LVEF did not improve in 48% of patients with substantial viability, peak stress LVEF did improve compared with before revascularisation.

Beneficial effect of coronary revascularisation on resting LV function

Postoperative improvement of LV function has been considered the bench mark against which the preoperative methods to assess viability are measured.[8] Initial studies showed that regional LV function improved after revascularisation, whereas in more recent studies global LV function improved.[8] It has become clear that substantial myocardial viability is needed to obtain functional improvement.[4–7 16] Bax and colleagues[5] showed that LVEF improved in 82% of patients with substantial viable myocardium. However, other studies have shown that resting LVEF does not always improve after revascularisation.[3 4 6–10 14 16] In the present study, only patients with a substantial amount of viable myocardium (at least 25% of the LV) were included. After revascularisation, however, only 52% of the patients had significantly improved resting LVEF. Similarly, in the study by Pasquet and colleagues[7] resting LVEF after revascularisation improved significantly in only 47% of patients shown by low and high dose DSE and nuclear imaging to have extensive viability.[7] These varying percentages of patients experiencing recovery in LVEF after revascularisation are likely to be related to different characteristics of study populations. In particular, besides myocardial viability, additional factors may play a part in determining functional recovery after coronary revascularisation. It has been shown that the presence of extensive scar tissue may prohibit the increase of LVEF after revascularisation, despite viable myocardium.[11 17] Accordingly, in the present study the extent of scar tissue was larger in the patients who did not have improved LVEF. Also advanced LV remodelling may limit the improvement in LVEF despite the presence of viable myocardium.[2 18–20] In the present study, baseline LV end diastolic and end systolic volumes were significantly larger in patients who did not have improved LVEF after revascularisation. Finally, delayed revascularisation and graft occlusion or restenosis after intervention may prevent functional recovery of viable myocardium.[21 22]

Effect of coronary revascularisation on LVEF response to dobutamine challenge

In the present study, resting LVEF improved in only 52% of patients, despite the presence of substantial viability. It has been suggested that, although resting function does not improve, the contractile reserve may increase during inotropic challenge after revascularisation.[9 10] In the study by Lombardo and colleagues,[9] resting function did not improve after revascularisation in 57% of the dysfunctional regions shown by DSE to be viable before revascularisation. However, the contractile reserve was observed to increase during low dose dobutamine infusion in these regions after revascularisation. Elhendy and colleagues[10] showed that LVEF during low dose dobutamine challenge increased even in patients who did not have improved resting LVEF after revascularisation. The responses of LVEF to high dose dobutamine after revascularisation (representing cardiac stress performance) have not been reported thus far.

In the present study, we evaluated the response of LVEF to combined low and high doses of dobutamine infusion in patients with (group 1) and without (group 2) improved resting LVEF after revascularisation. Before revascularisation, LVEF improved at low dose followed by a deterioration at high dose dobutamine (biphasic response). After revascularisation, although resting LVEF did not improve in 48% of patients with viable myocardium, peak stress LVEF did improve. Therefore, postoperative DSE identified additional patients who benefited from revascularisation in terms of global stress function, even though resting function did not improve. Although previous studies have shown that additional benefits (besides recovery of resting function) may be present after revascularisation, the present study uniquely showed that peak LVEF improved in patients without improved resting LVEF.

In a previous study that used a comparable low and high dose DSE protocol, Afridi and colleagues[23] showed that the wall motion score index at peak stress also improved in patients without improved resting function (defined as an improvement of the wall motion score by $\geqslant 2$ grades in at least two contiguous segments). The findings in the present study are in line with this observation and show the beneficial effect of revascularisation on cardiac stress performance. Relief of ischaemia by restoration of the coronary flow reserve may be the mechanism responsible for maintaining the contractile function up to peak stress. This hypothesis is supported by data from Elhendy and colleagues[10] showing that the ischaemic score according to thallium-201 imaging decreased significantly after revascularisation in both patients with and patients without improved resting LVEF. Also, in the study by Afridi and colleagues,[23] the majority of the improvement in stress wall motion score occurred in patients with evidence of ischaemia before revascularisation.

In line with previous studies, the observations in the present study suggest that assessment of resting LVEF after revascularisation may not be the ideal end point to evaluate the success of coronary revascularisation. Assessment of LVEF response to low and high dose DSE after revascularisation may be a more appropriate strategy to evaluate fully the benefit of revascularisation. The improvement of LVEF up to high dose dobutamine suggests the presence of a sustained contractile reserve and the absence of significant ischaemia. Preservation of contractile reserve and relief of ischaemia may be important in improving the prognosis of patients with

ischaemic cardiomyopathy by preventing LV remodelling and ischaemia related arrhythmias.[24]

Implications of improved stress function

Post-revascularisation improvement of heart failure symptoms has been shown to relate to the presence of viable myocardium before revascularisation.[5 9 25 26] This was also observed in the current study. It is conceivable that improved stress LVEF may relate to improved functional class. It has been also shown that patients with myocardial viability who underwent revascularisation had a better prognosis than did medically treated patients.[27 28] This superior prognosis may also (in part) be related to the improvement of stress LVEF (reflecting absence of ischaemia). Further studies are needed to clarify this issue.

Limitations

Coronary angiography was not repeated after revascularisation, nor was perfusion imaging performed. Therefore, failure of resting LVEF to improve because of graft closure or restenosis after intervention cannot be excluded. However, none of the patients had an ischaemic response to DSE after revascularisation. The study population is relatively small. Further studies with more patients are needed to clarify the prognostic implications of these findings.

Conclusion

Assessment of resting LV function has been used as the yard stick to evaluate the success of coronary revascularisation in patients with ischaemic cardiomyopathy and viable myocardium. The findings in the present study showed that assessment of resting LVEF may underestimate the benefit of revascularisation, since stress LVEF may improve even in patients without improved resting LVEF. Moreover, the improvement in stress LVEF was accompanied by improved functional status.

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CHAPTER 9

Comparison of long-term effect of coronary artery bypass grafting in patients with ischemic cardiomyopathy with viable -vs- nonviable left ventricular myocardium

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Comparison of Long-Term Effect of Coronary Artery Bypass Grafting in Patients With Ischemic Cardiomyopathy With Viable Versus Nonviable Left Ventricular Myocardium

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In this study, 63% of patients with a substantial amount of viable myocardium showed an increased left ventricular ejection fraction (LVEF) 12 ± 3 months after coronary artery bypass grafting. In 93% of these patients, increased LVEF persisted at 4.5 ± 1 years of follow-up. Conversely, in nonviable patients, LVEF did not increase at 12 ± 3 months or at follow-up of 4.5 ± 1 years.
(Am J Cardiol 2004;94:757–760)

Whether increased left ventricular ejection fraction (LVEF) induced by coronary revascularization in patients who have viable myocardium persists over the long term is unclear.[1–3] This information may have prognostic implications. In the present study, assessment of LVEF in patients who had ischemic cardiomyopathy was performed before coronary artery bypass grafting (CABG) and was repeated at follow-up at 12 ± 3 months and 4.5 ± 1 years.

• • •

Sixty-six consecutive patients who had ischemic cardiomyopathy and symptoms of heart failure were included in the study. Patients had been scheduled for CABG before inclusion. The decision for revascularization was based on clinical grounds (symptoms, presence/absence of ischemia, and angiographic findings) and was made independently of the results of the viability study. All patients had a history of myocardial infarction (>6 months before the study). Patients who had associated moderate to severe valvular heart disease were excluded.

The study protocol was designed as follows: before CABG, echocardiography at rest and dobutamine stress echocardiography (DSE) were performed in all patients to evaluate regional wall motion abnormalities and myocardial viability in dysfunctional regions; radionuclide ventriculography was performed to assess baseline LVEF. LVEF follow-up was obtained by radionuclide ventriculography at a mean of 12 ± 3 months and 4.5 ± 1 years after revascularization. Before CABG and at follow-up, structured clinical interviews, including assessment of angina and symptoms of heart failure, were carried out. Clinical follow-up data were also obtained at ≤4.5 ± 1 years. The local ethics committee approved the protocol, and all patients gave informed consent.

All studies were performed on a Sonos-5500 imaging system (HP, Philips Medical Systems, Eindhoven, The Netherlands) equipped with a 1.8-MHz transducer using second harmonic imaging to optimize visualization of endocardial borders. Standard parasternal and apical views of the left ventricle were obtained according to recommendations by the American Society of Echocardiography.[4] After acquisition of images at rest, low- and high-dose DSE was performed as previously described[5] to assess myocardial viability. Dobutamine was administered intravenously, starting at a dose of 5 μg/kg/min for 5 minutes followed by 10 μg/kg/min for 5 minutes. Subsequently, dobutamine was administered in incremental doses of 10 μg/kg/min at 3-minute intervals to a maximum dose of 40 μg/kg/min. Atropine (≤2 mg) was also administered intravenously, if necessary. Blood pressure, cardiac rhythm, and ST segment were continuously monitored.

Interpretation of the dobutamine stress echocardiographic studies was performed off-line from cine loops that were displayed side-by-side in a quad-screen format by 2 experienced observers blinded to the clinical data. Inter- and intraobserver agreements for analysis of dobutamine stress echocardiographic studies have been previously reported (92% and 94%, respectively).[6] Regional wall motion and thickening were scored by using 16 segments and a 5-point grading scale: 1 = normal, 2 = mildly hypokinetic, 3 = severely hypokinetic, 4 = akinetic, 5 = dyskinetic.[5] Only severely dysfunctional segments (score 3 to 5) were subsequently evaluated for myocardial viability. Four patterns of wall motion responses were observed during DSE: 1 = biphasic response, 2 = sustained improvement, 3 = worsening, and 4 = no change.[7] Segments with biphasic, sustained improvement or worsening wall motion response during DSE were considered viable, with the exception of akinesia becoming dyskinesia.[5,7] Segments with unchanged wall

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TABLE 1 Baseline Characteristics of the Patients

Characteristic	Viable Myocardium + (n = 26)	Viable Myocardium − (n = 40)
Age (yrs)	60 ± 9	59 ± 9
New York Heart Association, median (range)	III (I–IV)	III (I–IV)
Canadian Cardiovascular Society, median (range)	III (I–III)	III (I–III)
LVEF (%)	29 ± 9	31 ± 9
No. of narrowed coronary arteries	2.7 ± 0.5	2.6 ± 0.6
Lipid-lowering drugs	13 (50%)	21 (53%)
Angiotensin-converting enzyme inhibitors	19 (73%)	25 (63%)
β Blockers	13 (50%)	21 (53%)
Nitrates	19 (73%)	30 (75%)
Diuretics	16 (63%)	25 (63%)
Digoxin	6 (23%)	10 (25%)
Aspirin/warfarin	26 (100%)	40 (100%)
Dysfunctional segments	8.0 ± 4*	12.2 ± 3*
Viable segments	7.8 ± 2	1.2 ± 1
Scar segments	5.3 ± 3	6.7 ± 4

*p <0.001.

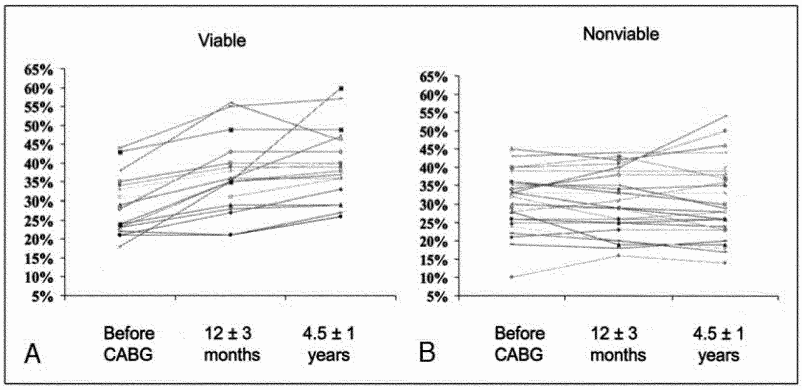

FIGURE 1. Changes in LVEF over the study period *(A)* in viable patients whose LVEF increased and *(B)* in nonviable patients.

motion were considered nonviable (scar) tissue.[5,7] Patients were considered as viable in the presence of ≥4 viable segments (≥25% of the left ventricle).[5]

LVEF was assessed before and 12 ± 3 months and 4.5 ± 1 years after revascularization by radionuclide ventriculography at rest. The methods for the assessment of LVEF have been previously described.[5] LVEF was calculated by standard methods (Odyssey VP, Picker, Cleveland, Ohio). Increased LVEF by ≥5% after revascularization was considered clinically significant.[5]

Before revascularization and at each follow-up (12 ± 3 months and 4.5 ± 1 years), functional status was assessed according to criteria of the New York Heart Association (for symptoms of heart failure) and the Canadian Cardiovascular Society (for angina pectoris). Clinical follow-up data at ≤4.5 ± 1 years were obtained by chart review and telephone contact. Cardiac events included cardiac death, new myocardial infarction (defined according to diagnostic electrocardiographic changes and enzymatic criteria), and hospitalization for heart failure.

All continuous data are expressed as mean ± SD, and dichotomous data are as expressed as percentages. Continuous variables were compared with Student's *t* test for paired and unpaired samples, as appropriate. Two-way analysis of variance analyses were performed for repeated measures to evaluate differences across times and groups. Comparison of proportions was performed with chi-square analysis. Changes in functional classes over the study period were compared by nonparametric analysis (McNemar's test). Cardiac event-free survival rate was evaluated with Kaplan-Meier analysis. Differences between survival curves were tested with log-rank chi-square statistics. For all tests, a p value <0.05 was considered statistically significant.

Of 66 patients (56 men; 61 ± 10 years old) initially included in the study, 6 died perioperatively and 6 died during the follow-up period. Hence, the study protocol was completed in the remaining 54 patients (24 patients who had viable myocardium and 30 who had nonviable myocardium). Patients who died perioperatively or during the follow-up were included in the long-term follow-up analysis.

All patients presented with symptoms of heart failure as assessed by median New York Heart Association functional class III (range I to IV). In addition, 42 patients (63%) had accompanying angina pectoris (median Canadian Cardiovascular Society class III, range I to III). Coronary revascularization was performed by CABG. Left anterior descending artery bypass was performed using the left internal mammary artery in 60 patients (90%). Whenever possible, the right internal mammary artery was used to revascularize the right coronary artery; complete coronary revascularization was obtained in all patients.

Analysis of myocardial viability was performed in all patients initially included in the study. Echocardiography at rest showed severe wall motion abnormalities in 617 segments (58%). According to DSE, 229 of 617 severely dysfunctional segments (37%) were viable: 105 (17%) showed a biphasic response, 98 (16%) showed sustained improvement, and 26 (4%) showed worsening of wall motion. The remaining 388 severely dysfunctional segments (63%) were nonviable. A substantial amount of viable myocardium was present in 26 patients (viable), whereas 40 patients had limited or absent viable myocardium (nonviable). Clinical characteristics of viable and nonviable patients were comparable (Table 1), but nonviable patients had a larger number of severely dysfunctional segments.

Over the study period, in viable patients, LVEF increased from 30 ± 7% to 34 ± 9% at 12 ± 3 months and to 35 ± 9% at 4.5 ± 1 years after revascularize-

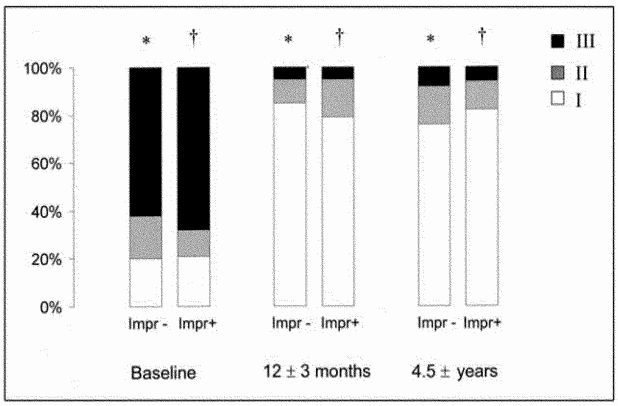

FIGURE 2. Canadian Cardiovascular Society functional class at each study point in patients whose LVEF increased *(Impr+)* and those whose LVEF did not increase *(Impr−)* after revascularization. Canadian Cardiovascular Society class persistently improved in patients whose LVEF increased and those whose LVEF did not increase. *p <0.01: †p <0.01.

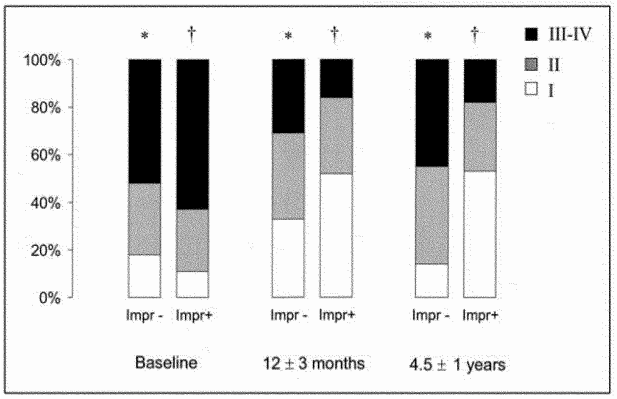

FIGURE 3. New York Heart Association functional class at each study point in patients whose LVEF increased *(Impr+)* and those whose LVEF did not increase *(Impr−)* after revascularization. New York Heart Association class persistently improved in patients whose LVEF increased but not in those whose LVEF did not increase. *p = NS; †p <0.01.

