



Universiteit
Leiden
The Netherlands

Left ventricular reconstruction in ischemic cardiomyopathy

Klein, P.

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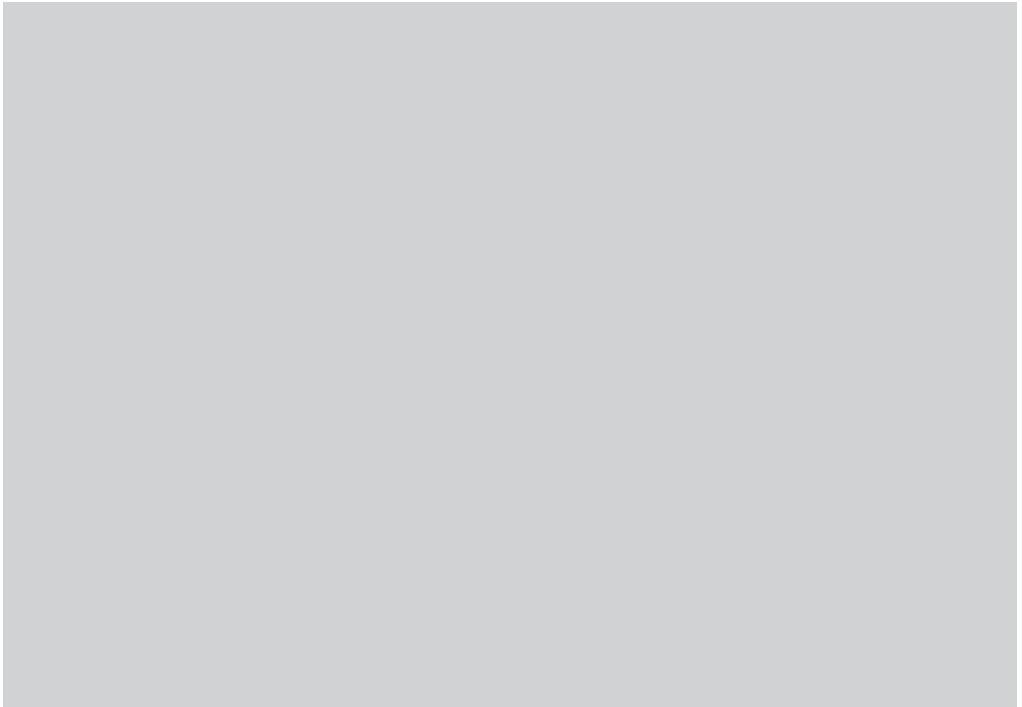
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Chapter 12

Thesis Summary



Chapter 1 is a general introduction to the subject of matter of this thesis. The disease of ischemic cardiomyopathy, the relation with heart failure as a clinical syndrome and its cause - obstructive coronary artery disease - are explained. The pathophysiology of myocardial infarction and (negative) cardiac remodelling are described, followed by its clinical characteristics and implications. Next, the rationale for surgical ventricular reconstruction and its history are described. Followed by an explanation of the STICH-trial, the first randomised controlled trial to address whether or not contemporary CABG surgery is superior to contemporary medical/secondary prevention therapy in prolonging survival in patients with heart failure and whether or not the addition of surgical ventricular reconstruction (SVR) to CABG improves hospitalisation-free survival among patients with significant anterior wall dysfunction. Last, the position and outcome of SVR after the STICH-trial is described followed by a detailed description of the aims and outline of this thesis.

Chapter 2 focuses on the early and late outcome of left ventricular (LV) reconstruction surgery in ischemic heart disease. A systematic review of the literature was performed to determine early and late mortality associated with LV reconstruction surgery and to assess the influence of different surgical techniques, concomitant surgical procedures, clinical and hemodynamic parameters on mortality. The MEDLINE database (January 1980—January 2005) was searched and from the pooled data, hospital mortality and survival were calculated. Summary estimates of relative risks (RR) were calculated for the techniques that were used and for concomitant CABG and mitral valve surgery. The risk-adjusted relationships between mortality and clinical and hemodynamic parameters were assessed by meta-regression. A total of 62 studies (12,331 patients) were identified. Weighted average early mortality was 6.9%. Cumulative 1-year, 5-year and 10-year survival were 88.5%, 71.5% and 53.9%, respectively. Endoventricular reconstruction (EVR) showed a reduced risk for both early (RR = 0.79, $p < 0.005$) and late (RR = 0.67, $p < 0.001$) mortality compared to the linear repair (early: RR = 1.38, $p < 0.001$; late: RR = 1.83, $p < 0.001$). Early and late mortality were mainly cardiac in origin, with as predominant cause heart failure in respectively 49.7% and 4.5% of the cases. Ventricular arrhythmias caused 16.6% of early deaths and 17.2% of late deaths. Concomitant CABG significantly decreased late mortality (RR = 0.28, $p < 0.001$) without increasing early mortality (RR = 1.018, $p = 0.858$). Concomitant mitral valve surgery showed both an increased risk for early (RR = 1.57, $p = 0.001$) and late mortality (RR = 4.28, $p < 0.001$). No clinical or hemodynamic parameters were found to influence mortality. It is noteworthy that only one third of patients included in the current analysis were operated for heart failure (14 studies, 4135 patients). In this group we noted an early mortality of 11.0% with a late mortality (3-year) of 15.2%. This analysis of pooled literature data

