REVIEW ARTICLE

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Revascularization surgery as a treatment concept for heart failure

J. Ennker[1,2], S. Bauer[1], I.C. Ennker[3]

[1]Mediclin Heart Institute Lahr/Baden, Lahr, Germany; [2]University Witten-Herdecke, Faculty of Health, School of Medicine; [3]Department of Plastic, Hand and Reconstructive Surgery, Hannover Medical School, Hannover, Germany

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ABSTRACT

Patients with heart failure symptoms due to ischemic cardiomyopathy face a poor prognosis without adequate treatment. In these patients with viable ischemic myocardium, revascularization surgery is not a new but an established treatment concept. The CASS study, published in 1983, was already able to document the superiority of coronary artery revascularization in patients with poor left ventricular function. It is of utmost importance to predict regional functional recovery in order to assess viability and, thus, the indication for revascularization. Late gadoliniium enhancement cardiovascular magnetic resonance is the new gold standard. By applying this technique, it can be demonstrated that the transmural extent of a scar predicts segmental functional recovery. Numerous studies describe the predictors of survival of surgical revascularization, the indication and impact of medical antiarrhythmic treatment or choice of graft. In addition to conventional surgery, off-pump procedures, minimal extracorporeal circulation and hybrid revascularization have a special role in the treatment of patients with ischemic cardiomyopathy. Surgical techniques and medical therapies continue to improve. The future revascularization in these patients will focus on improving results and making coronary artery bypass grafting for elective revascularization less invasive and safer. Technical evolution, including the use of robotics and anastomotic connectors, intraoperative imaging and protein enzyme therapies, have to be defined concerning their special impact in these patients.

Keywords: *coronary artery bypass grafting, heart failure, left ventricular reconstruction, hybrid revascularisation.*

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INTRODUCTION

Patients with heart failure symptoms due to severe left ventricular (LV) dysfunction and coronary heart disease face a poor prognosis with limited functional improvement and medical treatment only leading to limited survival. Some of the causes of heart failure are myocardial infarction and other forms of ischemic heart disease, hypertension, valvular heart disease and cardiomyopathy. These causes may lead to a reduced LV ejection fraction (EF), with the impaired heart not providing sufficient blood pumping action to meet the needs of the body. Commonly a reduced left ventricular ejection fraction (LVEF) is found in end-stage heart failure patients; this may be below 20%.

In these patients with viable ischemic myocardium, revascularization surgery is not a new but an established treatment concept.

Corresponding author:
Jürgen Ennker MD, PhD
Mediclin Heart Institute Lahr/Baden
77933 Lahr, Germany
e-mail: Juergen.Ennker@mediclin.de

To identify patients with viable ischemic myocardium, which means patients who can benefit from revascularization surgery, modern diagnostics are based on dobutamine stress echocardiography and nuclear imaging (positron emission tomography and cardiovascular magnetic resonance).
These are the mainstays of viability testing and provide information on contractile function, cellular metabolism and myocardial fibrosis.

Historical note

As early as 1983 the superiority of coronary artery revascularization in patients with poor LV function was documented in the CASS study. Aldermann and coworkers identified 420 medically treated and 231 surgically treated patients who had severe LV dysfunction (LVEF <0.36). Multivariate regression analysis of survival, adjusted for co-variabilities, showed that surgical treatment prolonged survival ($p<0.05$), although it ranked below severity of heart failure symptoms, age, ejection fraction and left main stenosis >70% in determining prognosis. Surgical benefit was most apparent for patients with EF <0.25 who had a 43% 5-year survival with medical treatment vs 63% with surgery. Surgically treated patients experienced substantially more symptomatic benefit than treated patients if their presenting symptoms were predominantly angina; however, there was no relief for symptoms caused primarily by heart failure (1).