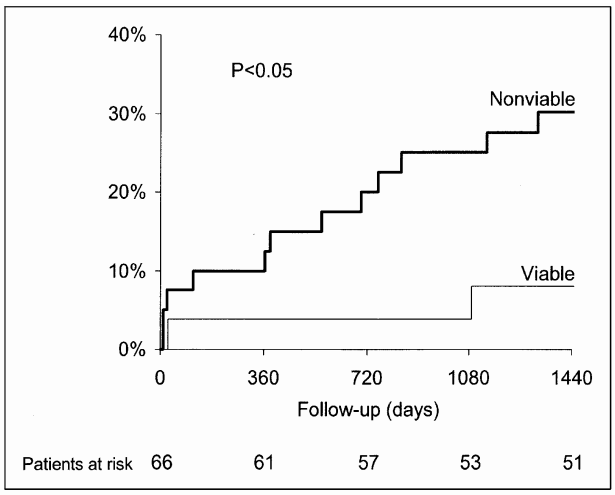

FIGURE 4. Cardiac event rate curves of patients who had and those who did not have a substantial amount of viable myocardium. Those who had viable myocardium had a significantly lower cardiac event rate than did those who had nonviable myocardium.

tion ($p < 0.01$ by analysis of variance). Conversely, in nonviable patients, LVEF did not increase significantly ($p < 0.05$ vs viable patients by analysis of variance). In particular, at 12 ± 3 months after coronary revascularization, LVEF increased ≥5% in 15 of 24 viable patients (63%) and remained at that level at 4.5 ± 1 years in 14 (93%). Three additional viable patients exhibited late recovery of LVEF at 4.5 ± 1 years. Hence, at 4.5 ± 1 year, LVEF increased in 18 of 24 viable patients (75%). LVEF increased at 12 ± 3 months in only 3 of 30 nonviable patients (10%, $p < 0.001$ vs viable patients), whereas LVEF did not increase in most patients at 12 ± 3 months (27 of 30, 90%) and 4.5 ± 1 years (25 of 27, 93%). Changes in LVEF during the study period are shown in Figure 1.

Figures 2 and 3 show the changes in class according to the Canadian Cardiovascular Society and the New York Heart Association, respectively, in patients whose LVEF increased and those whose LVEF did not increase. The Canadian Cardiovascular Society functional class persistently improved in patients whose LVEF increased and in those whose LVEF did not increase (Figure 2). Patients whose LVEF increased showed a persistent improvement in the New York Heart Association class over the study period ($p < 0.01$). Conversely, in patients whose LVEF did not increase, the New York Heart Association class did not improve significantly over the study period (Figure 3). In particular, at the follow-up at 12 ± 3 months, a trend toward an improvement in the New York Heart Association class was present ($p = 0.07$ vs baseline), followed by worsening at 4.5 ± 1 year ($p =$ NS vs baseline).

During follow-up, no patients developed new myocardial infarction. Overall, cardiac events occurred in 15 patients over the study. Cardiac events were significantly more frequent in nonviable than in viable patients (33% and 8%, respectively; $p < 0.05$; Figure 4). The cardiac events that occurred were 1 perioperative death and 1 hospitalization for heart failure during follow-up in viable patients and 5 perioperative deaths, 3 deaths during follow-up, and 5 hospitalizations for heart failure in nonviable patients. Although patients who had functional recovery after revascularization developed cardiac events less frequently than patients who did not have functional recovery (5% and 24%, respectively), this difference was not statistically significant.

• • •

The findings in the present study showed that the increased LVEF observed 12 ± 3 months after revascularization in patients who had viable myocardium persisted into long-term follow-up (≤4.5 ± 1 years) in most patients (93%). Conversely, in the absence of substantial myocardial viability, functional recovery did not occur at 12 ± 3 months or at long-term follow-up. In addition, even 12 ± 3 months after revascularization, some viable patients still exhibited additional improvement in LVEF. This finding confirms that, in patients who have ischemic cardiomy-

opathy and viable myocardium, the time needed to recover left ventricular function is extremely variable[8–10] and that late follow-up studies may be required to accurately evaluate the benefit of revascularization on left ventricular function. The present study also showed that viable patients have a better outcome after revascularization than do nonviable patients. Further studies are needed to clarify the prognostic value of postoperative improvement in LVEF.

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CHAPTER 10

Relation of improvement in LVEF versus improvement in heart failure symptoms after coronary revascularization in patients with ischemic cardiomyopathy

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Relation of Improvement in Left Ventricular Ejection Fraction Versus Improvement in Heart Failure Symptoms After Coronary Revascularization in Patients With Ischemic Cardiomyopathy

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ABSTRACT

Background. It is unclear whether improvement in LVEF after revascularization of patients with viable myocardium always translates in an improvement in heart failure symptoms; this issue was the subject of the current study.

Methods. 116 consecutive patients with ischemic cardiomyopathy and heart failure symptoms, underwent low-high dose dobutamine stress echocardiography to assess myocardial viability. Patients with ≥4 viable segments were considered to have substantial viability (viable patients). Patients with <4 viable segments were considered as nonviable patients. Before and 9-12 months after revascularization, radionuclide ventriculography was performed to assess LVEF improvement (an increase ≥5%); heart failure symptoms (NYHA class) were assessed at baseline and 12 months follow-up.

Results. 55 patients had substantial viability. Follow-up was completed in 100 pts, since 16 died during follow-up. After revascularization, LVEF and NYHA class improved more often in viable as compared to nonviable patients (61% vs 16%, P<0.001 and 76% vs 20%, p<0.001, respectively). The majority (80%) of viable patients with improvement in LVEF after revascularization demonstrated also an improvement in NYHA class. Interestingly, even 15 of 20 viable patients without improvement in LVEF exhibited improvement in NYHA class. On the other hand, most (83%) of nonviable patients who did not improve in LVEF after revascularization failed to improve in heart failure symptoms.

Conclusions. Improvement in LVEF occurs in the majority of viable patients and is accompanied by an improvement in heart failure symptoms; however, some viable patients improve in NYHA class without an improvement in LVEF.

INTRODUCTION

In patients with ischemic cardiomyopathy, assessment of myocardial viability allows identification of patients that may improve in left ventricular ejection fraction (LVEF) after coronary revascularization (1-3). Since LVEF is a strong determinant of prognosis, prediction of improvement in LV function after revascularization is a clinically relevant issue (4-5). However, improvement in heart failure symptoms is also an important end-point after revascularization since it reflects patients' quality of life (6). Various studies, using different techniques to assess myocardial viability, showed that patients with a substantial amount of viable myocardium are likely to improve in LVEF after revascularization (7-12). Some data are available suggesting that a significant improvement in heart failure symptoms is frequently observed after revascularization in patients with substantial viable myocardium but not in patients without viable myocardium (7, 12-15). The majority of the studies however only focused on the change in LVEF after revascularization, and whether improvement in LVEF is always associated with improvement in heart failure symptoms is currently unknown. Also, improvement in symptoms may occur in the absence of improvement of LVEF in viable patients, indicating that the benefit of revascularization extends beyond improvement of function. Accordingly, in the present study, the relationship between viability, on the one hand, and improvement in LVEF and/or heart failure symptoms, on the other hand, was evaluated in patients with ischemic cardiomyopathy undergoing revascularization.

METHODS

Study Population. The study population existed of 116 patients (96 men, mean age 60 ± 9 years) with ischemic cardiomyopathy (LVEF 30 ± 8 %) and symptoms of heart failure who were already scheduled for coronary revascularization. A history of myocardial infarction was present in 107 patients (92%). In these patients, myocardial infarction had occurred ≥6 months before the study. The decision for revascularization was based on clinical grounds (symptoms, presence/absence of ischemia and angiographic findings). Patients with severe (3-4+) mitral regurgitation were not included.

Study Protocol. The study protocol was prospectively designed as follows. Before revascularization, patients underwent dobutamine stress echocardiography (DSE) to assess myocardial viabilty. Radionuclide ventriculography was also performed before and 9 to 12 months after revascularization to assess improvement in resting LVEF. In addition, heart failure symptoms were evaluated before and 9 to 12 months after revascularization. The local ethics committee approved the protocol and all patients gave informed consent to participate to the study.

Dobutamine Stress Echocardiography. All echocardiograms were performed using commercially available equipment (Sonos-5500, Hewlett-Packard, Philips Medical Systems, Eindhoven, The Netherlands) with a second harmonic 1.8-3.6 MHz transducer to optimize endocardial border visualization. After acquisition of resting images, low-high dose DSE (up to 40 μg/kg/min plus 2 mg atropine, if necessary) was performed as described previously (16). Off-line measurement of LV end-diastolic and end-systolic volumes was performed from the resting images by an independent investigator using the biplane Simpson's rule (17). Interpretation of DSE studies was performed off-line from cineloops, displayed side-by-side in a quad-screen format, by 2 experienced observers blinded to the clinical data. Inter- and intra-observer agreement for analysis of DSE studies were 92% and 94% respectively (18). Regional function was scored using a 16-segment-5-point scoring model: 1=normal, 2=mildly hypokinetic, 3=severely hypokinetic, 4=akinetic, 5=dyskinetic (7). Only severely dysfunctional segments (score 3 to 5) were evaluated for the presence of viability. Segments with a sustained improvement in wall motion up to high-dose dobutamine and segments with a biphasic response or worsening of wall motion during DSE were considered viable (7). Segments with unchanged wall motion and segments with akinesia becoming dyskinesia were considered nonviable (7). A substantial amount of viable myocardium was defined as the presence of ≥4 viable segments (7).

Assessment of Left Ventricular Ejection Fraction. Before and 9 to 12 months after revascularization, radionuclide ventriculography was performed to assess LVEF improvement by an independent technique. Radionuclide ventriculography was performed at rest with the patient in the supine position after the administration of 740 MBq of ^{99m}technetium. Images were acquired with a small-field-of-view gamma camera (Orbiter, Siemens Corp, Iselin, NJ, USA), oriented in the 45° left anterior oblique position with a 5-10° caudal tilt. The LVEF was calculated from the 45° left anterior oblique view by an automated technique. An improvement in LVEF ≥5% after revascularization was considered clinically significant (7).

Assessment of Heart Failure Symptoms. Before and 9 to 12 moths after revascularization, structured clinical interviews were performed, by an independent physician blinded to all data, to assess the severity of symptoms of heart failure according to the New York Heart Association (NYHA) criteria.

Statistical Analysis. Continuous data are expressed as mean (SD) and dichotomous data as proportions. Continuous data were compared using the Student's *t* test for paired and unpaired samples as indicated. Comparison of proportions was performed by chi-square analysis. A P value < 0.05 was considered significant.

RESULTS

Study Population. According to DSE, the study population was divided in 2 groups: Group 1 consisted of 55 patients (47%) showing substantial myocardial viability (viable patients) and Group 2 consisted of 61 patients with limited or no myocardial viability (nonviable patients). Coronary revascularization was performed by coronary artery bypass grafting in 43 (78%) patients in Group 1 and in 52 (85%) patients in Group 2 (P=NS). Percutaneous coronary intervention was performed in 12 patients in Group 1 and in 9 patients in Group 2 (P=NS). Complete revascularization was obtained in all patients. Table 1 shows baseline clinical and echocardiographic characteristics of study population. Clinical characteristics and baseline LVEF were similar between the 2 groups of patients, however hypercholesterolemia was more frequently observed in Group 1. Resting echocardiography showed that also the number of severely dysfunctional segments was significantly higher in Group 1, whereas both end-diastolic and end-systolic volumes were comparable between the 2 groups.

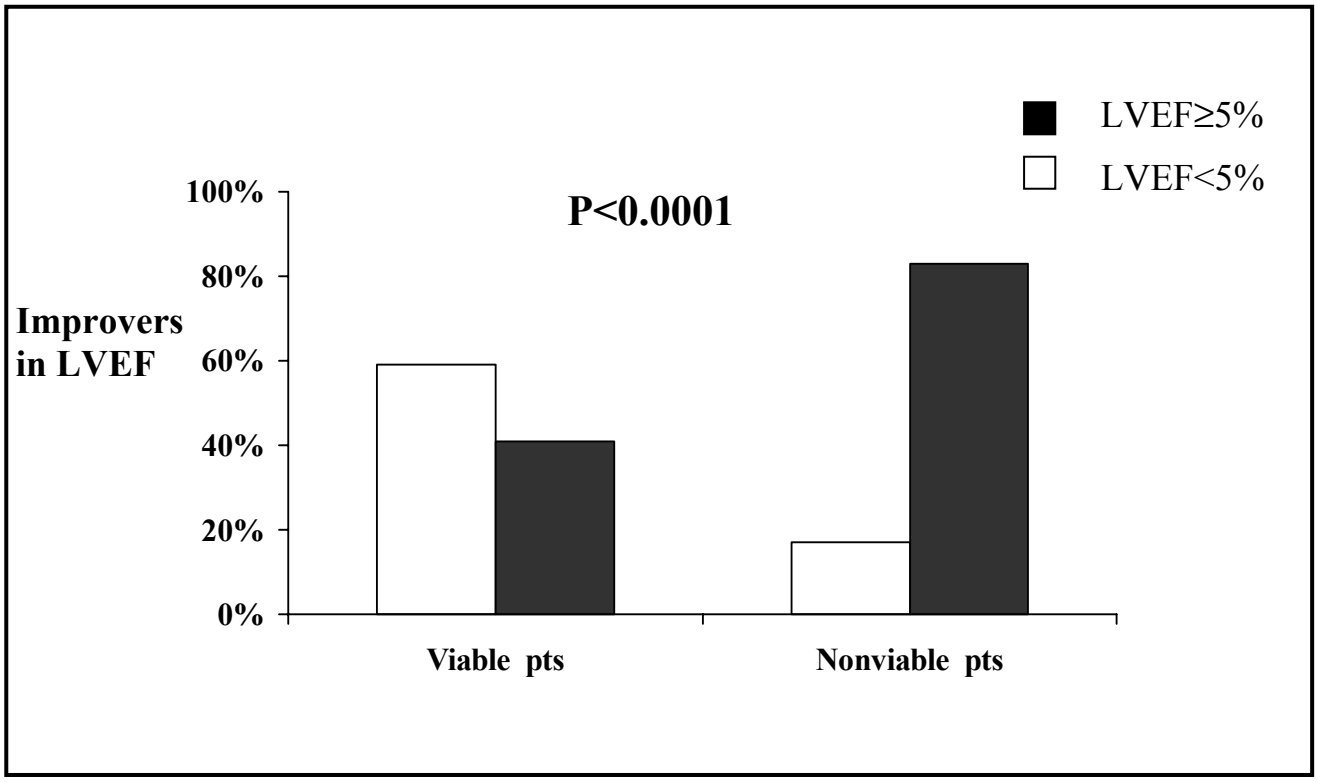
Table 1. Characteristics of the Study Population

Characteristic	Group 1 (55 patients)	Group 2 (61 patients)	P value
Age, years (mean±SD)	60±9	58±10	NS
Men (%)	45 (82%)	51 (84%)	NS
New York Heart Association class (mean±SD)	2.9±0.9	2.6±1	NS
Previous myocardial infarction (%)	49 (89%)	58 (95%)	NS
Stenosed vessels (mean±SD)	2.6±0.7	2.4±0.7	NS
Diabetes mellitus (%)	17 (31%)	11 (18%)	NS
Hypertension (%)	48 (87%)	51 (84%)	NS
Smoking (%)	25 (45%)	21 (34%)	NS
Hypercholesterolemia (%)	16 (29%)	33 (54%)	<0.05
LVEF (mean±SD)	30±8%	30±9%	NS
LV end-diastolic volume, ml (mean±SD)	174±57	181±50	NS
LV end-systolic volume, ml (mean±SD)	121±32	115±45	NS
Dysfunctional segments (mean±SD)	12.8±4	9.4±4	<0.001
Viable segments (mean ± SD)	7.4±2.3	1.4±1.2	<0.001
Nonviable segments (mean ± SD)	5.5±3.3	7.7±3.8	<0.05

LVEF: left ventricular ejection fraction.

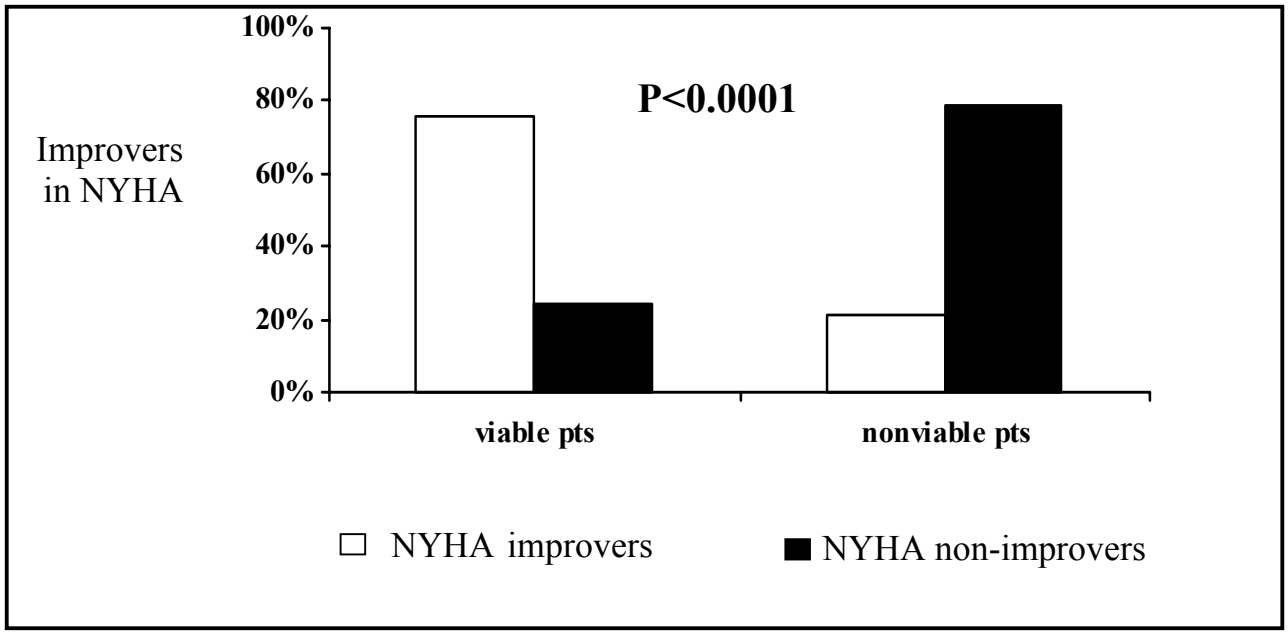
Assessment of Improvement in LVEF and NYHA Class after Revascularization. Sixteen patients died early after revascularization, including 4 patients in Group 1 and 12 patients in Group 2 (P=0.09). In these patients, post-operative evaluation was not available. Therefore improvement in LVEF as well as NYHA class were evaluated in the remaining 100 patients (51 viable and 49 nonviable patients). After revascularization, the LVEF improved slightly in the entire population (from 30±8% to 33±10%, P<0.05), however only 39 patients (39%) showed a clinically significant improvement in LVEF (defined as an increase ≥5%). Viable patients showed a significant improvement in LVEF more frequently (31 patients, 61%) as compared to nonviable patients (8 patients,16%) (Figure 1).