showed that LV reconstruction surgery is performed with acceptable mortality and EVR may be the preferred technique with a reduced risk for early and late mortality. Concomitant CABG improved outcome, whereas the need for mitral valve surgery appeared an index of gravity. No clinical or hemodynamic parameters were found to influence mortality; specifically LV ejection fraction and LV volumes both did not predict outcome.

Advanced ischemic heart failure can be treated with SVR. While numerous risk factors for mortality and recurrent heart failure have been identified, no plain predictor for identifying SVR patients with left ventricular damage beyond recovery is yet available. In **Chapter 3**, echocardiographic wall motion score index (WMSI) was tested as a predictor for mortality or poor functional result after SVR. One hundred and one patients electively operated between April 2002 and April 2007 were included for analysis. All patients had advanced ischemic heart failure (NYHA-class \geq III and LVEF \leq 35%). Mean logistic EuroSCORE was 10 ± 8 . All patients were evaluated at 1-year follow-up. Risk factors for poor outcome, defined as mortality or poor functional result (NYHA class \geq III) at 1-year follow-up were identified by univariable logistic regression analysis. Preoperatively, a 16-segment echocardiographic WMSI was calculated and receiver operating characteristic curve analysis was used to identify cut-off values for WMSI in predicting poor outcome. Early mortality was 9.9%, late mortality 6.6%. NYHA class improved from 3.2 ± 0.4 to 1.5 ± 0.7 . At 1-year follow-up, 10 patients (12%) were in NYHA class III and the remaining patients were in NYHA class I or II (75 patients, 88%). WMSI was found to be the only statistically significant predictor for poor outcome (odds ratio 139, 95% confidence interval (CI) 17 - 1116, $p < 0.0001$). The optimal cut-off value for WMSI in predicting mortality or poor functional result was 2.19 with a sensitivity and specificity of 82% (95% CI 81.5 - 82.5% and 81.4 - 82.6%). The area under the curve was 0.94 (95% CI 0.90 - 0.99). Positive and negative predictive values were 67% and 92% respectively (95% CI 66.4 - 67.6% and 91.4 - 92.6%). We concluded that sufficient residual remote myocardium is necessary to recover from a SVR procedure and to translate the surgically induced morphological changes into a functional improvement. Preoperative WMSI is a surrogate measure of residual remote myocardial function and is a promising tool for better patient selection to improve results after SVR procedures for advanced ischemic heart failure.

Remodelling of the LV in ischemic cardiomyopathy frequently leads to functional mitral regurgitation (MR). The indication for correcting MR in patients undergoing LV reconstruction (LVR) is unclear. The study in **Chapter 4** was set out to evaluate our strategy of correcting MR \geq grade 2+ by restrictive mitral annuloplasty (RMA)

during LVR. We studied 92 consecutive patients (76 men, mean age 61 ± 10 years) who underwent LVR for ischemic heart failure (IHF). RMA was performed in all patients with MR \geq grade 2+ on preoperative echocardiography and in patients who showed increased MR to \geq grade 2+ immediately after LVR. Patients were attributed to a RMA and no-RMA group, depending on whether or not concomitant RMA had been performed. Mean clinical and structured echocardiographic follow-up was 47 ± 20 months and was 100% complete. In 38 out of 40 patients (95%) with preoperative MR \geq grade 2+, concomitant RMA was planned and performed. In 17 out of 52 patients (33%) with MR $<$ grade 2+ preoperatively, MR increased after LVR to \geq grade 2+ leading to additional RMA during a second period of aortic cross-clamping. Early mortality in the RMA group ($n = 55$) was 12.7% and survival at 36 months $78.2 \pm 11.2\%$. Early mortality in the no-RMA group ($n = 37$) was 5.4% and survival at 36 months $81.1 \pm 12.8\%$. Patients in the RMA group had significantly more reduced LV function with greater LV dimensions and volumes preoperatively. Echocardiography demonstrated sustained improvement in LVEF with reduction of LV volumes in both patient groups. Recurrence of MR at late follow-up was observed in 2 patients (1 patient per group). We concluded that patients with IHF eligible for LV reconstruction have MR \geq grade 2+ in 44% of cases. In one-third of IHF patients with MR $<$ grade 2+ preoperatively, MR increases to \geq grade 2+ after LVR. Concomitant mitral valve repair for MR \geq grade 2+, on either preoperative echocardiography or immediately after LVR, results in favourable late clinical and echocardiographic outcome that proved to be similar to patients without concomitant mitral valve repair, despite more advanced disease.