Diagnosis

Concerning the assessment of viability, it is of utmost importance to predict regional functional recovery. For this purpose, the new gold standard is late gadolinium enhancement cardiovascular magnetic resonance (LGE-CMR). This technique has demonstrated that the transmural extent of scar predicts segmental functional recovery. Pegg and co-workers examined 50 patients with reduced LVEF referred for coronary artery bypass grafting (CABG) and included 33 patients in their analysis. Patients underwent CMR to assess LV function and viability pre-operatively at 6 days and 6 months. Mean LVEF was 0.38 ± 0.11 which improved to 0.43 ± 0.12 after surgery. Twenty-one of the 33 patients had EF improvement of at least 0.3 (EF before 0.38 ± 0.13, after 0.47 ± 0.13); 12/33 did not (EF before 0.39 ± 0.6, after 0.37 ± 0.8).
The only independent predictor for global functional recovery after revascularization was a number of viable + normal segments. Based on a segmental transmural viability cut-off of <50%, receiver operating characteristic (ROC) analysis demonstrated that ≥10 viable + normal segments predicted ±3% improvement of LVEF with a sensitivity of 95% and specificity of 75% (Area under the curve (AUC) = 0.9, $p<0.001$). Transmural viability cut-offs of <25 and 75% and a cut-off of ≥4 viable segments were less useful predictors of global LV recovery. Their findings are important and may provide a simple approach to identify those patients who derive functional and prognostic benefit from CABG (2).

Prognosis

Pocar and co-workers analyzed the 17-year follow-up results for surgical revascularization in patients with ischemic cardiomyopathy. They retrospectively analyzed 45 consecutive angina free patients with ischemic left ventricular dysfunction (EF <0.35), heart failure and New York Heart Association (NYHA) functional class III-IV, who were selected for CABG between 1988 and 1995. Positron emission tomography was used for preoperative identification of myocardial viability. The 30-day

mortality was 4.4% at a medium follow-up of 117 months (maximum 205 months) and probability of survival at 1, 5, 10 and 15 years after CABG was 93.3%, 84%, 65%, and 44% respectively. Left ventricular end diastolic pressure (LVEDP) of 25 mm Hg or more predicted a threefold increase of hazard of death ($p=0.02$), whereas a LVEDP of 20 mm Hg or more correlated with the requirement of intraaortic balloon pump use perioperatively. As could be expected, independent predictors of survival were age >70 years and peripheral vascular disease. Cardiac events accounted for 88% of late deaths, which were primarily related to sudden death or progressive heart failure (3).

Indication and impact of medical and antiarrhythmic treatment

Lytle pointed out the impact of progress of pharmacologic and electric treatment for patients with heart failure. Angiotensin-converting enzyme inhibitors, beta-blockers and diuretics better the symptoms of heart failure. In some studies a decreased mortality was documented during short follow-up intervals. Implantable defibrillators decrease the risk of death due to sudden arrhythmias in certain patient cohorts. According to Lytle, in patients with ischemic cardiomyopathy there are three situations where surgery might not improve patient longevity: if the perioperative risk is greater than the long-term benefit, in patients where probable complications and death are unrelated to ischemia, e.g. in those with a high rate of death from non-ischemic arrhythmias, and if ischemia is not preventable by revascularization, e.g. in patients with diffuse disease (4).

Choice of graft

In order to analyze the choice of conduit for coronary artery bypass grafting in poor ventricles, Attaran and co-workers analyzed the outcome and survival rates of different conduits in patients with LVEF <0.30. In a 10-year period 979 patients were divided into three groups, A: total arterial grafts (n=257), B: total vein grafts (n=76) and C: left internal mammary artery and vein grafts (n=610). Multivariate logistic regression was used to assess the effect of graft type on mortality, while adjusting for patient and disease characteristics. Hospital mortality was 8.9% (group A), 11.8% (group B) and 5.7% (group C). Mortality at 5 years was 27.2%, 42.3% and 28.7% respectively. After risk adjustment, hospital mortality and mid- and long-term mortality showed no significant differences among the groups. Contrary to knowledge concerning the long-term superiority of complete arterial revascularization the authors concluded that patients with poor ventricular function have a high mortality rate in both the short and long term, with any type of conduit. Mortality rates with total arterial grafts and vein plus arterial grafts were comparable before and after risk adjustment (5).