Figure 1



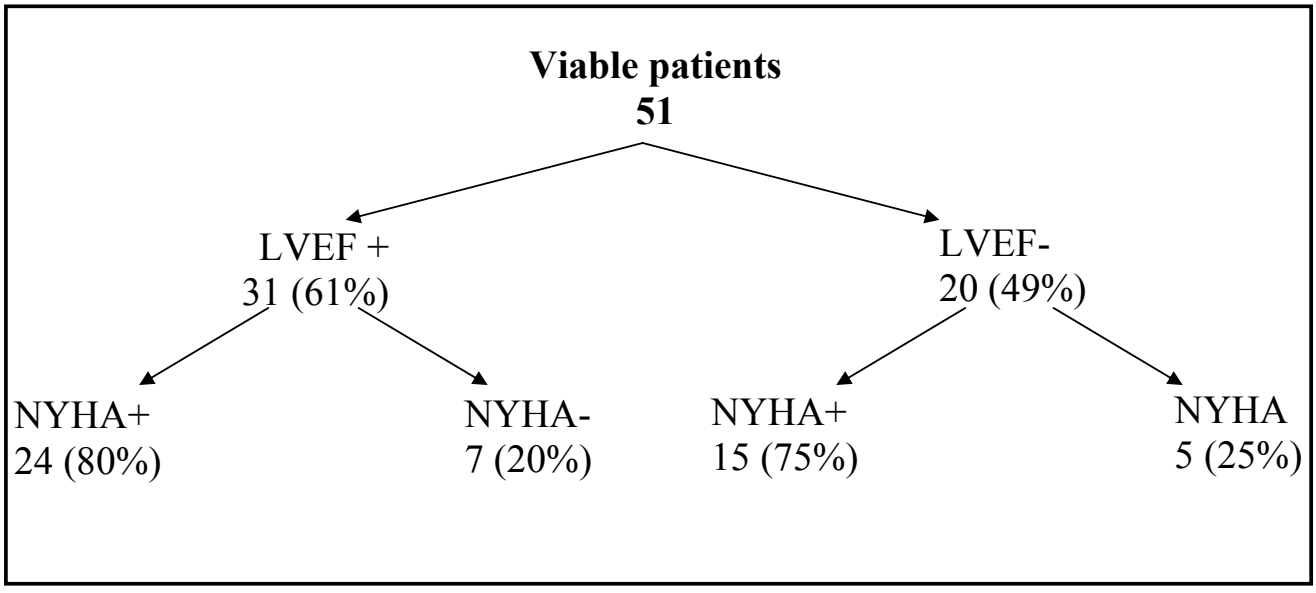
Improvement in NYHA class was also observed in the entire population after revascularization (from 2.7±1 to 2.3±0.9, P< 0.01). In particular, the NYHA class improved in 39 (76%) viable patients as compared to 10 (20%) nonviable patients (P<0.001, Figure 2). Improvement in HF symptoms occurred in 17/23 (74%) patients showing a prevalent (≥4 segments) sustained improvement pattern at DSE and in 16/25 (64%) patients showing a prevalent ischemic response (biphasic response or worsening) at DSE (P=NS).

Figure 2



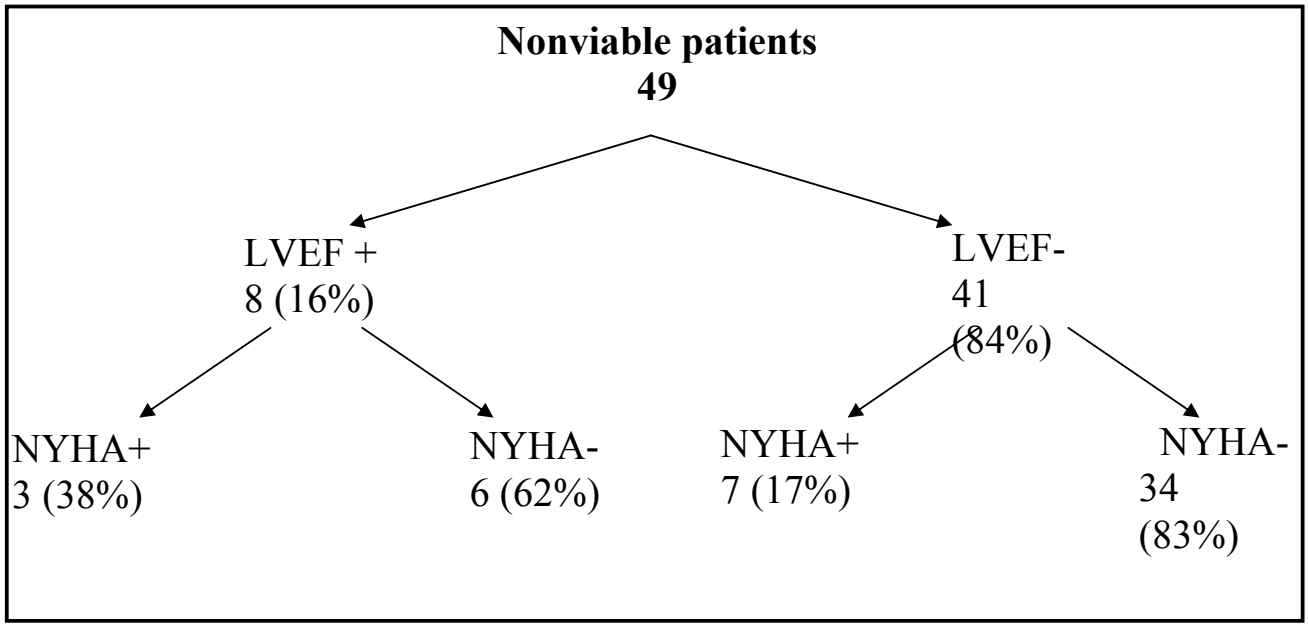
Relation between Improvement in LVEF and Improvement in NYHA Class. Of the 51 viable patients, 31 (61%) had a significant improvement in LVEF; the majority of these patients (80%) exhibited also an improvement in NYHA class. However, of the 20 patients without an improvement in LVEF, the majority (75%) also demonstrated an improvement in NYHA class. The relation between changes in LVEF and NYHA class in the viable patients is shown in Figure 3.

Figure 3



Of the 49 nonviable patients, only 8 (16%) improved in LVEF, whereas 41 (84%) did not improve in LVEF. Of the patients with improvement in LVEF, the majority (62%) did not improve in NYHA class. Of the 41 patients without an improvement in LVEF, the majority (83%) did also not improve in NYHA class. The relation between changes in LVEF and NYHA class in the nonviable patients is shown in Figure 4.

Figure 4



Among nonviable patients, those who had an improvement in HF symptoms showed a lower number of severely dysfunctional segments (6.9±4.2 vs 9.9±3.6, P=0.05) and a smaller extent of scars at DSE (4.6±3.9 vs 8.3±3.5, P=0.01) as compared to those nonviable patients without improvement in HF symptoms. LV volumes and LVEF at baseline were comparable in nonviable patients with and without improvement in NYHA functional class.

DISCUSSION

The observations in the present study illustrate that in patients with viable myocardium, improvement in LVEF after revascularization was accompanied by improvement in heart failure symptoms in the majority of patients (80%). However, the majority of viable patients (75%) without improvement in LVEF also showed an improvement in NYHA class after revascularization, indicating that the benefit of revascularization is beyond improvement in LVEF. In contrast, the vast majority of nonviable patients did not improve in LVEF or NYHA class.

Viability versus Change in LVEF after Revascularization. In patients with ischemic cardiomyopathy, LVEF is a strong determinant of prognosis. Cardiac mortality increases proportionally to the severity of LV dysfunction (4-5). Moreover, although in the last decades medical treatment has improved significantly (due to the use of beta-blockers, ACE-inhibitors and spironolactone), patients with low LVEF still need frequent hospitalizations for worsening of heart failure (19-21). Coronary revascularization may represent a therapeutic option in this population (8). Several studies have demonstrated that assessment of myocardial viability may help to identify those patients who are likely to benefit from revascularization in terms of LVEF, heart failure symptoms and prognosis. From these studies it has become clear that patients with a substantial amount of viable myocardium (at least 25% of the LV) have a high likelihood of improvement in LVEF after revascularization, whereas patients with minimal or no viability are unlikely to benefit from revascularization in terms of improvement in LVEF (2, 3, 7-12, 22-23). Similar results were obtained in the current study: 61% of viable patients improved in LVEF, whereas 84% of nonviable patients did not improve in LVEF. However, only few studies have assessed both LVEF and heart failure symptoms after coronary revascularization (7,12, 22-24), and therefore the relationship between improvement in LVEF and heart failure symptoms after revascularization is unclear: does an improvement in LVEF always result in improvement of symptoms, and can symptoms improve in the absence of improvement in LVEF?

Viability versus Change in Symptoms after Revascularization. The findings in the present study illustrate that an improvement in NYHA class after revascularization occurs more frequently in viable patients as compared to nonviable patients (76% versus 20%, respectively). In addition, the relation between improvement in LVEF and heart failure symptoms was evaluated on a patient basis. The results indicate that 80% of viable patients with improvement in LVEF after revascularization also exhibit an improvement in NYHA class. It appears that if improvement in LVEF is accomplished, improvement in heart failure symptoms frequently occurs. This is an important finding indicating that improvement in LVEF ≥5% after revascularization of viable patients is clinically meaningful since it translates in improvement in NYHA functional class in the majority of patients. On the other hand, the present study demonstrates that in viable patients improvement in heart failure symptoms may occur even in the absence of improvement in LVEF after revascularization. Whether viable patients without improvement in contractile function after revascularization may show improvement in heart failure symptoms was not evaluated in previous studies (7, 12, 22-24). Only Samady et al have reported that improvement in NYHA class occurred both in patients with and without improvement in LVEF after revascularization (24).

However in that study, information on myocardial viability was lacking and also assessment of LVEF was performed early (within 6 weeks, median 7 days) after revascularization; some patients may need more time to improve in LVEF after revascularization (9). Still, the results in the current study demonstrate that after revascularization, 75% of viable patients without improvement in LVEF improved in NYHA class. This observation emphasizes that the benefit of revascularization of viable patients extends beyond improvement of function. The majority (80%) of nonviable patients did not improve in symptoms; these patients did also not improve in LVEF after revascularization (Figure 2). This observation further strengthens the hypothesis that improvement in symptoms is not a placebo-effect but is indeed related to the presence of substantial viability.

Study Limitations. Some limitations of the present study need to be addressed. First, coronary angiography was not repeated after coronary revascularization. Therefore, graft occlusion or restenosis may have prohibited improvement in LVEF and heart failure symptoms. Heart failure symptoms were evaluated using the NYHA classification; this is to some extent a subjective classification which could potentially influence the results. Evaluation of six minute walking distance, VO_2 max and quality of life may represent more objective parameters. However, the sharp contrast between the percentage of improvers in NYHA class in the viable patients as compared to the nonviable patients is reassuring that the NYHA class is clinically useful.

Conclusions. The findings in the present study showed that improvement in LVEF after coronary revascularization translates in improvement in heart failure symptoms in the majority of viable patients. However, the majority of the viable patients without an improvement in LVEF also exhibited an improvement in NYHA class, emphasizing that the clinical benefit of revascularization of viable myocardium is more than just improvement in function.

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CHAPTER 11

Long-term prognostic value of viability and ischemia during dobutamine stress echocardiography in patients with ischemic cardiomyopathy undergoing revascularization

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Long-term Prognostic Value of Myocardial Viability and Ischemia During Dobutamine Stress Echocardiography in Patients With Ischemic Cardiomyopathy Undergoing Coronary Revascularization

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ABSTRACT

Background. In patients with ischemic cardiomyopathy, the presence of jeopardized myocardium (including viability and/or ischemia) is associated with favourable prognosis after revascularization. The relative merits of viability and ischemia for prognosis after revascularization are unclear, and this was evaluated in the current study.

Methods. Low-high dose dobutamine stress echocardiography (DSE) was performed before revascularization in 128 consecutive patients with ischemic cardiomyopathy (mean left ventricular ejection fraction (LVEF) 31±8%). Viability (defined as contractile reserve, CR) and ischemia were assessed during low- and high-dose dobutamine infusion, respectively. Cardiac death was evaluated during a 5-year follow-up. Clinical, angiographic and echocardiographic data were analyzed to identify predictors of events.

Results. Univariable predictors of cardiac death were the presence of multi-vessel disease (HR 0.21, P<0.001), baseline LVEF (HR 0.90, P<0.0001), the wall motion score index (WMSI) at rest (HR 4.02, P=0.0006), low-dose (HR 7.01, P<0.0001) and peak-dose DSE (HR 4.62, P<0.0001), the extent of scar (HR 1.39, P<0.0001) and the presence of CR in ≥25% of dysfunctional segments (HR 0.34, P=0.02). The best multivariable model to predict cardiac death included the presence of multi-vessel disease, the WMSI at low-dose DSE and the presence of CR in ≥25% of the severely dysfunctional segments (HR 9.62, P<0.0001). Inclusion of ischemia to the model did not provide additional predictive value.

Conclusions. The findings in the present study illustrate that in patients with ischemic cardiomyopathy, the extent of viability (CR) is a strong predictor of long-term prognosis after revascularization. Ischemia did not add significantly in predicting outcome.

INTRODUCTION

Patients with chronic coronary artery disease and left ventricular (LV) dysfunction who undergo revascularization represent a high risk population. The prognosis is strongly related to the severity of LV dysfunction with a higher annual mortality in patients with impaired LV function (1-3). Conversely, dysfunctional but jeopardized (viable and/or ischemic) myocardium may improve in contractile function after revascularization (4). Several studies demonstrated that when a substantial amount of viable and/or ischemic myocardium is present, patients may benefit from revascularization since improvement in LV ejection fraction (LVEF) is likely to occur (5-9). Therefore, assessment of myocardial viability/ischemia has become important in the decision to revascularize patients with ischemic cardiomyopathy. Moreover, it has been demonstrated that in patients with viable and/or ischemic myocardium, the prognosis is superior in patients undergoing revascularization as compared to patients who are treated medically (10-15). An important issue that remains to be determined is to what extent viability on the one hand and ischemia on the other hand determine the prognosis after revascularization. Recent data suggest that viability may be more important for prognosis after revascularization as compared to ischemia (12-15). Moreover, studies with long-term follow-up after revascularization are scarce. Accordingly, we have evaluated the relative merits of viability and ischemia (using dobutamine stress echocardiography, DSE) for prediction of long-term prognosis after revascularization, over a 5-year follow-up period.

METHODS

Patient Population. The study population existed of 128 consecutive patients (105 men, 61$\pm$9 years) with ischemic cardiomyopathy and heart failure symptoms. Patients were already scheduled for revascularization according to clinical criteria (symptoms, presence/absence of ischemia and angiographic findings). Patients with acute coronary syndromes and/or decompensated heart failure (defined as the need for intravenous inotropic support to sustain an adequate hemodynamic status) were not included in the study.

Study Protocol. The study was prospectively designed to elucidate the long-term prognostic value of viability and ischemia in patients with ischemic cardiomyopathy who underwent coronary revascularization. Before revascularization (within 1 month), 2-dimensional echocardiography at rest was performed to identify baseline regional wall motion abnormalities, followed by low-high dose DSE to assess myocardial viability and ischemia in dysfunctional regions. Also, LVEF was assessed before revascularization by radionuclide ventriculography (RNV). Cardiac events (cardiac death, myocardial infarction and hospitalization for heart failure) were obtained up to 5 years of follow-up. The local ethics committee approved the protocol and all patients gave informed consent.

Resting and Low-High Dose Dobutamine Stress Echocardiography. Resting and DSE studies were performed using a Sonos-5500 imaging system (Philips Medical Systems, Eindhoven, The Netherlands) equipped with a 1.8 MHz transducer using second harmonic imaging to optimize endocardial border visualization. Standard parasternal and apical views of the LV were obtained (16). LV end-diastolic and end-systolic volumes (EDV and ESV, respectively) were measured from the 2- and 4-chamber views, using the biplane Simpson's rule (16). All measurements were performed off-line by 1 experienced reader blinded to the patients' data. Low-high dose DSE (up to 40 μg/kg/min plus 2 mg atropine, if necessary) was performed as described previously (17). Medications, in particular beta-blockers, were not stopped before DSE. Interpretation of DSE studies was performed off-line from cineloops, by 2 experienced observers blinded to the clinical data. Inter- and intra-observer agreement for analysis of DSE studies were reported previously (92% and 94% respectively) (18). Regional function was scored using a 16-segment, 5-point scoring model: 1=normal, 2=mildly hypokinetic, 3=severely hypokinetic, 4=akinetic, 5=dyskinetic (17). The wall motion score index (WMSI) at rest, low-dose (10 μg/kg/min) and peak-dose DSE was calculated by dividing the summed wall motion score at each step by the number of segments.

