Left Ventricular Reconstruction in Ischemic Heart Disease

Ulrik Sartipy

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Abstract


Background: Postinfarction cardiac remodeling with left ventricular dilatation is strongly associated with decreased survival. Surgical restoration of left ventricular size and form is proposed to improve survival, functional status, and quality of life.

Methods: In three retrospective studies, 101 (Study I), 53 (Study II), and 136 (Study III) patients were included. Patients were considered for LVR if they demonstrated an enlarged, either dyskinetic or akinetic, left ventricle accompanied by left ventricular dysfunction after myocardial infarction, and had symptoms of angina or heart failure with or without ventricular tachycardia. Survival, morbidity, and freedom from re-hospitalization were ascertained by review of patients' records, our institutional database, and national registers. In addition, freedom from postoperative ventricular tachycardia was evaluated by programmed ventricular stimulation in most patients in Study II. Conventional statistical methods were employed to identify factors associated with adverse outcome in Study III. Two prospective studies were conducted to investigate functional status and quality of life (Study IV, n=23) and changes in biomarkers for heart failure (Study V, n=29). Health-related quality of life and functional status was evaluated preoperatively, six months postoperatively, and at late follow-up almost two years after surgery, with the Short Form-36 questionnaire, the six-minute walk test, and New York Heart Association functional class. Blood samples were collected at equivalent time-points for analysis of biomarkers for heart failure (BNP and NT-pro-BNP).

Results and Conclusions: [1] LVR is a reproducible and safe surgical option in patients with left ventricular aneurysm or ischemic dilated cardiomyopathy. Early mortality was 7.4% and five year survival was 68%. [2] LVR including endocardectomy and cryoablation resulted in a very high (90%) freedom from spontaneous ventricular tachycardia. [3] LVR resulted in a high degree of freedom from re-admission for heart failure. We found a strong association between increasing grade of preoperative mitral regurgitation and both long-term mortality and re-admission for heart failure. [4] Functional status and health-related quality of life improved six months after LVR and the improvement was sustained at late follow-up. [5] Severe heart failure secondary to postinfarction left ventricular remodeling can be reversed by LVR. Clinical improvement was associated with reduced levels of BNP and NT-pro-BNP six months after surgery. Clinical improvement was maintained and peptide levels were further reduced at late follow-up.

Keywords: Left ventricular reconstruction, surgical ventricular restoration, heart failure surgery, left ventricular aneurysm, ischemic heart disease, cardiac remodeling, surgery for ventricular tachycardia
List of Publications

This thesis is based on the following original articles which will be referred to in the text by their Roman numerals.

I. Sartipy U, Albåge A, Lindblom D
The Dor procedure for left ventricular reconstruction. Ten-year clinical experience.

II. Sartipy U, Albåge A, Strååt E, Insulander P, Lindblom D
Surgery for ventricular tachycardia in patients undergoing left ventricular reconstruction by the Dor procedure.

III. Sartipy U, Albåge A, Lindblom D
Risk factors for mortality and hospital re-admission after surgical ventricular restoration.

IV. Sartipy U, Albåge A, Lindblom D
Improved health-related quality of life and functional status after surgical ventricular restoration.
_Ann Thorac Surg (In Press)_

V. Sartipy U, Albåge A, Larsson PT, Insulander P, Lindblom D
Changes in B-type natriuretic peptides after surgical ventricular restoration.
Submitted
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Abbreviations

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<th>Description</th>
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<tr>
<td>BNP</td>
<td>Brain natriuretic peptide</td>
</tr>
<tr>
<td>NT-pro-BNP</td>
<td>Amino terminal pro-brain natriuretic peptide</td>
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<td>NYHA</td>
<td>New York Heart Association</td>
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<td>SF-36</td>
<td>Short Form-36</td>
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A note on terminology

In the literature, and also in publications by our group, the terms left ventricular reconstruction and Surgical Ventricular Restoration (SVR) are used interchangeably.

For consistency, the term *left ventricular reconstruction* is used throughout this text.
Introduction

Despite improvements in pharmacologic treatment, many patients with heart failure have severe and persistent symptoms, and their prognosis remains poor. In patients with severe heart failure, the one year mortality is more than 50% [1].

The progression of heart failure is associated with left ventricular remodeling, which manifests as gradual increases in left ventricular end-diastolic and end-systolic volumes, wall thinning, increased chamber sphericity and progressive worsening of systolic and diastolic function.

Since left ventricular dilatation is one of the strongest predictors of mortality in heart failure [2-4], prevention or reversal of maladaptive remodeling represents a very important therapeutic target. In addition to pharmacological therapy, several surgical procedures have been developed or refined to counteract the ventricular remodeling process.