Conventional revascularization

In order to evaluate the importance of completeness of revascularization during long-term follow-up after coronary artery operation, Jones and co-worker analyzed 2057 patients with multi-vessel disease with complete revascularization and 803 with incomplete revascularization; mean age was 57 ± 9 years. They found out that the complications of perioperative infarction and stroke did not differ but that there were more prior myocardial infarctions, worse left ventricular function and more triple-vessel disease in the incomplete revascularization group. Completeness of revascularization correlated with improved overall patient survival, as well as survival in patients with normal left ventricular function. The survival curves continued

to separate over time, such that the difference was greater at 8 years than at 4 years, although by 12 years the curves started to converge (6).

Concerning decision-making in end-stage coronary artery disease, Hausmann et al. compared revascularization and heart transplantation. For this purpose they analyzed 514 patients between April 1986 and December 1994 with end-stage coronary artery disease and LVEF of between 0.10 and 0.30 who underwent coronary artery bypass grafting. Of these patients 225 had been referred as possible candidates for heart transplantation. The prime criterion for bypass grafting at that time was ischemia diagnosed by myocardial scintigraphy and echocardiography ("hibernating myocardium"). Operative mortality for the group was 7.1%. The actuarial survival rate was 90.8% after 2 years, 87.6% after 4 years and 78.9% after 6 years. Left heart catheterizations performed 1 year after the operation showed that LVEF increased from a mean of 0.24 ± 0.03 preoperatively to 0.39 ± 0.06 postoperatively ($p < 0.0001$). Preoperatively 91.6% of the patients were in NYHA class III or IV. Six months postoperatively 90.2% of the surviving patients were in NYHA class I or II. A total of 231 patients with end-stage coronary artery disease and predominant heart failure underwent heart transplantation. Their actual survival rate was 74.9% after 2 years, 73.22% after 4 years and 68.9% after 6 years. All of the patients could be re-categorized into NYHA class I or II postoperatively. The authors concluded that both coronary artery bypass grafting and heart transplantation can be used successfully to improve the life expectancy of patients with end-stage coronary artery disease. Coronary artery grafting leads to an excellent prognosis of these high-risk patients where the myocardium is preoperatively identified as being viable (7).

For definition of the preoperative ejection fraction as a predictor of survival after coronary artery bypass grafting, Hamad et al. analyzed 10662 patients between 1998 and 2007 in comparison with a matched general population. In 10285 patients the results of multivariate logistic regression and Cox regression analysis identified the ejection fraction as a predictor of early and late mortality. Comparing long-term survival and expected survival they found a relatively poorer outcome in all subjects with an ejection fraction of $< 50\%$. In patients with an ejection fraction of between 35 and 50%, 1-year mortality was 90%, 2-year mortality $78 \pm 1.2\%$ and 10-year mortality $50.7 \pm 6.8\%$. In patients with an EF < 0.35 the numbers were $79 \pm 2.2\%$, $74.8 \pm 2.9\%$ and $44.7 \pm 6.5\%$ (8).

A prospective 10-year follow-up study was performed to prospectively analyze all-cause mortality predictors of survival and late functional results after myocardial revascularization for ischemic cardiomyopathy over a 10-year follow-up. For this purpose Shah and colleagues studied 57% with stable coronary artery disease and poor LVEF (< 0.35) enrolled between 1989 and 1994. To avoid patients with stunned myocardium, those with unstable angina or myocardial infarction within the previous 4 weeks were excluded. Mean age was 67 ± 8 years and 93% of patients were male. Mean LVEF was 0.28 ± 0.04 and 65% were in NYHA functional class III-IV. Operative mortality was 1.7%. The mean LVEF (0.30) at 15 months postoperatively did not change from before operation (0.28). There were eight deaths at 1 year and 42 deaths over the course of the study, producing a survival of 82.5% at 1 year, 55.7% at 5 years and 23.9% at 10 years (95% confidence interval 14.6%-39.1%). Symptom-free survival was 77.2% at 1 year and 20.3% at 10 years. The leading cause of death was heart failure in 29% (12/42).