Assessment of Myocardial Viability and Ischemia. Myocardial viability was evaluated only in severely dysfunctional segments (score 3 to 5). Segments showing contractile reserve (CR) were considered viable (5, 19). CR was defined as an improvement by at least 1 point in the wall motion score, during DSE, without further worsening (5, 19). Dyskinesia becoming akinesia was not considered as CR (5, 19). The WMSI at low-dose DSE was considered a measure of CR. The lower the WMSI during low-dose DSE, the more extensive the CR. Ischemia was defined as the presence of a biphasic response (improvement in wall motion at low-dose followed by worsening at high-dose dobutamine) or a worsening in wall motion at low- or high-dose dobutamine infusion (without any improvement of contraction at any stage) (5, 19). Nonviable myocardium (scar) was defined as severely dysfunctional myocardium without change during DSE; akinetic segments becoming dyskinetic were also considered scar tissue (5, 19). Patients showing CR in ≥25% of severely dysfunctional segments were considered to have substantial viability (CR+ patients). Conversely, patients showing CR in <25% of dysfunctional segments were considered to have minimal or no viability (CR- patients). This cutoff value was based on previous work using ROC curve analysis showing that recovery of function is likely to occur when ≥4 viable segments are present (5). Similarly, extensive ischemia was defined as the presence of ≥4 ischemic segments.

Long-term Follow-up. The long-term follow-up was performed by chart review and telephone contact by an independent physician, blinded to all data. Events included: cardiac death, myocardial infarction and hospitalization for heart failure. Cardiac death was defined as sudden death, death due

to acute myocardial infarction or heart failure. Myocardial infarction was defined according to classical criteria (symptoms, electrocardiographic changes and elevated cardiac enzymes). Hospitalization for heart failure was defined according to the hospital discharge diagnosis.

Statistical Analysis. Continuous data were expressed as mean ± SD and compared using the paired/unpaired Student's *t*-test as appropriate. Percentages for categorical variables were rounded and compared using the chi-square test. Repeated measures were compared by ANOVA analysis. Uni- and multivariable logistic regression analysis were performed to identify pre-operative predictors of cardiac death and composite cardiac events (cardiac death, myocardial infarction and hospitalization for heart failure). The variables included in the analysis were: age, gender, diabetes, hypertension, hypercholesterolemia, smoking, medications (beta-blockers, angiotensin covering enzyme and nitrates), New York Heart Association (NYHA) functional class, presence of multi-vessel disease, Q wave myocardial infarction, mode of revascularization, additional procedures in combination with surgical revascularization (aneurysmectomy, mitral valve repair), baseline LVEF, resting LVEDV and LVESV and WMSI at rest. In addition, the following continuous variables were included in the analysis: WMSI at low-dose and number of segments with CR (indicating the extent of viable myocardium); WMSI at peak-dose DSE, number of segments with a biphasic response or worsening of the wall motion and total number of ischemic segments (indicating the extent of ischemic myocardium); number of scar segments (indicating the extent of scar tissue). Finally, the presence of CR in ≥25% of severely dysfunctional segments (as categorical variable) was also included in the analysis. All variables, independently from the results of the univariable analysis, entered the multivariable stage. Multivariable regression was then performed by a stepwise backward deletion. All variables with a P-value <0.25 remained in the final model. The cardiac event rate during the 5-year follow-up was evaluated using Kaplan-Meier curve analysis. Differences between curves were tested with the log-rank chi-square statistics. For all tests, a P-value <0.05 was considered significant.

RESULTS

Study Population. All patients presented with heart failure symptoms and 62% had associated angina pectoris. The NYHA and Canadian Cardiovascular Society class were 2.6±1.1 and 2.3±1.1, respectively. A history of myocardial infarction was present in 118 patients (92%). In these patients, myocardial infarction had occurred >6 months before the study entrance. Medication included angiotensin converting enzyme inhibitors in 69%, beta-blockers in 59% and nitrates in 72% of patients. Coronary revascularization was performed by percutaneous transluminal coronary angioplasty in 25 patients (19%) and by coronary artery bypass grafting in 103 patients (81%).

The left internal mammary artery was used in 98% of the patients. Mitral valve repair and LV aneurysmectomy (11 patients) were additionally performed in combination in 2 and 11 patients respectively.

Myocardial Viability and Ischemia. During low-high dose DSE the target heart rate (85% of the age-predicted maximum heart rate) was achieved in 113 patients (88%). In particular, 68 of 76 (89%) patients using beta-blockers and 45 of 52 (86%) patients not using beta-blockers achieved the target heart rate. Analysis of the DSE studies showed that CR was present in 523 (36%) severely dysfunctional segments, whereas in the remaining 874 (64%) segments CR was absent. Similar proportions of the patients with and without beta-blockers showed CR during low-dose DSE (34% vs 31%, respectively, P=NS). Ischemia was present in 257 segments (49%) with CR (biphasic response) and in 58 segments (7%) without CR that showed a worsening of the wall motion during high-dose dobutamine infusion. Extensive CR (in ≥25% of the dysfunctional segments) was present in 64 patients (CR+ patients) whereas the remaining 64 patients had minimal or no CR (CR- patients). Table 1 summarizes the clinical, angiographic and procedural characteristics of the 2 groups.

Table 1. Characteristics of CR+ and CR- Patients

Characteristics	CR+ 64 Patients	CR- 64 Patients	P-value
Male (%)	46 (72)	54 (84)	NS
Age, years, mean±SD	62±9	62±10	NS
CCS class, mean±SD	2.1±1.1	2.4±0.9	0.03
NYHA class, mean±SD	2.7±1.0	3.1±0.8	NS
History of MI (%)	57 (89)	61 (95)	NS
Diabetes (%)	10 (15)	5 (8)	NS
Smoking (%)	32 (50)	44 (69)	0.05
Hypertension (%)	39 (61)	53 (83)	<0.05
Hypercholesterolemia (%)	25 (39)	31 (48)	<0.001
Stenotic vessels, n , mean±SD	2.5±0.7	2.4±0.7	NS
Previous CABG (%)	15 (23)	6 (9)	NS
LVEF %, mean±SD	30±8	31±9	NS
Aneurismectomy (%)	5 (8)	6 (9)	NS
PTCA (%)	15 (23)	10 (17)	NS
On-pump CABG	49 (77)	54 (83)	NS
Complete revascularization	63 (98)	62 (97)	NS

CABG: coronary artery bypass graft; CR: contractile reserve; CCS: Canadian Cardiovascular Society; LVEF: left ventricular ejection fraction; NYHA: New York Heart Association; PTCA: percutaneous transluminal coronary angioplasty.

In addition, 55 CR+ (86%) and 17 CR- (27%) patients showed at least 1 ischemic segment during high-dose dobutamine infusion. Extensive ischemia was present in 34 (53%) CR+ and 4 (6%) CR- patients. In CR+ patients, the WMSI improved from 3.0±0.5 to 2.5±0.6 at low-dose and deteriorated to 2.9±0.6 at high-dose DSE, respectively (P<0.0001). In CR- patients, the WMSI was 2.7±0.7 at

rest, 2.5±0.7 at low-dose and 2.7 ±0.6 at high-dose DSE (P<0.001). The deltas in WMSI during low-high dose DSE in the 2 groups are shown in Table 2. In CR+ patients the deltas at low- and high-dose DSE were significantly higher as compared to CR- patients.

Table 2. Echocardiographic Characteristics of CR+ and CR- Patients

Characteristics	CR+ 64 Patients	CR- 64 Patients	P-value
LV end-diastolic volume, ml, mean±SD	176±61	179±48	NS
LV end-systolic volume, ml, mean±SD	122±54	113±44	NS
WMSI at rest, mean±SD	3.0±0.5	2.7±0.7	<0.001
Scar segments, n, mean±SD	5.4±2	7.3±4	<0.01
Viable segments, n, mean±SD	7.21±2	1.7±1	<0.001
Δ low-dose WMSI - rest WMSI	-0.56±0.23	-0.15±0.24	<0.0001
Δ peak-dose WMSI - low-dose WMSI	0.45±0.42	0.14±0.31	<0.0001

CR: contractile reserve; LV: left ventricular; WMSI: wall motion score index.

Follow-up. During the 5-year follow-up period, cardiac death occurred in 27 patients (21%). In 9 patients (2 CR+ patients [3%] and 7 CR- patients, [11%], P=NS) cardiac death had occurred in the early postoperative period (<30 days). In addition, 6 patients (4%) had non-cardiac death. In the survival analysis, these 6 patients were considered event-free and were censored at their date of death. Three patients (2%) experienced a new acute myocardial infarction and 15 (12%) patients were hospitalized for severe heart failure.

Predictors of Cardiac Death. Predictors of cardiac death are shown in Table 3. Among the clinical variables (Table 3) the baseline LVEF (HR 0.90, P<0.0001) and the presence of multi-vessel disease (HR 0.21, P<0.001) were univariable predictors of cardiac death. Also diabetes mellitus showed a trend towards a higher rate of cardiac death (HR 2.42, P=0.07). Among the echocardiographic variables (Table 3), univariable predictors of cardiac death were the WMSI at rest (HR 4.02, P=0.0006), low-dose (HR 7.01, P<0.0001) and peak-dose DSE (HR 4.62, P<0.0001). Also the extent of scar was predictive of cardiac death (HR 1.39, P<0.0001), whereas the presence of CR in ≥25% of severely dysfunctional segments was associated with a favourable prognosis (HR 0.34, P=0.02). The extent of ischemia was not predictive of cardiac death (HR 0.60, P=0.19). At multivariate analysis, the presence of multi-vessel disease (Chi-square 12.8, HR 0.20, P<0.001), the WMSI at low-dose DSE (Chi-square 18.2, HR 7.1, P<0.0001) and the presence of CR in ≥25% of severely dysfunctional segments (Chi-square 4.6, HR: 0.30, P=0.03) were the independent

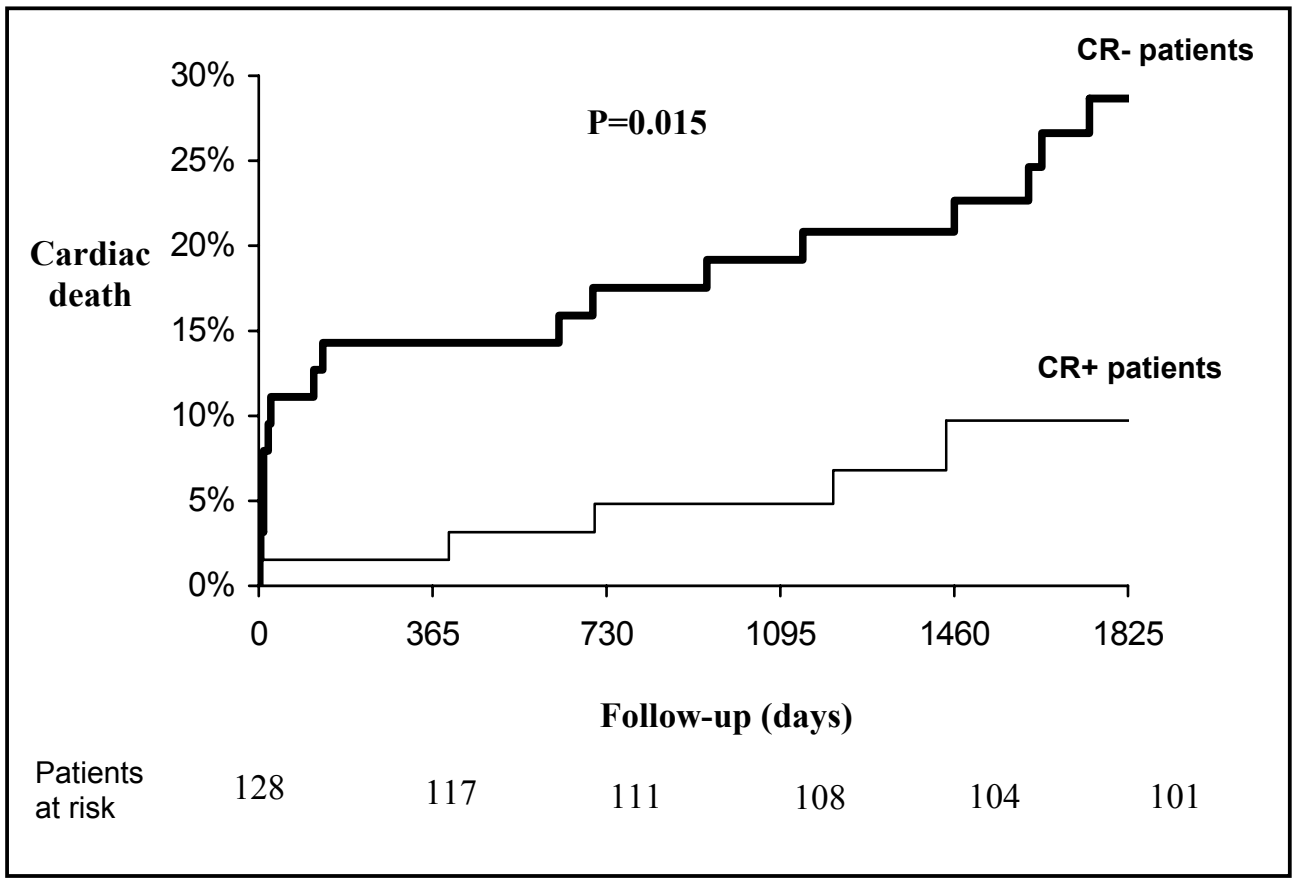
predictors. A lower cardiac death risk was associated with the presence of multi-vessel disease, a lower WMSI during low-dose DSE and with the presence of CR in ≥25% of dysfunctional segments. The best model to predict cardiac death included the presence of multi-vessel disease, the WMSI at low-dose DSE and the presence of extensive CR (Chi-square 43.96, HR 9.62 CI 3.99-23.14, P<0.0001). Inclusion of the extent of ischemia to the model did not provide any additional predictive value. Also, the extent of scar tissue did not add significant prognostic information. During the 5-year follow-up, cardiac death occurred less frequently in CR+ patients as compared with CR- patients (10% vs 29%, P=0.015, Figure 1).

Table 3. Predictors of Cardiac Death

	Univariable analysis			Multivariable analysis		
	HR	**95% CI**	**P value**	**HR**	**95% CI**	**P-value**
Age	1.008	0.97-1.05	NS			
Gender	0.56	0.24-1.34	NS			
Hypertension	2.79	0.82-10.41	NS			
Hypercholesterolemia	0.92	0.36-2.34	NS			
Diabetes	2.42	0.91-6.42	0.08			
Smoking	1.21	0.45-3.32	NS			
Family history	0.98	0.37-2.64	NS			
Previous CABG	0.17	0.10-1.27	NS			
ACE-inhibitors	1.93	0.73-5.11	NS			
Beta-blockers	0.55	0.26-1.17	NS			
Nitrates	1.15	0.40-3.37	NS			
NYHA class	1.05	0.41-2.67	NS			
Q wave myocardial infarction	0.54	0.24-1.24	NS			
Multi-vessel disease	0.21	0.09-0.49	<0.001	0.20	0.08-0.48	<0.001
Mode of revascularization (CABG)	0.64	0.24-1.7	NS			
LVEF	0.90	0.86-0.95	<0.0001			
LV end-diastolic volume	1.006	0.99-1.01	NS			
LV end-systolic volume	1.009	1-1.02	0.05			
WMSI at rest	4.02	1.82-8.91	<0.001			
WMSI at low-dose dobutamine	7.01	3.12-15.78	<0.0001	9.12	3.80-21.92	<0.0001
WMSI at peak-dose dobutamine	4.62	2.15-9.96	<0.0001			
Scar segments	1.39	1.20-1.60	<0.0001			
Segments with biphasic response	0.93	0.76-1.13	NS			
Segments with worsening	0.83	0.50-1.36	NS			
Total ischemic segments	0.60	0.28-1.30	NS			
Segments with CR	0.88	0.76-1.01	0.08			
CR ≥25%	0.34	0.13-0.84	0.02	0.30	0.12-0.74	<0.01

ACE: angiotensin converting enzyme; CABG: coronary artery bypass graft; CR: contractile reserve; LVEF: left ventricular ejection fraction; NYHA: New York Heart Association; WMSI: wall motion score index.

Figure 1



Predictors of Total Cardiac Events. Table 4 summarizes uni- and multivariable predictors of cardiac events (death, myocardial infarction and hospitalization for heart failure). Several univariable predictors were identified, including baseline LVEF, multi-vessel disease, diabetes, surgical revascularization, WMSI at rest, low-dose and peak-dose DSE, number of scar segments and CR in ≥25% of dysfunctional segments. At multivariable analysis only diabetes, surgical revascularization, the WMSI at low-dose DSE and the presence of extensive CR remained predictive of cardiac events. Ischemia did not add significantly to the model. During the 5-year follow-up, cardiac events occurred less frequently in CR+ patients as compared with CR- patients (24% vs 39%, P=0.04).