In patients with ischemic heart disease, left ventricular reconstruction targets vessel, ventricle and valve. The procedure includes complete revascularization, ventricular reconstruction to restore near-normal shape and volume and, when necessary, mitral valve repair.

Our experience with left ventricular reconstruction began in 1994 and to date, more than 150 patients have been operated at Karolinska University Hospital. The total number of procedures per year in Sweden and in Stockholm is shown in Figure 1.

Figure 1. Left ventricular reconstruction. Number of operations performed in Stockholm and in Sweden.
Background

HEART FAILURE

The majority of patients with heart failure have symptoms due to an impairment of left ventricular myocardial function. The most common cause of heart failure is coronary artery disease.

What is heart failure?
Heart failure is a syndrome in which the patients should have the following features: symptoms of heart failure, typically shortness of breath or fatigue, either at rest or during exertion, or ankle swelling and objective evidence of cardiac dysfunction at rest [1].

Heart failure should never be the only diagnosis and there is no single diagnostic test for heart failure because it is largely a clinical diagnosis that is based on a careful history and physical examination.

New approach to the classification of heart failure
The guidelines for the evaluation and management of chronic heart failure from the American College of Cardiology and the American Heart Association [5] presented a new approach to the classification of heart failure. This classification system was not intended to replace the New York Heart Association (NYHA) functional classification (Table 1), but can serve as a complement.

Four stages were defined:

- Patients with stage A heart failure are at high risk for the development of heart failure but have no apparent structural abnormality of the heart.
- Patients with stage B heart failure have a structural abnormality of the heart but have never had symptoms of heart failure.
- Patients with stage C heart failure have a structural abnormality of the heart and current or previous symptoms of heart failure.
- Patients with stage D heart failure have endstage symptoms of heart failure that are refractory to standard treatment.

The new classification differs from the traditional NYHA classification and recognizes that heart failure, like coronary artery disease, has established risk factors and structural prerequisites. The development of heart failure has asymptomatic and symptomatic phases. Specific treatments targeted at each stage can reduce morbidity and mortality. An important feature of the staging classification is that patients can only progress in one direction; from Stage A to D. This was intended to reflect the progressive nature of heart failure.
Patophysiology

A number of factors contribute to the syndrome of heart failure as it is understood today (Table 2).

BNP and NT-pro-BNP in heart failure

There is extensive documentation of elevated levels of BNP and NT-pro-BNP in patients with heart failure. In addition, studies have demonstrated an association between severity of heart failure, in terms of NYHA-class, left ventricular systolic and diastolic function, and BNP levels. Also, higher concentrations of these peptides are associated with increased cardiovascular and all-cause mortality in patients with heart failure [6-8]. The diagnostic performance of BNP and NT-pro-BNP are considered comparable [8].

Physiology of BNP and NT-pro-BNP

Brain natriuretic peptide is a hormone released primarily from the cardiac ventricles in response to myocardial wall stress. It is synthesized as an inactive prohormone that is cleaved in equal proportions into the active hormone BNP and the inactive N-terminal fragment (NT-pro-BNP). Both BNP and NT-pro-BNP are constantly released. The main stimulus for increased BNP and NT-pro-BNP secretion is myocardial wall stress but myocardial ischemia is also of importance. In addition, natriuretic peptide synthesis can be increased by tachycardia, glucocorticoids, thyroid hormones, and

Table 1.

New York Heart Association classification of functional capacity.

<table>
<thead>
<tr>
<th>Class</th>
<th>Description</th>
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<tbody>
<tr>
<td>I</td>
<td>No limitation; ordinary physical exercise does not cause undue fatigue, dyspnea, or palpitations</td>
</tr>
<tr>
<td>II</td>
<td>Slight limitation of physical activity: comfortable at rest but ordinary activity results in fatigue, palpitations, or dyspnea</td>
</tr>
<tr>
<td>III</td>
<td>Marked limitation of physical activity: comfortable at rest but less than ordinary activity results in symptoms</td>
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<tr>
<td>IV</td>
<td>Unable to carry out any physical activity without discomfort: symptoms of heart failure are present even at rest with increased discomfort with any physical activity</td>
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Table 2.