Chapter 5 describes the study to evaluate outcomes after an integrated approach of left ventricular reconstruction with concomitant procedures (mitral/tricuspid valve repair, coronary revascularization), and assess risk factors for event-free survival, focusing on left ventricular geometry/function and presence of functional mitral regurgitation (MR). A total of 159 consecutive heart failure patients who underwent left ventricular reconstruction between 2002 and 2011 were included. Mid-term echocardiographic and long-term clinical outcomes were evaluated. Preoperative risk factors were correlated to event-free survival (freedom from mortality, left ventricular assist device implantation, and heart-transplantation). Mid-term echocardiography demonstrated decreased indexed left ventricular end-systolic volumes (89 ± 42 mL/m² preoperatively; 51 ± 18 at mid-term, $p < 0.001$), and absence of MR \geq grade 2. Event-free survival was $83\% \pm 3\%$ at 1-year, $68\% \pm 4\%$ at 5-year, and $46\% \pm 4\%$ at 10-year follow-up. Preoperative wall motion score index (WMSI; hazard ratio [HR] 3.1, 95% confidence interval [CI] 1.7–5.8, $p < 0.001$) and presence of MR \geq grade 2 (HR 1.9, 95% CI 1.1–3.1, $p [0.014]$) were independently associated with adverse event-free

survival. We concluded that event-free survival is favourable in patients with WMSI < 2.5 and significantly worse when WMSI is ≥ 2.5 . In both groups, the presence of preoperative MR \geq grade 2 negatively affects event-free survival, despite successful correction of MR. Risk stratification by preoperative WMSI and MR grade supports the Heart team in choosing the optimal surgical strategy for patients with refractory heart failure.

Besides implantation of an implantable cardioverter-defibrillator (ICD), a proportion of patients with LV dysfunction due to ischemic cardiomyopathy are potential candidates for surgical LV reconstruction (Dor procedure), which changes LV ejection fraction (LVEF) considerably. In these patients, LVEF as selection criterium for ICD implantation may be difficult. The study in **Chapter 6** aimed to determine the value of LVEF as criterium for ICD implantation in heart failure patients undergoing surgical LV reconstruction. Consecutive patients with end-stage heart failure who underwent ICD implantation and LV reconstruction were evaluated. During admission, two-dimensional (2D) echocardiography (LV volumes and LVEF) was performed before surgery and was repeated at 3 months after surgery. Over a median follow-up of 18 months, the incidence of ICD therapy was evaluated. The study population consisted of 37 patients (59 ± 11 years). At baseline, mean LVEF was $23 \pm 5\%$. Mean left ventricular end-systolic volume (LVESV) and left ventricular end-diastolic volume (LVEDV) were 175 ± 73 mL and 225 ± 88 mL, respectively. At 3-month follow-up, mean LVEF was $41 \pm 9\%$ ($P < 0.0001$ vs. baseline), and mean LVESV and LVEDV were 108 ± 65 mL and 176 ± 73 mL, respectively ($P < 0.0001$ vs. baseline). During 18-month follow-up, 12 (32%) patients had ventricular arrhythmias, resulting in appropriate ICD therapy. No significant relations existed between baseline LVEF ($P = 0.77$), LVEF at 3-month follow-up ($P = 0.34$), change in LVEF from baseline to 3-month follow-up ($P = 0.28$), and the occurrence of ICD therapy during 18-month follow-up. We concluded that LVEF before and after surgical LV reconstruction is of limited use as criterium for ICD implantation in patients with end-stage heart failure.