Table 4. Predictors of Cardiac Events

	Univariable analysis			Multivariable analysis		
	HR	**95% CI**	**P value**	**HR**	**95% CI**	**P-value**
Age	0.98	0.95-1.01	NS			
Gender	0.53	0.57-2.90	NS			
Hypertension	2.79	0.82-10.41	NS			
Hypercholesterolemia	0.92	0.36-2.34	NS			
Diabetes	2.47	1.14-5.39	0.02	2.39	1.01-5.69	0.04
Smoking	1.21	0.45-3.32	NS			
Family history	0.98	0.37-2.64	NS			
Previous CABG	1.21	0.53-2.73	NS			
ACE-inhibitors	1.93	0.73-5.11	NS			
Beta-blockers	0.65	0.36-1.16	NS			
Nitrates	1.15	0.40-3.37	NS			
NYHA class	1.53	0.75-3.10	NS			
Q wave myocardial infarction	0.70	0.35-1.39	NS			
Multi-vessel disease	0.38	0.18-0.80	<0.05			
Mode of revascularization (CABG)	0.42	0.21-0.84	0.01	0.27	0.13-0.55	0.0004
LVEF	0.93	0.89-0.96	<0.0001			
LV end-diastolic volume	1.005	0.99-1.01	NS			
LV end-systolic volume	1.006	0.99-1.01	0.08			
WMSI at rest	2.34	1.36-4.01	0.002			
WMSI at low-dose dobutamine	3.41	1.90-6.13	<0.0001	6.03	2.97-12.22	<0.0001
WMSI at peak-dose dobutamine	2.89	1.65-5.07	0.0002			
Scar segments	1.24	1.121.37	<0.0001			
Segments with biphasic response	0.95	0.83-1.01	NS			
Segments with worsening	1.10	0.84-1.44	NS			
Total ischemic segments	0.98	0.54-1.76	NS			
Segments with CR	0.92	0.83-1.02	NS			
CR ≥25%	0.51	0.27-0.97	0.04	0.29	0.14-0.62	0.001

Abbreviations as in Table 3.

DISCUSSION

In the present study, the long-term prognostic value of viability and ischemia has been evaluated in a large group of patients with ischemic cardiomyopathy who underwent coronary revascularization. The presence of a considerable amount of viability (CR) during low-dose DSE was a strong predictor of long-term prognosis being associated with a favourable outcome. The extent of ischemia did not add significantly to the prediction of cardiac events.

Prognostic Implications of Viable Myocardium in Patients with Ischemic Cardiomyopathy.

Several studies have demonstrated that patients with ischemic cardiomyopathy and viable myocardium are at high risk for cardiac events when treated medically (10-15). Williams et al studied 108 patients with ischemic cardiomyopathy who were treated medically and observed that

cardiac events occurred more frequently in patients with viable or ischemic myocardium than in patients with nonviable myocardium (43% vs 8%, P=0.01) (20). The presence of viable or ischemic myocardium during low-high dose DSE was predictive of cardiac events during the 16±8 months of follow-up (20). These preliminary results were confirmed in a recent meta-analysis by Allman et al, showing that in patients who were treated medically the cardiac death rate was higher in patients with viable myocardium than in nonviable patients (16% vs 6% respectively, P=0.001) (15). On the other hand, several studies have demonstrated a favourable prognosis in patients with viable myocardium undergoing coronary revascularization (5, 12-14, 21). Meluzin et al showed that patients with >6 dysfunctional but viable segments had a better event-free survival during a 20±8 months of follow-up as compared to patients with <6 viable segments (13). Afridi et al demonstrated that the presence of myocardial viability was the only multivariable predictor of good outcome after revascularization, after correction for age, severity of the coronary disease and LVEF (21). Finally, Allman et al showed a lower cardiac death rate in viable as compared to nonviable patients undergoing revascularization (3.2% vs 7.7% respectively, P<0.0001) (15). However, in these previous studies, the relative prognostic value of viability and ischemia was not evaluated. Therefore, it is still unclear whether viability or ischemia predominantly determines the prognosis of patients with ischemic cardiomyopathy undergoing revascularization.

Relative Prognostic Value of Viability and Ischemia. ***Previous studies.*** Since viability and ischemia represent different aspects of jeopardized myocardium it can be hypothesized that they may differently affect prognosis. In a previous study by Picano et al, including 314 patients with acute myocardial infarction who were treated medically, ischemia at high dose DSE was associated with a higher cardiac death rate during the 1 year of follow-up, whereas viability without ischemia (sustained CR) showed a protective effect on survival (22). Similar findings were reported by Smart et al in patients with chronic LV dysfunction treated with medical therapy (23). Data on the relative prognostic value of viability and ischemia in patients undergoing revascularization are scant (24-27). Pasquet et al demonstrated that the presence of viability (indicated by CR during low-dose DSE), but not ischemia, was a strong predictor of good outcome after revascularization (24).

Similarly, Sicari et al demonstrated that the larger the extent of viability, the lower the likelihood of cardiac death (25-26). However, in these 2 studies, a low-dose dobutamine infusion protocol was applied, limiting a complete estimation of ischemia. More recently, Sawada et al used low-high dose DSE allowing for the assessment of viability and ischemia (27). The authors demonstrated that the presence of myocardial viability was associated with a favourable outcome after revascularization, whereas ischemia was not predictive of prognosis (27). In particular, the WMSI during low-dose

dobutamine (a measure of myocardial viability) was predictive of outcome after revascularization, whereas the WMSI during high-dose dobutamine (a measure of ischemia) was not predictive (27).

Findings in the current study. The findings in the present study are in line with the observations by Sawada et al (27). The results confirmed that low-dose WMSI was a strong predictor of cardiac events, whereas the presence of ischemia did not add significantly. In addition, the presence of a substantial amount of viability (CR≥ 25% of dysfunctional segments) was also predictive of outcome. In particular, the cardiac death rate was 10% in patients with CR ≥25% as compared to 29% in patients with CR< 25% (Figure 1). Also the composite end-point of cardiac death, myocardial infarction and hospitalization for heart failure occurred less frequently in patients with CR ≥25%. The predictive value of viability was superior to that provided by clinical characteristics, severity of LV dysfunction, extent of coronary artery disease and resting echocardiographic variables. Indeed, although smoking, hypertension, and hypercholesterolemia were more common in CR- patients (Table 1), these variables were not predictive for outcome in the regression analyses. Among the clinical characteristics, only diabetes was predictive for the composite end-point, but not for cardiac death. At univariable analysis, baseline LVEF was inversely related to cardiac death risk and the WMSI at rest and the LVESV showed a positive relation to cardiac death risk. Also the extent of scar and the WMSI at peak-dose DSE were univariable predictors of outcome. However, these variables were no longer predictive in the multivariable analysis when viability was included. The best multivariable model to predict cardiac death included the presence of multi-vessel disease, the WMSI at low-dose DSE and the presence of CR ≥25% of severely dysfunctional segments (Chi-square 43.96, HR 9.62). Addition of ischemia did not improve the final model to predict prognosis. These findings, together with the observations by Sawada et al, suggest that ischemia is not the main determinant of prognosis in patients with ischemic cardiomyopathy undergoing revascularization and that viability plays a major role. In addition, the extent of scar was not predictive in the multivariable analysis, illustrating that the extent of viability is more important than the extent of scar for long-term prognosis after revascularization. Although data from prospective, randomized trials are still awaited, it appears that in the presence of substantial viability, patients should be considered for revascularization. In these patients the long-term outcome is mainly determined by revascularization of dysfunctional but viable myocardium, and a large extent of viability is associated with a superior long-term outcome.

Study Limitations. Follow-up coronary angiography was not routinely performed. Therefore, graft occlusion or restenosis could not be excluded. Also, in the design of the study only patients already scheduled to revascularization were included and were followed prospectively.

Since patients who were treated medically were not included, a comparison between revascularized and non-revascularized patients was not available.

Additional end-points of coronary revascularization such as improvement of LVEF or LV volumes were not evaluated in the current study, which is a limitation.

Finally, we used DSE with second harmonic imaging to assess myocardial viability. Although a very high accuracy in the detection of viable myocardium has been reported with DSE, still the subjective and semiquantitative analysis of wall motion by DSE forms a limitation of the study (18). Tissue Doppler imaging and strain/ strain-rate analysis allows quantitative and objective evaluation and quantification of wall motion and may further improve the detection of myocardial viability (28).

Conclusions. In patients with ischemic cardiomyopathy, the presence and extent of myocardial viability are strong determinants of long-term outcome after revascularization. The presence of ischemia did not contribute significantly to the prediction of long-term prognosis.

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CHAPTER 12

Prognosis of patients with ischemic cardiomyopathy after coronary revascularization: relation to viability and improvement in LVEF

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Prognosis of Patients With Ischemic Cardiomyopathy after Coronary Revascularization: Relation to Viability and Improvement in LVEF

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ABSTRACT

Objective. To evaluate the prognosis of viable patients with and without improvement of left ventricular ejection fraction (LVEF) after coronary revascularization.

Background. In patients with ischemic cardiomyopathy and viable myocardium, LVEF does not always improve after revascularization. Whether this may affect prognosis is unclear.

Methods. Before revascularization, radionuclide ventriculography (RNV) and dobutamine stress echocardiography (DSE) were performed to assess LVEF and myocardial viability, respectively. Nine to 12 months after revascularization, LVEF improvement was assessed by RNV. Patients were divided into 3 groups: Group 1, viable patients with LVEF improvement (n=27); Group 2, viable patients without LVEF improvement (n=15), Group 3, nonviable patients (n=48). Cardiac events were evaluated during a 4 years follow-up.

Results. After revascularization, the LVEF improved from 32 ± 9% to 42 ± 10% in Group 1, but did not change significantly in Group 2 and in Group 3, $P < 0.001$ by ANOVA. Heart failure symptoms improved both in Groups 1 (NYHA class from 3.1 ± 0.9 to 1.7 ± 0.7) and 2 (from 3.2 ± 0.7 to 1.7 ± 0.9), but not in Group 3 (from 2.8 ± 1.0 to 2.7 ± 0.5), $P < 0.001$ by ANOVA. During the follow-up, the cardiac event rate was low (4%) in Group 1, intermediate (21%) in Group 2 and high (33%) in Group 3 ($P = 0.01$).

Conclusions. The best prognosis after revascularization may be expected in those viable patients who improve in LVEF. Conversely, viable patients without functional improvement have an intermediate prognosis.

INTRODUCTION

Patients with ischemic cardiomyopathy represent a subgroup at high risk of further cardiac events when treated medically (1-3). Several studies demonstrated that coronary revascularization may improve left ventricular ejection fraction (LVEF), symptoms and prognosis if a substantial amount of viable myocardium is present (4-12). A recent meta-analysis (13), including 24 studies with 3088 patients, demonstrated that the cardiac death rate was 3% in patients with viable myocardium who underwent revascularization as compared to 16% in patients with viable myocardium who were treated medically. The presence of myocardial viability has been shown to be predictive of LVEF improvement and better prognosis after coronary revascularization (4-12). However, the proportion of patients with viable myocardium showing a significant improvement of LVEF after revascularization is extremely variable in the different studies. It ranged from 36% (4) to 88% (7). Hence, not all patients with viable myocardium show an improvement of LVEF post-operatively. Whether the prognosis of viable patients who do not improve is different than viable patients who do improve in LVEF is unclear. To clarify this issue, in the present report, a long-term follow-up study was performed in a large group of patients with ischemic cardiomyopathy undergone coronary revascularization.

METHODS

Study Population and Study Protocol. Ninety-seven consecutive patients with ischemic cardiomyopathy were initially included in the study. Patients were already scheduled for coronary revascularization according to clinical criteria (symptoms, presence/absence of ischemia and angiographic findings), independently from the results of the viability studies. Patients with severe (3-4+ mitral regurgitation) valvular disease were not included. Seven patients (7%) did not complete the study protocol since they died in the post-operative period (within 30 days). The study population, therefore, consisted of 90 patients who survived the post-operative period and completed the study protocol. This was designed as follows: before revascularization radionuclide ventriculography (RNV) and resting 2-dimensional echocardiography were performed to assess LVEF and regional wall motion abnormalities, respectively. Also LV volumes were measured from the resting echocardiographic images. Subsequently, dobutamine stress echocardiography (DSE) was performed to assess myocardial viability in dysfunctional segments. Nine to 12 months after revascularization, RNV was repeated to evaluate improvement in LVEF. Patients were divided into 3 groups according to presence of myocardial viability and LVEF improvement: Group 1, viable patients with LVEF improvement; Group 2, viable patients without LVEF improvement, Group 3, nonviable patients.

Functional status (NYHA and CCS class) before and after revascularization and cardiac events during a long-term follow-up (up to 4 years) were evaluate in the 3 groups. The local ethics committee approved the protocol and all patients gave informed consent before the study.

Two-Dimensional Echocardiography at Rest. All echocardiograms were performed using a Sonos-5500 imaging system (Hewlett-Packard, Philips Medical Systems, Eindhoven, The Netherlands) equipped with a second harmonic 1.8-3.6 MHz transducer to optimize endocardial border visualization. Standard parasternal and apical views of the LV were obtained (14). Regional wall motion and thickening were scored using the 16-segment model with a 5-point grading scale: 1=normal, 2=mildly hypokinetic, 3=severely hypokinetic, 4=akinetic, 5=dyskinetic (4). The wall motion score index was calculated by dividing the summed wall motion score by the number of segments. From the apical 2- and 4-chamber views also LV end-diastolic and end-systolic volume were measured using the biplane Simpson's rule (14). Measurements were performed off-line in separate reading sessions and in random order by 2 independent experienced readers blinded to patient data.

Assessment of Myocardial Viability: Dobutamine Stress Echocardiography. Only severely dysfunctional segments (score 3 to 5) were evaluated for myocardial viability. Low-high dose DSE (up to 40 μg/kg/min with addition of 2 mg atropine, if necessary) was performed as described previously (4). Four patterns of wall motion response were observed during DSE: 1=sustained improvement; 2=worsening; 3=biphasic response; 4=no change (15). Segments with biphasic response, sustained improvement or worsening of the wall motion during DSE were considered viable, with the exception of akinesia becoming dyskinesia (15). Segments with unchanged wall motion were considered nonviable (scar) tissue (15). Patients were defined as viable in the presence of a substantial amount of viable myocardium (≥4 viable segments, ≥25 of the LV), whereas patients with <4 viable segments were defined nonviable (4). Interpretation of the studies was performed off-line from cineloops, displayed side-by-side in a quad-screen format, by 2 experienced observers blinded to the clinical data. Inter- and intra-observer agreement for analysis of DSE studies was reported previously (92% and 94% respectively) [16].

Assessment of Left Ventricular Ejection Fraction. Before and 9 to 12 months after revascularization the LVEF was assessed by RNV at rest. A small field-of-view gamma camera system (Orbiter, Siemens, Erlangen, Germany) was used, oriented in a 45° left anterior oblique position with a 5° to 10° caudal tilt. After injection of Tc-99m (740 MBq), radionuclide ventriculography was performed at rest with the patient in supine position. The LVEF was calculated by standard methods (Odyssey VP, Picker, Cleveland, Ohio, USA). An improvement in LVEF ≥5% after revascularization was considered clinically significant (4).

Assessment of Functional Status and Long-term Follow-up. Before and after revascularization, structured clinical interviews were performed, by an independent physician blinded to all data, to assess the functional status according to the NYHA (for symptoms of heart failure) and the CCS criteria (for angina pectoris). The long-term follow-up was obtained by chart review and telephone contact and was complete in all 90 patients. Events included: cardiac death, new myocardial infarction, hospitalization for heart failure. Cardiac death was defined as death unwitnessed sudden death, death within 1 hour of new symptoms of myocardial ischemia or death due to heart failure. Myocardial infarction was defined according to classical criteria (symptoms, electrocardiographic changes and elevated cardiac enzymes). Hospitalization for heart failure was defined according to the hospital discharge diagnosis.

Statistical Analysis. Continuous data are expressed as mean ± SD and dichotomous data as proportions. Continuous data were compared using the Student's *t* test for paired and unpaired samples and ANOVA analysis as indicated. Comparison of proportions was performed by chi-square analysis. Cardiac event rate during the long-term follow-up was evaluated using the Kaplan-Meier method. Differences between curves were tested with the log-rank chi-square statistics. For all tests, a P-value <0.05 was considered significant.

RESULTS

Study Population. Before revascularization, all patients had heart failure symptoms (NYHA class: 2.9 ± 0.9). Angina pectoris was also present in 82 patients (CCS class: 2.7 ± 0.6). Previous myocardial infarction (≥6 months) had occurred in the majority of the population (97%). Baseline LVEF was on average 33 ± 9%. In 49 patients (54%) a severe reduction of LVEF (<30%) was present. Coronary revascularization was performed by coronary artery bypass grafting in 75 patients (83%), using the left internal mammary artery in 97% of the patients. In the remaining 15 patients (17%), coronary revascularization was performed by coronary angioplasty. Nine to 12 months after revascularization, LVEF improved significantly in the entire population (from 33 ± 9% to 35 ± 10%, P = 0.01). However, an improvement of LVEF ≥5% was observed in 33 patients (37%).

Myocadial Viability. The analysis of resting echocardiographic images showed that 808 out of 1440 segments (56%) were severely dysfunctional (wall motion score 3-5). Patients had on average 9 ± 4 severely dysfunctional segments. The mean wall motion score index was 2.8 ± 0.7. During DSE, 356 of 808 (44%) severely dysfunctional segments were considered as viable, whereas 452 segments were nonviable. A substantial amount of viable myocardium (≥4 segments, ≥25% of the

LV) was present in 42 patients (47%) which were defined as viable patients. Limited or no viable myocardium was present in the remaining 48 patients who were considered as nonviable patients.