Multivariate analysis showed that large reversible defects identified by the thallium stress test were associated with improved LVEF at 1 year, but only male sex was associated with improved long-term survival. The authors concluded that myocardial revascularization for ischemic cardiomyopathy is associated with good functional relief from symptoms of angina initially and, to a lesser extent, of heart failure. Revascularization may have the advantage of preserving the remaining left ventricular function. However, the long-term mortality remains high (9).

The predictors of long-term outcome in patients with left ventricular dysfunction following coronary artery bypass grafting were described by Rybicka-Musialik and co-workers. They pointed out that the prognostic significance of clinical non-invasive risk markers in patients after surgical revascularization remains unclear, especially in post-infarction patients with left ventricular dysfunction. For this purpose they followed a cohort of 61 patients (age 59±9 years, 49 males, LVEF 0.33±0.6) 6-12 months after CABG. Demographics, clinical data, medication, LVEF, QRS >120 ms or presence of late potentials, QT dispersion >180 ms, premature ventricular contractions (PVC) >10/h, non-sustained ventricular tachycardia and standard deviation of normal to normal intervals (SDNN) >70 ms in ambulatory were analyzed. All-cause and cardiovascular mortality were evaluated. Fourteen patients died, 10 of them due to cardiovascular causes. Univariable Cox analysis showed that incomplete revascularization, history of angina, heart failure, low LVEF, use of nitrates, digitalis or diuretics in presence of late potentials or prolongation of QRS complex were predictors of poor outcome.

Combination of angina and low LVEF was the best model in a multivariable Cox analysis for the prediction of both types of death. Main predictors of all-cause and cardiovascular mortality were LV dysfunction, angina class and low LVEF. A combination of LVEF <30% with QRS >120 ms or late potentials may also be helpful in the identification of high-risk subjects (10).

Carr and colleagues analyzed the potential for long-term survival in patients with severe left ventricular dysfunction after coronary bypass. Between 01/1990 and 11/1999, 86 patients with severe left ventricular dysfunction (mean ejection fraction 0.18±0.03; range, 0.20) underwent coronary artery bypass grafting; 10 perioperative deaths (11% mortality) occurred. The mean survival was 55 months with an extra 5-year survival rate of 59% (actuarial 5-year 65%, 10-year 33%). Postoperatively they were able to document an improvement of the ejection fraction as shown in echocardiography with unchanged diastolic left ventricular dimension. The systolic left ventricular dimension decreased significantly from 5.02±0.77 cm to 4.26±0.91 cm (6 months), 3.98±1.43 cm (1 year) and 4.10±1.14 cm (2 years). The preoperative NYHA classification for all patients improved from 2.8±0.8 to 1.6±0.6 after a mean of 53 months (standard deviation ±34 months). The authors concluded that patients with left ventricular dysfunction can derive long-term benefit from coronary bypass through improved left ventricular contractility as documented by a significantly decreased systolic left ventricular dimension and increased ejection fraction. The NYHA functional class improved significantly (11).

Off-pump, minimal extracorporeal circulation and hybrid revascularization

The potential effect of off-pump beating heart (OPBH) surgery with the help of minimized extracorporeal circulation for

CABG was analyzed by Munos and co-workers in patients with a high-risk EuroSCORE to compare the strategy to other procedures, including off-pump coronary artery bypass (OPCAB) and minimal extracorporeal circulation (MECC) or conventional extracorporeal circulation (CECC) with cardiac arrest. Two hundred fourteen patients (mean age 74.26±8.5 years, 68.7% male) were operated upon. Mean EuroSCORE was 12.1±2.9, left ventricular function 0.374±0.123, recent myocardial infarction (MI) was present in 49.5%, renal failure in 48.1%, chronic obstructive pulmonary disease (COPD) in 42.2% and peripheral vascular disease (PVD) in 55.6%. Mean number of grafts per patient was 2.4±0.7. The study showed that it was possible, in very high-risk patients, to carry out revascularization with OPBH similar to that using MECC or CECC under cardiac arrest. This technique reduces troponin release (3.23 vs 6.56 (u/l), $p<0.01$). Postoperative myocardial complications (2% vs 8%, $p<0.01$), cardiotonic drug prescription (15.7% vs 31.3%, $p<0.01$), ventilation time (4.57 h vs 6.48 h, $p<0.01$) and length of stay (LOS) in ICU (2.16 vs 2.53 days, $p=0.02$). The authors concluded that OPBH surgery combining MECC without aortic cross-clamping makes it possible to perform complete revascularization and is an interesting alternative to CABG in high-risk patients (12).