Chapter 7 to **Chapter 10** describe the hybrid left ventricular reconstruction. In **Chapter 7**, a novel hybrid transcatheter technique is described to reconstruct the remodelled LV by plication of the anteroseptal LV scar, in order to reduce the enlarged LV volume, decrease the wall stress and increase the EF. The procedure, called less invasive ventricular enhancement (LIVE), has the objective of reconstructing the LV by plication of fibrous scar and relies on micro-anchoring technology. This system consists of a number of paired anchors connected by a poly-ether-ether-ketone (PEEK) tether that, once properly positioned, are pulled together with a controlled force by means of a specialised force gauge and finally released. Both

sternotomy and extracorporeal circulation are avoided. Patients eligible for the procedure present with symptomatic heart failure (NYHA Class \geq II) and ischaemic cardiomyopathy (EF $<$ 40%) after anteroseptal MI resulting in a dilated LV with an akinetic/dyskinetic scar in the anteroseptal wall and apex. Preoperative planning requires gadolinium-enhanced magnetic resonance imaging (MRI) (or alternatively contrast computed tomography [CT]) to define the scar morphology clearly. Scarred regions must comprise at least 50% of the wall thickness to enable safe anchor implantation. The LIVE procedure is a hybrid transcatheter procedure performed by both an interventional cardiologist(IC) and a cardiothoracic surgeon (CTS) in cooperation. Additional support is provided by the presence of a cardiologist skilled in three-dimensional transoesophageal echocardiography (3D-TEE). This minimally invasive and off-pump technique has the promise of offering an effective LV reconstruction at lower risk in a very high-risk group of patients. The main limitation of this technique is represented by its applicability only in patients with previous antero-septal-lateral infarction, while patients with infarctions in other territories are not candidates for this procedure. In **Chapter 8**, we describe preliminary multicenter results of the LIVE procedure in the Netherlands. Between October 2016 and April 2017, 9 patients (8 men, 1 woman; mean age 60 ± 8 years) were operated on in 2 Dutch centres. Procedural success was 100%. On average, 2.6 anchor pairs were used to reconstruct the LV. Comparing echocardiographic data preoperatively and directly postoperatively, LV ejection fraction increased from $28 \pm 8\%$ to $40 \pm 10\%$ (change +43%, $P < 0.001$) and LV volumes decreased LV end-systolic volume index 53 ± 8 ml/m² to 30 ± 11 ml/m² (change -43%, $P < 0.001$) and LVEDVI 75 ± 23 ml/m² to 45 ± 6 ml/m² (change -40%, $P = 0.001$). In 1 patient, an RV perforation occurred which necessitated conversion to full sternotomy. One patient underwent a postoperative revision because of RV restriction. After the removal of 1 'RV-LV' anchor pair, the patient recovered completely. Hospital mortality was 0%. The median duration of intensive care unit stay was 2 days [interquartile range (IQR) 1–46 days], and the median length of hospital stay was 9 days (IQR 3–57 days). We concluded that hybrid transcatheter LV reconstruction is a promising novel treatment option for patients with symptomatic heart failure and ischaemic cardiomyopathy after anteroseptal MI and that the early results demonstrate that the procedure is safe and results in a significant improvement in EF and reduction in LV volumes in the early postoperative period. In **Chapter 9** we present 12-months follow-up data of an international (European) multicenter study of the LIVE procedure with BioVentric Revivent TC System. Patients were considered eligible for the procedure when they presented with symptomatic HF [New York Heart Association (NYHA) class \geq II], left ventricular (LV) dilatation and dysfunction caused by myocardial infarction, and akinetic and/or dyskinetic transmural scarred myocardium located in the anteroseptal, anterolat-

eral, and/or apical regions. A total of 89 patients were enrolled and 86 patients were successfully treated (97%). At 12 months, a significant improvement in LV ejection fraction ($29 \pm 8\%$ vs. $34 \pm 9\%$, $P < 0.005$) and a reduction of LV volumes was observed (LV end-systolic and end-diastolic volume index both decreased: 74 ± 28 mL/m² vs. 54 ± 23 mL/m², $P < 0.001$; and 106 ± 33 mL/m² vs. 80 ± 26 mL/m², respectively, $P < 0.0001$). Four patients (4.5%) died in hospital and survival at 12 months was 90.6%. At baseline, 59% of HF patients were in NYHA class III compared with 22% at 12-month follow-up. Improvements in quality of life measures (Minnesota Living with Heart Failure Questionnaire 39 vs. 26 points, $P < 0.001$) and 6-min walking test distance (363 m vs. 416 m, $P = < 0.001$) were also significant. We concluded that treatment with the Revivent TC System in patients with symptomatic HF results in significant and sustained reduction of LV volumes and improvement of LV function, symptoms, and quality of life. Finally, in **Chapter 11**, the challenges of surgical ventricular volume reduction and reshaping in ischemic heart failure patients is discussed together with the concept of a more individualised or patient-tailored approach.