Myocardial Viability and LVEF Improvement After Revascularization. After revascularization, 27 viable patients (64%) showed a significant improvement in LVEF (Group 1), whereas 15 viable patients (36%) did not improve in LVEF after revascularization (Group 2). An improvement in LVEF ≥5% was observed infrequently (12%, P < 0.001 vs viable patients) in the nonviable patients (Group 3). After revascularization, the LVEF was 42 ± 10 % in Group 1, 32 ± 9% in Group 2 and 32 ± 10% in Group 3 (P < 0.001).

Comparison Between Viable Patients With and Without LVEF Improvement and Nonviable Patients. Pre-operative clinical characteristics were comparable in the 3 groups.

Table 1. Pre-operative Clinical Characteristics

Clinical characteristic	Group 1 viable improvers 27 pts	Group 2 viable non-improvers 15 pts	Group 3 nonviable 48 pts	P value
Age, mean ± SD	60 ± 9	60 ± 10	59 ± 9	NS
Male (%)	22 (81)	11 (73)	40 (83)	NS
CCS, mean ± SD	2.5 ± 0.7	2.8 ± 0.6	2.9± 0.7	NS
NYHA, mean ± SD	3.1 ± 0.9	3.2 ± 0.7	2.8 ± 1.0	NS
Diabetes Mellitus (%)	1 (4)	1 (7)	6 (12)	NS
Smoking (%)	13 (50)	8 (53)	27 (56)	NS
Hypercolesteremia (%)	20 (74)	12 (80)	37 (77)	NS
Hypertension (%)	21 (78)	12 (80)	40 (83)	NS
Previous MI	25 (93)	15 (100)	47 (98)	NS
Q wave MI	18 (67)	13 (87)	41 (85)	NS
LVEF, mean ± SD	32 % ± 9 %	32 % ± 8 %	33 % ± 10 %	NS
Stenotic vessels, mean ± SD	2.3 ± 0.8	2.5 ± 0.7	2.5 ± 0.6	NS
Medications				
Lipid-lowering	13 (48)	6 (40)	22 (46)	NS
Ace-inhibitors	17 (63)	12 (80)	35 (73)	NS
Nitrates	23 (85)	11 (73)	37 (77)	NS
Diuretics	13 (48)	9 (60)	30 (62)	NS
Beta-blockers	18 (67)	9 (60)	28 (58)	NS
Digoxine	1 (4)	6 (40)	16 (33)	<0.01
Aspirine/Anticoagulant	27 (100)	14 (93)	48 (100)	NS

ACE: angiotensin-converting enzyme; CCS: Canadian Cardiovascular Society; LVEF: left ventricular ejection fraction; MI: myocardial infarction.

In particular, the 3 groups were similar with respect to number of stenotic vessels, angina pectoris and heart failure scores. Also the frequency of previous myocardial infarction as well as the pre-operative LVEF were similar in the 3 groups (see Table 1).

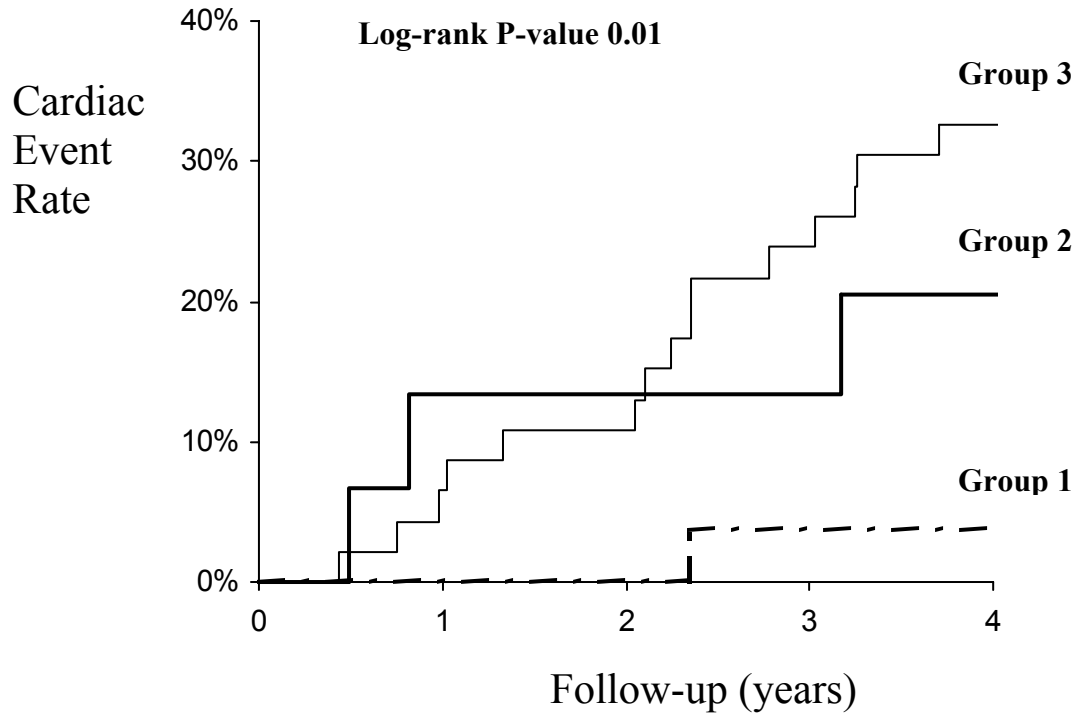
The analysis of resting wall motion showed that the wall motion score index was 2.7 ± 0.8, 2.9 ± 0.6 and 2.7 ± 0.5 in Group 1, 2 and 3, respectively (P = NS). However, both the end-diastolic volume and end-systolic volume of the LV were significantly larger in Groups 2 and 3 as compared to Group 1 (see Table 2)

Table 2. Pre-operative Echocardiographic Characteristics

	Group 1 viable improvers 27 pts	**Group 2 viable non-improvers 16 pts**	**Group 3 nonviable 44 pts**	**P value**
End-diastolic volume mean ± SD	161 ± 59	207 ± 33	206 ± 53	<0.01
End-systolic volume mean ± SD	103 ± 54	141 ± 37	140 ± 48	<0.05
Wall motion score index, mean ± SD	2.7 ± 0.8	2.9 ± 0.6	2.7 ± 0.5	NS
Viable segments mean ± SD	7.1 ± 3.4	6.7 ± 1.9	1.3 ± 1.1	<0.001
Nonviable segments mean ± SD	3.6 ± 3.3	5.5 ± 3.1	6.5 ± 4.2	<0.05

Functional Class After Revascularization and Clinical Follow-up. Improvement of heart failure symptoms after revascularization was observed both Group 1 and Group 2, whereas in Group 3 the heart failure score did not improve significantly. The NYHA class after revascularization was 1.7 ± 0.7 in Group 1, 1.7 ± 0.9 in Group 2 and 2.7 ± 0.5 in Group 3 (P < 0.001). Angina pectoris score decreased in the entire population. The CCS class was 1.2 ± 0.7 in Group 1, 1.2 ± 0.6 in Group 2 and 1.2 ± 0.5 in Group 3 (P = NS). On long-term follow-up (up to 4 years after revascularization), only 1 patient died in Group 1 and none had myocardial infarction or hospitalization for heart failure. In Group 2, 1 patient died and 2 patients were hospitalized for heart failure. In Group 3, 6 patients died, 2 patients had acute myocardial infarction and 8 had hospitalization for heart failure. Overall, the cardiac event rate was low (4%) in Group 1, intermediate (21%) in Group 2 and high (33%) in Group 3 (P = 0.01, Figure 1).

Figure 1



DISCUSSION

In patients with ischemic cardiomyopathy, myocardial viability is associated to improvement in LVEF and better prognosis after coronary revascularization. The findings in the present study demonstrated that after revascularization a very good prognosis is present only in viable patients with improvement in LVEF. Conversely, patients without viable myocardium had a relatively poor prognosis and of interest, an intermediate prognosis was observed in viable patients without improvement in LVEF.

Coronary Revascularization of Viable Myocardium versus Improvement in LVEF. The presence of myocardial viability has been associated with improvement of global LV function after revascularization (17). In the present study, significant improvement of LVEF (≥5%) after revascularization was observed in 64% of viable patients. Previous studies reported post-operative improvement of LVEF in variable proportions of viable patients.

In the study by Cuocolo et al, 36% of patients with evidence of viable myocardium on thallium-201 imaging improved in LVEF after revascularization (5). Whereas Cornel et al used a comparable DSE protocol to assess viability and demonstrated an improvement in LVEF in 68% of patients, in line with the current findings (11). In addition, the various studies suggested that at least 25-30% of the LV needed to be viable to allow improvement in global LV function (4-12). However, not all patients with this extent of viable myocardium exhibit improvement in LVEF after revascularization. This may be related to various issues. First, extensive remodeling may prohibit improvement in LVEF despite the presence of viable myocardium (18-20). Second, it has been shown that besides viable myocardium, also the extent of scar tissue is an important predictor of improvement in LVEF (21-22). Accordingly, in the present study, LV dilatation and the extent of scar tissue were larger in the patients who did not improve in LVEF (see Table 2). Also delayed revascularization and graft closure or restenosis may inhibit functional recovery of viable myocardium (23). Still, besides improvement in LVEF, improvement of symptoms after coronary revascularization is also an important clinical end-point. It has been shown that heart failure symptoms may significantly improve after revascularization in the presence of substantial amount of viable myocardium (4, 24-27). Accordingly, in the present study, the NYHA functional class significantly improved in all viable patients (both Groups 1 and 2), but did not change significantly in patients with limited or nonviable myocardium (Group 3).

Coronary Revascularization of Viable Myocardium versus Improvement of Prognosis. Previous studies have shown that coronary revascularization may improve prognosis in patients with ischemic cardiomyopathy and viable myocardium (13). In a recent meta-analysis, Allman et al demonstrated a high event-rate in patients with viable myocardium who were treated medically, whereas a favourable prognosis was present in patients with viability who underwent revascularization (13). In the present study, only patients who underwent coronary revascularization were included. During the 4 years follow-up, a low event rate (4%) was observed only in those viable patients who improved in LVEF after revascularization (Group 1). In contrast, viable patients without improvement in LVEF (Group 2) had a considerable event-rate (21%); the highest event-rate was observed in nonviable patients (See Figure 1). It appears that, although all viable patients after revascularization have a better prognosis as compared to the nonviable patients, the best prognosis is observed in viable patients in whom coronary revascularization resulted in improvement in LVEF. In a previous study, Samady et al showed that failure to improve in LVEF after revascularization in patients with ischemic cardiomyopathy was not associated with worse outcome (28). It should be noticed, however, that viability data were not available in that study (28).

More importantly, assessment of LVEF was performed on average 16 ± 33 days after revascularization, which may be too early to demonstrate improvement in LV function (18, 29-30).

Study Limitations. Coronary angiography was not performed after revascularization. Therefore, graft-occlusion may have prohibited LVEF improvement and affected long-term prognosis.

Moreover, recent studies have suggested that in addition to revascularization, surgical remodeling of the LV (resections of LV aneurysms, or akinetic regions) may improve long-term prognosis (31).

Conclusions. In patients with ischemic cardiomyopathy, coronary revascularization is associated with a favourable outcome if a substantial amount of myocardial is present. In the present study, it has been shown that after revascularization of viable myocardium the best prognosis is observed in viable patients who exhibited improvement in LVEF after revascularization. Conversely, viable patients without improvement in LVEF had an intermediate prognosis, and nonviable patients had the worst prognosis.

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CHAPTER 13

Benefits of coronary revascularization in diabetic and non-diabetic patients with ischemic cardiomyopathy: role of myocardial viability

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Benefits of Coronary Revascularization in Diabetic and Non-Diabetic Patients With Ischemic Cardiomyopathy: Role of Myocardial Viability

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ABSTRACT

Background. Diabetes mellitus in patients with coronary artery disease is associated with poor outcome. In this study the relation between viability, diabetes, coronary revascularization and outcome was evaluated.

Methods. 129 patients (31 diabetic and 98 non-diabetic) with ischemic cardiomyopathy underwent dobutamine stress echocardiography to assess myocardial viability. Patients with ≥4 viable segments were defined viable and patients with <4 viable segments, nonviable. Left ventricular ejection fraction (LVEF) was assessed before and 9-12 months after revascularization. At the same time-points, LV volumes were measured to evaluate LV remodeling. Finally, cardiac events were noted during 5-year follow-up.

Results. Viable myocardium extent was comparable between diabetic and non-diabetic patients. After revascularization, LVEF increased ≥5% in 44% of diabetic and in 40% of non-diabetic patients. LVEF improved only in patients with viable myocardium. Ongoing LV remodeling occurred in 36% and 35% of diabetic and non-diabetic patients respectively, and was related to non-viability, whereas viability protected against ongoing LV remodeling, both in diabetic and non-diabetic patients. Viability was the only predictor of survival after revascularization.

Conclusions. Diabetic, viable patients with ischemic LV dysfunction exhibit improvement in LVEF post-revascularization with prevention of ongoing LV remodeling, similar to non-diabetic patients. Viability was also the only predictor of long-term outcome.

INTRODUCTION

Over the last 2 decades, many studies have demonstrated that patients with ischemic cardiomyopathy can improve significantly in left ventricular ejection fraction (LVEF) after revascularization (1-5). Still peri-operative morbidity and mortality is substantial (6) and therefore an adequate selection of patients who may benefit from revascularization is needed. Based on the pre-operative assessment of myocardial viability, patients with a high likelihood of improvement in LVEF can be identified (1-5). Indeed, Haas et al (7) have demonstrated a reduction in peri-operative morbidity and mortality, with a better outcome, when only patients with viable myocardium underwent revascularization.

Whether the same holds true for patients with diabetes is currently unclear. This is an important issue, since many patients with diabetes and coronary artery disease develop LV dysfunction over time (8-10). Moreover, diabetic patients have a worse short- and mid-term outcome after revascularization as compared to non-diabetic patients (11-13), stressing the need for identification of patients who may potentially benefit from revascularization.

Accordingly, in the current study, the relation between the pre-operative presence of viability and the outcome after revascularization was evaluated in patients with diabetes; the results were compared with non-diabetic patients undergoing viability testing and revascularization.

METHODS

Study Population. The study population existed of 129 patients (105 men, mean age 62±9 years) with ischemic cardiomyopathy (LVEF 31±7 %) and symptoms of heart failure, already scheduled for coronary revascularization. The decision of revascularization was based on clinical information (symptoms, presence/absence of ischemia and angiographic findings). A history of myocardial infarction was present in 119 patients (92%). In these patients, infarction had occurred ≥6 months before the study entry. Patients with moderate to severe mitral regurgitation were not included. Diabetes mellitus was present in 31 patients, whereas 98 patients were non-diabetic. Diabetes mellitus was defined as a fasting glucose level ≥7.8 mmol/L or the need for insulin or hypoglycemic agents. Eight patients had insulin-dependent diabetes and 23 patients had non-insulin-dependent diabetes.

Study Protocol. Before revascularization, all patients underwent radionuclide ventriculography to assess LVEF and dobutamine stress echocardiography (DSE) to assess myocardial viability. LV volumes were derived from resting echocardiographic images.

Nine to 12 months after revascularization, radionuclide ventriculography was repeated to evaluate improvement in LVEF. In addition, resting 2-dimensional echocardiography was repeated at 9-12 months after revascularization to assess changes in LV volumes (LV remodeling).

Finally, cardiac events (cardiac death, myocardial infarction and hospitalization for heart failure) were evaluated during a 5-year follow-up. The local ethics committee approved the protocol and all patients gave informed consent.

Echocardiographic Studies. All echocardiograms were performed using a Sonos-5500 device (Hewlett-Packard, PMS, Eindhoven, The Netherlands) equipped with a second-harmonic 1.8-3.6 MHz transducer. Standard views of the LV were obtained (14).

Myocardial Viability. Low-high dose DSE (up to 40 μg/kg/min plus 2 mg atropine, if necessary) was performed as described previously (15). Interpretation of DSE studies was performed off-line from cine-loop images, by 2 experienced observers blinded to the clinical data. Inter- and intra-observer agreement for analysis of DSE studies were 92% and 94% respectively (16). Regional function was scored using a 16-segment and 5-point scoring model with 1=normal, 2=mildly hypokinetic, 3=severely hypokinetic, 4=akinetic, 5=dyskinetic (15). The wall motion score index (WMSI) was calculated by dividing the summed wall motion score by the number of segments. Myocardial viability was evaluated only in severely dysfunctional segments (score 3 to 5). Segments showing a sustained improvement in wall motion up to high dose and segments with biphasic response or worsening of wall motion during DSE were considered viable (17). Segments with unchanged wall motion or with akinesia becoming dyskinesia were considered nonviable (17). A patient was defined as viable in the presence of ≥4 viable segments and nonviable in the presence of <4 viable segments (3). Also the absolute changes in WMSI (delta, Δ) during DSE (low-dose minus rest and peak- minus low-dose DSE) were calculated.

LV Volumes. LV end-diastolic and end-systolic volumes (LVEDV and LVESV) were measured from the resting echocardiographic images. All measurements were performed off-line by 2 experienced readers blinded to patient data and acquisition time (before or after revascularization). LV volumes were measured using the biplane Simpson's rule (14). An increase >15% in the LVEDV or LVESV after revascularization was considered ongoing LV remodeling (18).