The effect of off-pump coronary artery revascularization in terms of the long-term survival in patients with ventricular dysfunction was analyzed by Attaran and co-workers. In a 10-year period, a total of 934 patients with poor left ventricular function (EF <30%) undergoing isolated first-time coronary artery bypass graft surgery were studied. Two groups were analyzed: the ONCAB group (528 patients) and the OPCAB group (406 patients).

The EuroSCORE was significantly higher in the OPCAB group ($p=0.049$). Mid-term survival rate (5 years) and long-term survival rate (10 years) were compared after adjusting for preoperative characteristics, postoperative complications and in-hospital mortality. Postoperative complications of both groups, such as atrial fibrillation (29.6% vs 28.6%), renal failure (9.3% vs 9.6%), stroke (2.3% vs 0.7%) and perioperative myocardial infarction (3.8% vs 2.0%) were comparable between ONCAB and OPCAB patients. The average number of grafts was ONCAB: 3.7 and OPCAB: 3.1 ($p<0.01$). In the OPCAB group, length of intensive care stay, hospital stay and ventilation time were considerably shorter ($p<0.01$). In OPCAB patients the incidence of wound infection was also lower ($p<0.05$). After adjusting for preoperative characteristics, only mitral infarction was lower in the OPCAB group ($p<0.04$) while most other postoperative complications remained the same in both groups. The same holds for the rate of stroke (OPCAB: 0.09%; ONCAB: 1.6%). In-hospital mortality was higher in ONCAB compared to OPCAB (7.8% vs 5.7%), but it was not statistically significant ($p=0.21$). The survival rate for each group was (30-day survival, 5-year survival, 10-year survival) OPCAB: 94.7%, 75.4%; 71.8%, ONCAB: 93.0%, 76.5%, 69.5%. The authors concluded that, despite the reported benefits of OPCAB, there was no statistically significant influence on in-hospital mortality, mid-term survival or long-term survival in patients with left ventricular dysfunction. With adequate myocardial protection in ONCAB and complete revascularization in OPCAB, similar results are achievable (13).

In a meta-analysis Jarral and co-workers searched 17 studies that dealt with the question of whether off-pump coronary artery bypass surgery has a beneficial effect on mortality in patients with left ventricular dysfunction. By comprising 7

studies and 1512 patients, the meta-analysis showed no significant difference in terms of operative mortality. The authors concluded that there is limited evidence to associate the OPCAB technique with improved short-term mortality (14). The lack of high-quality data indicates that prospective randomized trials are needed.

Hybrid coronary revascularization is combining minimally invasive coronary artery surgery and percutaneous coronary intervention, thus allowing sternal preservation for the treatment of patients with multi-vessel coronary artery disease. Revascularization of the left anterior descending coronary artery can be achieved by a robotically assisted endoscopic approach or conventional minimally invasive direct coronary artery bypass (MIDCAB) surgery. Early experience demonstrates the safety of the procedure, with perioperative clinical results comparable to those of conventional coronary artery revascularization (15). However, Leacche et al. reported that in high risk patients with complex coronary artery disease (Syntax score greater than or equivalent to 33, EuroSCORE 5) coronary artery bypass grafting is superior to hybrid coronary revascularization. Special publications addressing the role of hybrid revascularization procedures in patients with ischemic cardiomyopathy are not listed in the literature currently. The role of hybrid revascularization has yet to be defined (16).

