Surgery for Acquired Cardiovascular Disease

ACD

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.

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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 (%).

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 (%).

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.

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.

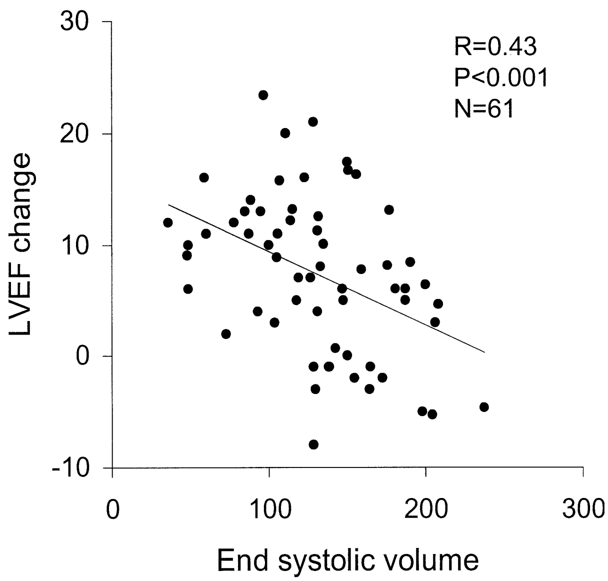

Figure 1. Scatter plot indicating the relation between the end systolic volume (in mL) and the LVEF change following myocardial revascularization in the 61 patients with a substantial amount of viability (R = 0.43, $P < .001$).

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 $\geq$ 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 $\pm$ 3 mm vs 81 $\pm$ 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 $\geq$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 echocardiography 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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