Assessment of Improvement in Left Ventricular Ejection Fraction. Radionuclide ventriculography was performed at rest with the patient in the supine position after the administration of 740 MBq of ^{99m}technnetium. Images were acquired with a small-field-of-view gamma camera (Orbiter, Siemens Corp, Iselin, NJ, USA), oriented in the 45° left anterior oblique position with a 5-10° caudal tilt. The LVEF was calculated from the 45° left anterior oblique view by an automated technique. An improvement in LVEF ≥5% at 9 to 12 months after revascularization was considered clinically significant (3).

Long-term Follow-up. The long-term follow-up was obtained by chart review and telephone contact. Events included: cardiac death, myocardial infarction and hospitalization for heart failure. Cardiac death was defined as sudden death, death due to acute myocardial infarction or heart failure.

Myocardial infarction was defined according to classical criteria (symptoms, electrocardiographical changes and elevated cardiac enzymes). Hospitalization for heart failure was defined according to the hospital discharge diagnosis.

Statistical Analysis. Continuous data are expressed as mean (SD) and dichotomous data as proportions. Continuous data were compared using the Student's *t* test for paired and unpaired samples as indicated. Comparison of proportions was performed by chi-square analysis. Cardiac event rate was evaluated using Kaplan-Meier analysis. Differences between curves were tested by log-rank chi-square statistics. Cox regression analysis was performed to identify predictors of cardiac death. For all tests, a P value <0.05 was considered significant.

RESULTS

Study Population. Clinical characteristics were comparable between diabetic patients and non-diabetic patients; however, LVEF before revascularization was significantly lower in diabetic patients (Table 1). Twelve (9%) patients died early after revascularization and 12 additional patients refused to undergo assessment of LVEF and LV volumes after revascularization. These patients were included in the follow-up analysis, but LV volumes and LVEF after revascularization were not available.

Table 1. Clinical Characteristics of Diabetic and Non-Diabetic Patients

Clinical Characteristics	Diabetes (n-=31)	No Diabetes (n=98)	P value
Male (%)	22 (71)	83 (85)	NS
Age (years)	63±8	60±9	NS
CCS	2.6±0.8	2.2±1.1	NS
NYHA	2.9±1.0	2.5±1.1	NS
History of myocardial infarction (%)	28 (90)	91 (93)	NS
Q wave MI (%)	22 (81)	88 (90)	NS
Anterior MI (%)	18 (58)	48 (49)	NS
Sinus Rhythm (%)	30 (97)	96 (98)	NS
Smoking (%)	18 (58)	55 (56)	NS
Hypertension (%)	28 (90)	83 (85)	NS
Hypercholesterolemia (%)	15 (48)	39 (40)	NS
Family History (%)	19 (61)	58 (59)	NS
Stenosed coronary arteries	2.6±0.5	2.5±0.7	NS
LVEF %, mean±SD	28±8	32±9	0.04
Medical Therapy			
Statins	14 (45)	50 (51)	NS
Nitrates	24 (80)	69 (70)	NS
β-Blockers	16 (52)	69 (70)	0.07
Diuretics	20 (67)	59 (60)	NS
Aspirin/Anticoagulant	30 (98)	95 (97)	NS
Digoxine	11 (35)	25 (26)	NS

Resting and DSE Results. Table 2 summarizes the results of resting and stress echocardiography. The number of segments showing severe wall motion abnormalities was comparable in diabetic and non-diabetic patients. Also, baseline LV volumes were similar in the 2 groups. Diabetic patients showed a higher WMSI at rest as compared to non-diabetic patients. The analysis of myocardial viability showed that the number of viable segments was similar in the 2 groups (4.6±3.0 in diabetic and 4.2±3.5 in non-diabetic patients, P=NS). Also, the Δ in WMSI at low-dose and peak-dose of dobutamine infusion were comparable (Table 2). Based on the presence of ≥4 viable segments, the population was divided in 4 groups: 18 diabetic viable patients, 13 diabetic nonviable patients, 48 non-diabetic viable patients and 50 non-diabetic nonviable patients.

Table 2. Echocardiographic Data

Characteristic	Diabetes (n=31)	No Diabetes (n=98)	P value
Severely dysfunctional segments	11.6±3.8	10.4±4	NS
Viable segments	4.6±3.04	4.2±3.5	NS
Scar segments	6.9±3.1	6.2±3.1	NS
WMSI at rest	3.02±0.6	2.8±0.6	0.03
WMSI at LD	2.6±0.6	2.4±0.6	NS
WMSI at peak	2.9±0.7	2.7±0.6	NS
ΔWMSI at LD	-0.39±0.26	-0.35±0.33	NS
ΔWMSI at peak	0.26±0.34	0.31±0.41	NS
LVEDV (ml)	181±48	177±57	NS
LVESV (ml)	122±46	116±51	NS

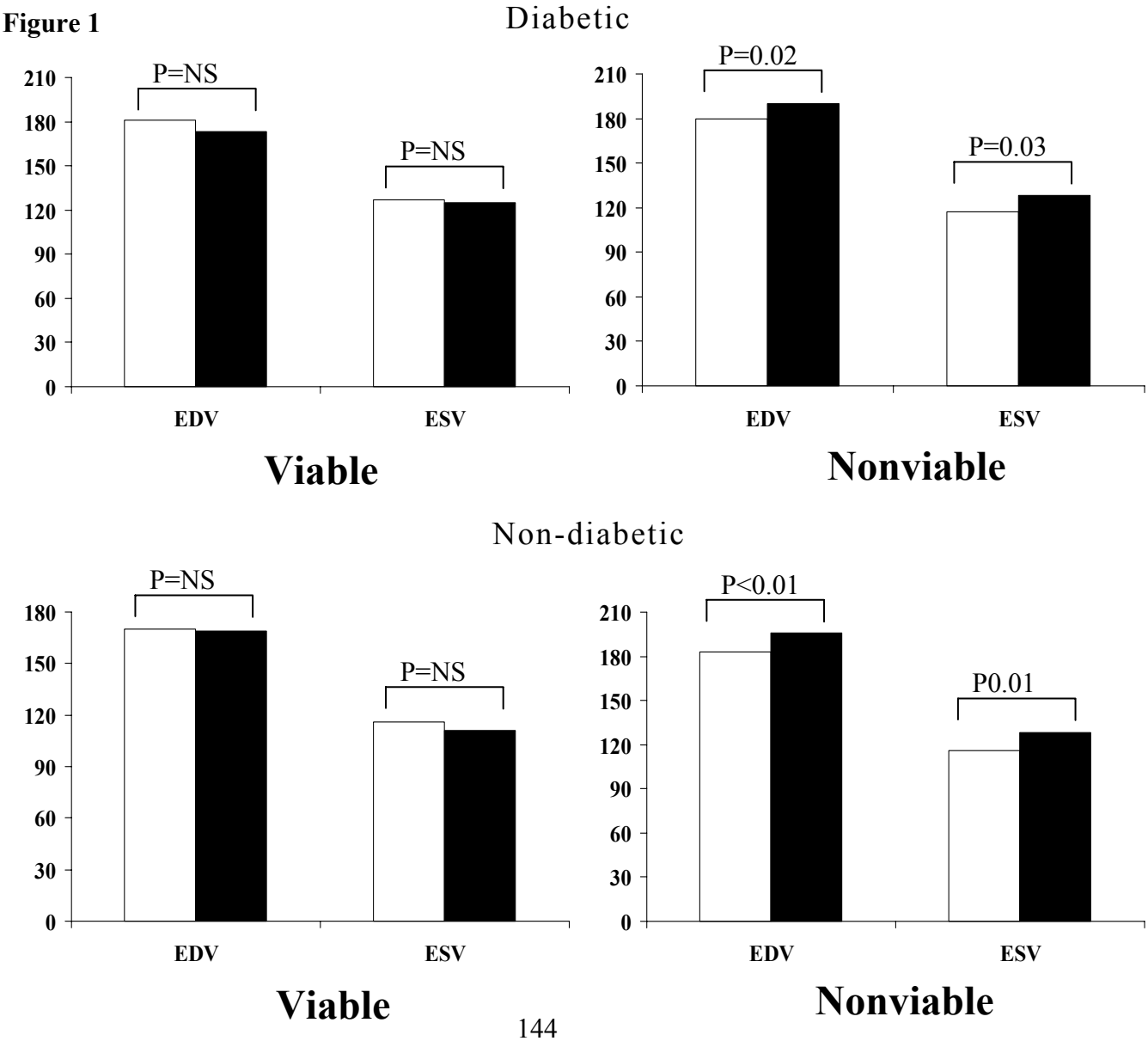
LD: low-dose of dobutamine infusion; LVEDV: left ventricular end-diastolic volume; LVESV: left ventricular end-systolic volume; WMSI: wall motion score index.

Improvement in LVEF after Revascularization. An increase in LVEF ≥5% occurred after revascularization in 11/25 (44%) diabetic patients and in 31/80 non-diabetic patients (40%) (P=NS). In particular, in diabetic, viable patients the LVEF increased from 29±9% to 34 ±8% (P= 0.001), whereas the LVEF did not improve in diabetic, nonviable patients (from 32±6% to 30 ±8% , P= NS).

Similarly, in non-diabetic patients, LVEF increased from 31±9% to 35 ±11% (P=0.004) in viable patients whereas LVEF did not improve in nonviable patients (from 32±6% to 34 ±11%, P= NS).

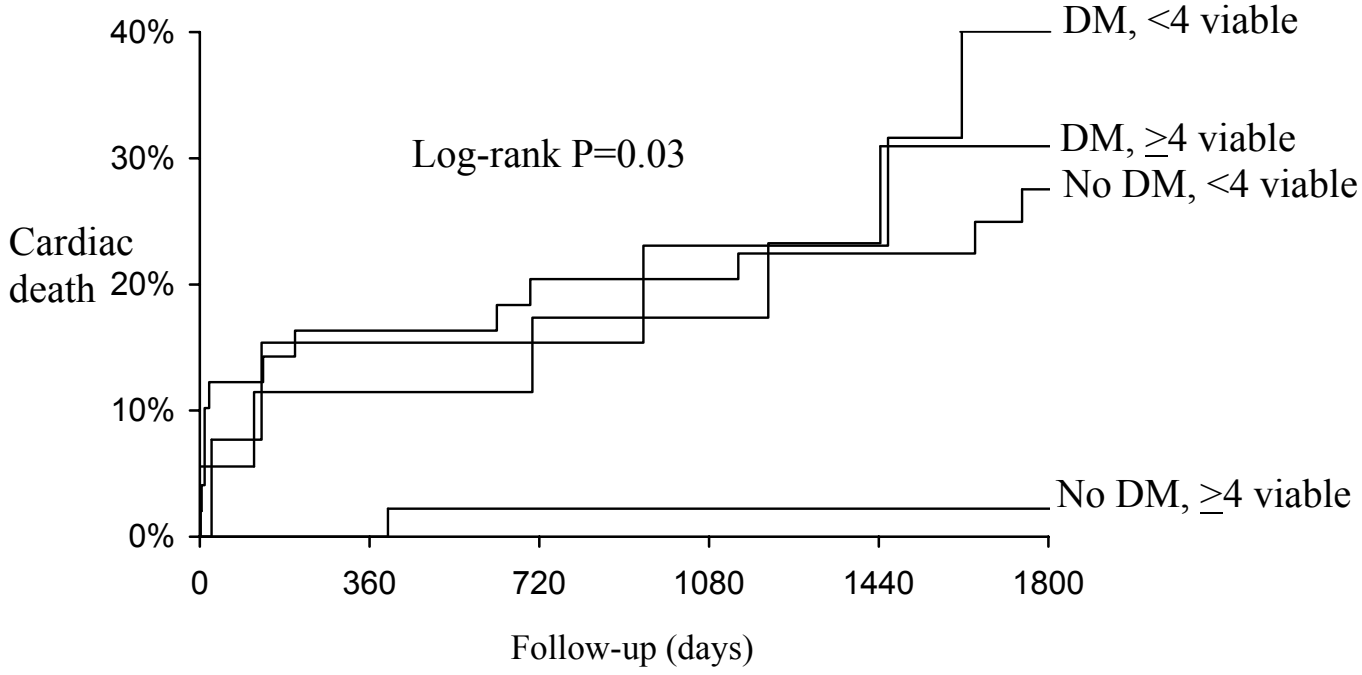
LV remodeling after Revascularization. After revascularization, LV remodeling occurred in 9/25 (36%) diabetic and in 28/80 (35%) non-diabetic patients (P=NS). In Figure 1, the LV volumes are displayed before and after revascularization, according to diabetes and viability. In non-diabetic patients, LV volumes did increase after revascularization in nonviable patients (LVEDV increased from 183±51 ml to 193±50 ml, P<0.01 and LVESV from 116±46 ml to 124±48 ml, P<0.01). In contrast, LV volumes did not increase in viable patients, indicating prevention of LV remodeling (LVEDV: 170±62 ml at baseline vs 169±67 ml, P=NS and LVESV: 116±55 ml vs 111±58 ml, P=NS). Similar results were obtained in diabetic patients. In nonviable patients the LVEDV increased from 181±43 ml to 196±49 ml (P=0.01), whereas the LVESV increased from 119±43 ml to 136±45 ml (P=0.03). In viable patients, the LV volumes did not change significantly (LVEDV: 181±54 ml vs 173±67 ml, P=NS and LVESV: 127±48 ml vs 125±63 ml, P=NS).

Figure 1



Cardiac Events During Follow-up. A total of 68 cardiac events occurred during the 5-year follow-up, including 29 cardiac deaths, 3 myocardial infarctions and 36 hospitalizations for decompensated heart failure. Overall, cardiac events were comparable between diabetic and non-diabetic patients (48% vs 54% respectively, P=NS). However, in the non-diabetic patients, the viable patients had a significantly lower event rate during follow-up as compared to the nonviable patients (8 of 48, 17% vs 23 of 50, 46% P=0.03). Cardiac death was more frequent in diabetic as compared to non-diabetic patients although the difference was not statistically significant (32% vs 17%, P=NS). The cardiac death rates according to the presence of diabetes mellitus and a substantial amount of viable myocardium (≥ 4 viable segments) are shown in Figure 2. The highest cardiac death rate was observed in the diabetic, nonviable patients (5 of 13, 39%); the lowest cardiac death rate was observed in the non-diabetic, viable patients (2 of 48, 4%). Intermediate cardiac death rates were observed in diabetic, viable patients (5 of 18, 28%) and in non-diabetic, nonviable patients (17 of 50, 34%). In diabetic patients, the cardiac death rate during the 5-year follow-up was lower in viable patients, although the difference did not reach statistical significance (28% vs 39% respectively, P=NS). In non-diabetic patients, cardiac death was significantly less in viable as compared to nonviable patients (4% vs 34% respectively, P=0.005).

Figure 2



The multivariable analysis showed that only the presence of substantial amount of viable myocardium was an independent predictor of cardiac death (HR 0.35, 95% CI 0.15-0.83, P=0.02) whereas diabetes mellitus was not (HR 1.9, 95% CI 0.9-4.1, P=0.10). The interaction term between diabetes and viability was borderline significant for death (P=0.08).

DISCUSSION

The findings in the present study demonstrate that the effect of viability on LVEF and LV remodeling is similar in patients with and without diabetes. In particular, a comparable increase in LVEF post-revascularization was observed in the 2 groups. Also, patients with viable myocardium did not exhibit ongoing LV dilatation. In contrast, patients without viability did not improve in LVEF and showed ongoing LV remodeling; the effects were similar in patients with and without diabetes. These observations demonstrate that pre-operative assessment of viability has comparable clinical value in patients with diabetes.

Finally, patients with viable myocardium had a favourable prognosis as compared to patients without viable myocardium. However, *diabetic patients with viable myocardium* had a similar prognosis as compared to *non-diabetic patients without viable myocardium*.

Improvement in Left Ventricular Function. The number of patients with ischemic cardiomyopathy is increasing rapidly and, despite optimal medical therapy, the prognosis remains poor (19). In particular, the prevalence of patients with diabetes who develop ischemic LV dysfunction is rising exponentially (20), and the combination of diabetes and ischemic LV dysfunction is associated with worse outcome (21-24). Data from the Framingham Study demonstrated that patients with diabetes have a 4-fold increased risk of developing heart failure after myocardial infarction (21) and in the SOLVD and RESOLVD trials, diabetes was an independent predictor of death (22, 23). Accordingly, aggressive management of patients with diabetes is needed and revascularization should be performed if the patient has a high likelihood to benefit from revascularization. It is known from studies in non-diabetic patients that improvement in LVEF can occur when a substantial amount of viable myocardium (≥25% of the LV) is present but not in the absence of substantial viability (1-5). Whether pre-operative assessment of viability is equally predictive for recovery of function in diabetic patients is unclear. Accurate identification of patients with viable myocardium who can improve in function post-revascularization is of high importance in diabetic patients, since revascularization is associated with significantly higher peri-operative morbidity and mortality as compared to non-diabetic patients, and also long-term outcome after revascularization is worse in diabetic patients (6, 11-13). In the current study, low-high dose DSE was used to assess viability; this technique has been extensively validated in previous studies in patients with ischemic cardiomyopathy (25). In particular, in the present study, 58% of diabetic and 49% of non-diabetic patients showed substantial viability on DSE. Similar findings were reported using metabolic imaging with positron emission tomography or single photon emission computed tomography (26, 27).

In addition, the results in the present study indicate that prediction of functional recovery was comparable between diabetic and non-diabetic patients, with a significant increase in LVEF in 44% of diabetic and 40% of non-diabetic patients.