Concomitant left ventricular reconstruction

Marchenko et al. analyzed the results of coronary artery bypass grafting alone and combined with surgical ventricular reconstruction for ischemic heart failure. They included 236 patients with ischemic heart failure and ejection fraction <35% who underwent surgical treatment. Patients were randomized in two cohorts: 120 patients underwent CABG alone and 116 patients underwent CABG with surgical ventricular reconstruction (SVR). Hospital mortality was 5.8% after isolated CABG and 3.5% after CABG plus SVR. The survivors had a follow-up ranging between 4 months and 5 years with a mean follow-up time of 31±13 months. Mean New York Heart Association functional class decreased from 2.9±0.5 to 2.2±0.7 one year after CABG and from 3.1±0.4 to 2.0±0.6 one year after CABG plus SVR. The authors were able to demonstrate that SVR significantly decreased end diastolic volume from 237±52 to 176±30 ml and correspondingly increased EF from 0.32±0.6 to 0.39±0.9. After isolated CABG, EF did not increase significantly (0.32±0.7 preoperatively and 0.34±0.11 postoperatively). One and 3-year survival rates were 95% and 78% after SVR with CABG versus 83% and 78% after CABG alone. The authors concluded that the combined procedure did not prolong longevity and reduce mortality in patients with ischemic cardiomyopathy (17).

Two years ago, a paper in the the New England Journal of Medicine by Velazquez and co-workers addressed also the question of coronary artery bypass surgery in patients with left ventricular dysfunction. They enrolled 1212 patients with an EF of <35% or less and coronary artery disease amenable to CABG. The patients were randomly assigned to medical therapy alone (602 patients) or medical therapy plus CABG (610 patients). The primary outcome was the rate of death from any cause. Major secondary outcomes included death from cardiovascular causes and death from any cause or hospitalization for cardiovascular causes. The primary outcome occurred in 244 patients (41%) in the medical-therapy group and 218 (36%) in the CABG group (hazard ratio with CABG, 0.86; 95% confidence interval [CI] 0.72 to 1.04; p=0.12). A

total of 201 patients (33%) in the medical-therapy group and 168 (28%) in the CABG group died from an adjusted cardiovascular cause (hazard ratio with CABG, 0.81; 95% CI, 0.66 to 1.00; p=0.05). Death from any cause or hospitalization for cardiovascular causes occurred in 411 patients (68%) in the medical-therapy group and 351 (58%) in the CABG group (hazard ratio with CABG, 0.74; 95% CI, 0.64 to 0.85; p<0.001). By the end of the follow-up period (median, 56 months), 100 patients in the medical-therapy group (17%) underwent CABG, and 555 patients in the CABG group (91%) underwent CABG. The authors concluded that in this randomized trial there was no significant difference between medical therapy alone and medical therapy plus CABG with respect to the primary end-point of death from any cause. However, patients assigned to CABG, as compared with those assigned to medical therapy alone, had lower rates of death from cardiovascular causes and of death from any cause or hospitalization for cardiovascular causes in comparison to those patients assigned to medical therapy alone. The authors commented that clinical circumstances led to crossover in the case of 70% of patients who had been randomly assigned to medical therapy and 9% who had been randomly assigned to CABG. The treatment analysis suggests that this imbalance in crossover rates between groups modified the results of the primary intention-to-treat analyses by diminishing the effect of CABG relative to medical therapy (18).

CONCLUSION

In patients with ischemic cardiomyopathy and with viable ischemic myocardium, revascularization surgery is not a new but an established treatment concept. Concerning the assessment of viability, it is of utmost importance to predict regional functional recovery. For this purpose, the new gold standard is LGE-CMR. Patients with ischemic cardiomyopathy will remain the recipients of on- and off-pump CABG as surgical techniques and medical therapies continue to improve.

The future of revascularization in these patients will focus on improving results and making CABG for elective revascularization less invasive and safer. Promising techniques that have to be employed on a larger scale are minimally invasive techniques including the use of robotics and anastomotic connectors, intraoperative imaging, hybrid procedures and protein enzyme therapies.

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