Effects Beyond Improvement of Function? Besides improvement of function, LV remodeling is an important end-point in patients with ischemic cardiomyopathy. Numerous studies have demonstrated the high mortality in patients with a severely dilated left ventricle (28-30). Moreover, prevention of ongoing remodeling resulted in improved survival, both in diabetic and non-diabetic patients (31, 32). In the current study, LV remodeling occurred in 36% of diabetic patients and 35% non-diabetic patients. In particular, LV volumes increased significantly after revascularization in patients without viability (indicating ongoing LV remodeling), whereas LV volumes did not change significantly in patients with viable tissue (indicating prevention of further LV remodeling). This pattern was observed both in diabetic and non-diabetic patients (Figure 1). Other factors influencing LV remodeling (history of (anterior) myocardial infarction, baseline LV volumes, medical therapy including ACE-inhibitors and beta-blockers) were comparable between diabetic and non-diabetic patients, suggesting that the effect on LV volumes is related to the presence/absence of viable myocardium. Limited data are available on the long-term prognosis in diabetic patients in relation to viability. It is known from studies in non-diabetic patients that survival is poor in medically treated patients with viable myocardium. In a meta-analysis performed by Allman et al (33), the mortality rate was 16% in viable patients who were treated medically, in sharp contrast to the 3.2% mortality rate in viable patients who underwent revascularization. Only one study reported on the inter-relation between viability, diabetes, therapy and long-term outcome. Pasquet and colleagues (34) demonstrated that medically treated patients with diabetes and viability showed a higher risk of death as compared to non-diabetic patients during 3 years follow-up (34). This risk was significantly reduced in diabetic patients with viability undergoing revascularization, but not in diabetic patients without viability (34). The current study specifically focused on the prognosis in diabetic patients undergoing revascularization in relation to pre-operative viability. During a 5-year follow-up period, the lowest cardiac death rate after revascularization was observed in non-diabetic viable patients (4%), in line with the results from the meta-analysis by Allman et al (33). Conversely, non-diabetic, nonviable patients had a cardiac death rate of 34% (P=0.005 vs viable patients). A similar trend (although not significant) was observed in the diabetic patients: viable, diabetic patients had a lower cardiac death rate as compared to non-viable, diabetic patients (28% vs 39%, NS). It is of interest that the cardiac death rate of non-diabetic, nonviable patients is almost comparable to diabetic, viable patients (28% vs 34%, NS). These findings suggest that besides viability, diabetes is important for prognosis.

Still, multivariable analysis demonstrated that the presence of viable myocardium was the only independent predictor of prognosis after revascularization. However, the interaction between viability and diabetes was borderline significant for prediction of cardiac death, suggesting that the combination of these 2 parameters is useful for risk stratification before revascularization. Clearly, more studies are needed to provide more insight on the prognostic value of viability in diabetic patients with ischemic LV dysfunction.

Study Limitations. A relatively small group of diabetic patients was studied, and larger studies are needed. After revascularization, coronary angiography was not repeated. Therefore graft closure or restenosis could not be excluded, and may have influenced outcome.

Conclusions. In diabetic patients with ischemic LV dysfunction, the presence of viable myocardium is associated with an improvement in LVEF post-revascularization, similarly to non-diabetic patients. In addition, revascularization of viable patients prevented ongoing LV remodeling in diabetic patients comparable to non-diabetic patients. Viability was the only predictor of survival after revascularization, although the interaction of viability and diabetes was borderline significant. Indeed, viable, non-diabetic patients had a better survival compared to viable, diabetic patients. Larger studies are needed to further elucidate this issue.

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Summary and Conclusions

SUMMARY

Several studies have demonstrated that coronary revascularization is likely to improve left ventricular ejection fraction (LVEF), heart failure symptoms and prognosis predominantly in patients with ischemic cardiomyopathy and a substantial amount of viable myocardium but not in patients without viability. Some issues about myocardial viability in patients with ischemic cardiomyopathy are still unsolved. In particular, why LVEF does not improve after revascularization in all patients with a substantial amount of viable myocardium is unknown. Also, it is unclear whether additional benefits, beyond improvement of LVEF, may be present after revascularization of viable myocardium. These issues were addressed in the present thesis.

Part I of the thesis deals with the following question: why LVEF does not always improve after revascularization of patients with a substantial amount of viable myocardium? To answer this question, the impact of additional factors, besides viability, on the improvement of LVEF after revascularization was investigated. In chapter 2, the presence of subendocardial scar (showing a sustained improvement pattern during DSE) was associated with a low likelihood of improvement in segmental function after revascularization. This suggests that subendocardial scar may limit improvement in function after revascularization of viable myocardium.

In chapter 3 a scar-to-biphasic model was developed to predict in the individual patient the likelihood of improvement of LVEF after revascularization. The model showed that the number of both biphasic (viable) and scar (nonviable) segments during DSE needs to be considered to accurately predict improvement of LVEF. Indeed, despite the presence of viable myocardium, the likelihood of LVEF improvement decreases with the increase of scar segments.

Next, the impact of the timing of revascularization was investigated. A comparison of early versus delayed revascularization in patients with viable myocardium was performed in chapter 4. This study, showed that early revascularization (waiting time for revascularization <30 days) was associated with high likelihood of improvement in LVEF and favourable prognosis during the follow-up. Conversely, delayed revascularization (waiting time >30 days) did result in failure to improve in LVEF and was associated with a worse prognosis during the follow-up period. It appears that early revascularization of patients with ischemic cardiomyopathy is mandatory in the presence of viable myocardium.

Finally, the impact of LV dilatation on the improvement of LVEF was evaluated in chapter 5 and 6. Our findings showed that despite myocardial viability, the presence of a severely dilated LV

may prohibit improvement of LVEF after revascularization. The cut-off value of 140 ml in end-systolic volume accurately identified patients who did not improve in LVEF (chapter 5). This results indicates that both viability and LV volumes need to be taken in account to predict improvement in LVEF. In addition, in chapter 6 it has been demonstrated that considering together viability and LV volumes a better stratification of patients risk may be obtained. This study showed that the lowest event rate (5%) after revascularization was present in patients with a substantial amount of viable myocardium (≥25% of LV) and end-systolic volume <130 ml, whereas the highest event rate (67%) was observed in patients without viable myocardium and end-systolic volume ≥130 ml. Intermediate event-rate were observed in patients with a substantial viable myocardium and end-systolic volume >130 ml (38%), as well as in patients without viable myocardium and end-systolic volume <130 ml (24%).

Part II of the thesis deals with the additional benefits of revascularization of viable myocardium, beyond improvement of function. Traditionally, improvement of LVEF has been considered the gold-standard to define successful revascularization. This is because LVEF represents an important prognostic indicator in patients with ischemic cardiomyopathy. However, from a clinical point of view, LV remodeling, improvement in heart failure symptoms and in cardiac stress function as well as the reduction of cardiac events during the follow-up may be relevant end-points after revascularization. Accordingly, in chapter 7, it has been demonstrated that myocardial viability prevents ongoing LV remodeling after revascularization and that the extent of myocardial viability is significantly related to the delta in LV volumes after revascularization: the higher the extent of viability, the smaller the enlargement of the LV. Also the presence of viability, was associated with reverse remodeling (decrease in LV volumes) after revascularization. This beneficial effect of viability on LV remodeling was independent from the improvement in LVEF. Indeed, in this study, coronary revascularization resulted in improvement in LVEF in 65% of viable patients, whereas ongoing LV remodeling was prevented in 88% of viable patients. Hence, after revascularization some viable patients did improve in terms of LV remodeling, although failed to improve in LVEF. Conversely, in patients without viability, ongoing LV remodeling occurred after revascularization The beneficial effect of revascularization of viable myocardium on LV remodeling may have important prognostic implications. In the same study, patients with a substantial amount of viable myocardium, together with the improvement of LV remodeling, had a persistent improvement of heart failure symptoms and less cardiac events during the long-term follow-up. Conversely, nonviable patients demonstrated ongoing LV remodeling without an improvement in

heart failure symptoms after revascularization. Moreover, the cardiac event rate was higher in these patients.

Next, in chapter 8, it has been demonstrated that, in patients with a substantial amount of viable myocardium, although resting LVEF not always improves after revascularization, LVEF at peak dobutamine stress echocardiography does improve. In particular, in this study, resting LVEF did not improve in 48% of viable patients. However, the peak-stress LVEF did improve in 19 of 24 patients (79%) without improvement in resting LVEF. Therefore, post-operative DSE identified additional patients who benefit from revascularization in terms of global stress function, despite failure to improve in resting function. This finding indicates that assessment of the LVEF response to low-high dose DSE after revascularization may be a more appropriate strategy to fully evaluate the benefit of revascularization.

The next important issue was whether improvement in LVEF after revascularization always translates in an improvement in heart failure (chapter 10). Interestingly, this study showed that in patients with viable myocardium improvement in LVEF is virtually always accompanied by an improvement in heart failure symptoms; however, in a high proportion of viable patients (75%) heart failure symptoms did improve even though LVEF failed to improve after revascularization. Conversely, in nonviable patients both LVEF and heart failure symptoms failed to improve after revascularization.

Thereafter, the effect of myocardial viability on long-term outcome was evaluated. In chapter 9, it has been demonstrated that improvement of LVEF at 1 year after revascularization does persist during a long-term follow-up of 4 years. In chapter 11 it has been shown that the presence of myocardial viability is an independent predictor of favourable prognosis after revascularization. In this study, the cardiac death rate during the 5 years follow-up was 10% in viable patients as compared to 29% in nonviable patients. This difference was statistically significant. The prognostic value of myocardial viability hold true also in diabetic patients (chapter 13).

Finally, the impact of improvement in LVEF after revascularization on long-term prognosis was evaluated. This study showed that the best prognosis after revascularization may be observed in viable patients who improve in LVEF, whereas the worse prognosis is observed in nonviable patients. Viable patients who do not improve in LVEF after revascularization have an intermediate prognosis. This suggests that although LVEF is an important determinant of prognosis, still alternative beneficial effects of viability may prevent a very poor prognosis in viable patients who do not improve in LVEF.

Conclusions. The findings in this thesis indicate that besides myocardial viability, additional factors may affect the outcome of coronary revascularization. Therefore a careful integration of data about viability, extent of scar tissue, degree of LV remodeling and duration of hibernation is needed in order to predict improvement of LVEF after revascularization. In addition this thesis shows that, beyond improvement of LVEF, other beneficial effects may occur after revascularization of viable myocardium. Therefore, prevention of LV remodeling, improvement in stress function, in heart failure symptoms and long-term prognosis need to be considered to evaluate fully the success of coronary revascularization.

Samenvatting en Conclusies

Samenvatting en Conclusies.

Verschillende studies hebben aangetoond dat coronaire revascularizatie een verbetering van de linker ventrikel ejectie fractie (LVEF), hartfalen symptomen en prognose kan verbeteren bij patiënten met ischemische cardiomyopathie en een substantiële hoeveelheid vitaal myocardweefsel . Meerdere vragen betreffende myocardvitaliteit bij patiënten met ischemische cardiomyopathie zijn nog onbeantwoord. In het bijzonder, waarom verbetert de LVEF niet in alle gevallen bij patiënten die wel een substantiële hoeveelheid vitaal myocardweefsel hebben? Ook is het onduidelijk of er additionele voordelen zijn, naast verbetering van LVEF, na revascularizatie van vitaal myocard. Deze zaken werden onderzocht in dit proefschrift.

Deel 1 van het proefschrift onderzoekt de volgende vraag: waarom verbetert de LVEF niet altijd na revascularizatie bij patiënten met een substantiële hoeveelheid vitaal myocardweefsel? Om deze vraag te beantwoorden werd de invloed van andere factoren, naast vitaliteit, op de verbetering van LVEF na revascularizatie onderzocht. In hoofdstuk 2, werd aangetoond dat de aanwezigheid van een subendocardiaal litteken is geassocieerd met een lage kans op verbetering van segmentele functie na revascularizatie. In hoofdstuk 3 werd aangetoond dat zowel het aantal vitale als nonvitale segmenten dient te worden beschouwd om verbetering van LVEF nauwkeurig te voorspellen. Ondanks de aanwezigheid van vitaal weefsel, verminderd de kans op verbetering van LVEF naarmate het aantal verlittekende segmenten toeneemt. Vervolgens werd de invloed van de timing van revascularizatie onderzocht. Deze studie (hoofdstuk 4) toont aan dat vroege revascularizatie geassocieerd is met een hogere kans op verbetering in LVEF en een gunstige prognose vergeleken met vertraagde revascularizatie. Het lijkt er op dat vroege revascularizatie bij patiënten met ischemische cardiomyopathie aangewezen is als er vitaal weefsel aanwezig is. Tenslotte werd de invloed van LV dilatatie op de verbetering van LVEF onderzocht in hoofdstuk 5 en 6. Onze bevindingen tonen dat ondanks de aanwezigheid van myocardvitaliteit, de aanwezigheid van een ernstig gedilateerde LV de verbetering in LVEF na revascularizatie kan verhinderen (hoofdstuk 5). Bovendien, werd in hoofdstuk 6 aangetoond dat als zowel vitaliteit als LV volumina in ogenschouw worden genomen een betere risicostratificatie kan worden verkregen. De laagste event rate (5%) na revascularizatie was aanwezig bij patiënten met een substantiële hoeveelheid vitaal myocard (>25% van de LV) en een eindsystolisch volumen <130 ml, terwijl de hoogste event rate (67%) werd waargenomen bij patiënten zonder vitaal myocardweefsel en een eindsystolisch volume >130 ml. Deel 2 van het proefschrift behandelt de toegevoegde voordelen van revascularizatie van vitaal myocardweefsel, naast verbetering van functie. Traditioneel wordt verbetering van LVEF beschouwd als de gouden standaard om een succesvolle revascularizatie te definiëren.

Echter vanuit klinisch oogpunt, kunnen ook LV remodeling, verbetering van hartfalen symptomen en reductie van het aantal cardiale events zinvolle eindpunten zijn. In hoofdstuk 7 werd aangetoond dat myocardvitaliteit het proces van LV remodeling kan verhinderen en dat de uitgebreidheid van myocardvitaliteit significant is gerelateerd aan verandering van LV volume na revascularizatie. Dit voordelige effect van myocardvitaliteit op LV remodeling trad op onafhankelijk van verbetering in LVEF. Vervolgens werd in hoofdstuk 8 aangetoond dat bij patiënten met een substantiële hoeveelheid vitaal weefsel, de LVEF gedurende dobutamine stress echocardiografie kan verbeteren ondanks een achterwege blijven van verbetering van LVEF in rust. Deze bevinding geeft aan dat het vaststellen van LVEF gedurende dobutamine stress echocardiografie een zinnige aanvulling kan zijn om de voordelen van revascularizatie volledig te onderzoeken. De volgende belangrijke vraag was of een verbetering van LVEF na revascularizatie zich altijd vertaald in een verbetering van hartfalen (hoofdstuk 10). Interessant genoeg toonde deze studie aan dat bij patiënten met vitaal myocardweefsel een verbetering van LVEF vrijwel altijd vergezeld gaat van een verbetering van hartfalen symptomen. Echter in een groot deel van de patiënten (75%) met vitaal myocardweefsel verbeterde de hartfalen symptomen ook als er geen verbetering van LVEF aantoonbaar was.

Omgekeerd, verbeterde de LVEF en hartfalen symptomen nooit bij patiënten zonder vitaal weefsel na revascularizatie. Tenslotte werd het effect van myocardvitaliteit op lange termijn prognose geëvalueerd. In hoofdstuk 9 werd aangetoond dat verbetering van LVEF na revascularizatie persisteert gedurende een lange termijn follow-up van 4 jaar. In hoofdstuk 11 werd aangetoond dat de aanwezigheid van myocardvitaliteit een onafhankelijke voorspeller is van een gunstige prognose na revascularizatie. In deze studie was het aantal cardiale sterfgevallen gedurende 5 jaar follow-up 10% bij de patiënten met myocardvitaliteit en 29% bij de patiënten zonder vitaliteit. Dit verschil was statistisch significant. De prognostische waarde van myocardvitaliteit geldt ook voor patiënten met diabetes mellitus (hoofdstuk 13). Tenslotte werd de invloed van verbetering in LVEF na revascularizatie op de lange termijn prognose bestudeerd. Deze studie toonde dat patiënten met myocardvitaliteit die verbeteren in LVEF de beste prognose hebben terwijl patiënten zonder myocardvitaliteit een ongunstige prognose hebben. Patiënten met myocardvitaliteit die niet verbeteren in LVEF na revascularizatie hebben een prognose die hier tussen in ligt. Dit suggereert dat alhoewel LVEF een belangrijke determinant van de prognose is er daarnaast alternatieve gunstige effecten van myocardvitaliteit bestaan die een gunstig effect hebben op de prognose.

Conclusies. De bevindingen in dit proefschrift tonen dat er naast myocardvitaliteit, additionele factoren bestaan die de prognose na coronaire revascularizatie beïnvloeden. Daarom is een zorgvuldig onderzoek van gegevens over vitaliteit, uitgebreidheid van littekenweefsel, graad van LV remodeling en de duur van hibernatie nodig om verbetering van LVEF na revascularizatie te kunnen

voorspellen. Daarnaast laat dit proefschrift zien dat naast verbetering van LVEF er andere gunstige effecten kunnen optreden na revascularizatie van vitaal myocardweefsel. Ook preventie van LV remodeling, verbetering van myocardfunctie gedurende een stress test, verbetering van hartfalen symptomen en lange termijn prognose dienen te worden bestudeerd om het succes van coronaire revascularizatie te bepalen.

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AKNOWLEDGEMENTS

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List of publications

1. **Rizzello V**, Poldermans D, Biagini E, Schinkel AFL, Elhendy A, Leone AM, Crea F, Maat A, Roelandt JRTC, Bax JJ. Relation of improvement in left ventricular ejection fraction versus improvement in heart failure symptoms after coronary revascularization in patients with ischemic cardiomyopathy. *Am J Cardiol* in press.
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