Patophysiological mechanisms important in the syndrome of heart failure

<table>
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<th>Pathophysiological mechanisms important in the syndrome of heart failure</th>
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<tr>
<td><strong>Cardiac abnormalities</strong></td>
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<td>Structural abnormalities</td>
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<td>Myocardium or myocyte</td>
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<td>Abnormal excitation—contraction coupling</td>
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<td>β-Adrenergic desensitization</td>
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<td>Hypertrophy</td>
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<td>Necrosis</td>
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<td>Fibrosis</td>
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<td>Apoptosis</td>
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<td>Left ventricular chamber</td>
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<td>Remodeling</td>
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<td>Dilatation</td>
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<td>Increased sphericity</td>
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<td>Aneurysmal dilatation or wall thinning</td>
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<td>Coronary arteries</td>
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<td>Obstruction</td>
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<td>Inflammation</td>
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<td><strong>Functional abnormalities</strong></td>
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<td>Mitral regurgitation</td>
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<tr>
<td>Intermittent ischemia or hibernating myocardium</td>
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<td>Induced atrial and ventricular arrhythmias</td>
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<td>Altered ventricular interaction</td>
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<td><strong>Biologically active tissue and circulating substances</strong></td>
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<td>Renin—angiotensin—aldosterone system</td>
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<td>Sympathetic nervous system (norepinephrine)</td>
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<td>Vasodilators (bradykinin, nitric oxide, and prostaglandins)</td>
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<td>Natriuretic peptides</td>
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<td>Cytokines (endothelin, tumor necrosis factor, and interleukins)</td>
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<td>Vasopressin</td>
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<td>Matrix metalloproteinases</td>
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<td><strong>Other factors</strong></td>
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<tr>
<td>Genetic background, including effects of sex</td>
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<tr>
<td>Age</td>
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<tr>
<td>Environmental factors, including use of alcohol, tobacco, and toxic drugs</td>
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<td><strong>Coexisting conditions</strong></td>
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<tr>
<td>Diabetes mellitus</td>
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<td>Hypertension</td>
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<td>Renal disease</td>
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<td>Coronary artery disease</td>
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<td>Anemia</td>
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<td>Obesity</td>
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<td>Sleep apnea</td>
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<td>Depression</td>
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vasoactive peptides such as endothelin-1 and angiotensin II, independent of the hemodynamic effects of these factors [6]. Natriuretic peptides reduce blood pressure by relaxing vascular smooth muscle and they cause diuresis by increasing glomerular filtration and inhibit sodium absorption. BNP block cardiac sympathetic nervous system, and inhibit the renin-angiotensin-aldosterone system. BNP also has direct relaxing properties in the myocardium, and might have antiproliferative and antifibrotic effects in vascular tissues [6]. The half-life of BNP is 20 minutes and the half-life of NT-pro-BNP is 120 minutes. Accordingly, the serum levels for NT-pro-BNP are approximately six times higher than for BNP. When comparing data from different studies, it is important to acknowledge that peptide measurements obtained with different assays are not comparable and there is no conversion factor for the comparison of BNP and NT-pro-BNP values [8].

**CARDIAC REMODELING**

Left ventricular remodeling is the process by which mechanical, neurohormonal, and possibly genetic factors alter ventricular size, shape, and function. Remodeling occurs in several clinical conditions, including after myocardial infarction (FIGURE 2). Left ventricular dilatation and further cardiac remodeling occurs in approximately 20% of patients after anterior myocardial infarction, despite early reperfusion [3, 10]. The beneficial effects of treatment for heart failure, e.g. angiotensin-converting enzyme inhibitors, beta-blockers and cardiac resynchronization therapy, has been shown to be associated with reverse remodeling, i.e. the process of restoration of a more normal ventricular size and shape. The reverse remodeling process is a mechanism through which a variety of treatments reduces symptoms in heart failure.

![Ventricular remodeling after acute infarction](image)

*Figure 2. Ventricular remodeling after myocardial infarction.*

At the time of an acute myocardial infarction - in this case, an apical infarction - there is no clinically significant change in overall ventricular geometry. Within hours to days, the area of myocardium affected by the infarction begins to expand and become thinner. Within days to months, global remodeling can occur, resulting in overall ventricular dilatation, decreased systolic function, mitral-valve dysfunction, and the formation of an aneurysm. Jessup M, Brozena S. Heart failure. N Engl J Med 2003;348:2007-18. Copyright © 2003 Massachusetts Medical Society. All rights reserved.
Mitral regurgitation

Another harmful consequence of remodeling is the development of mitral regurgitation. As the left ventricle dilates and the heart becomes more spherical, the geometric relation between the papillary muscles and the mitral leaflets changes, causing restricted opening and increased tethering of the leaflets and distortion of the mitral apparatus. Dilatation of the mitral annulus occurs as a result of increasing left ventricular or atrial size or as a result of regional abnormalities caused by myocardial infarction. The development of mitral regurgitation results in volume overload that further promotes remodeling – a vicious circle is created [11].

MEDICAL TREATMENT OF HEART FAILURE

Angiotensin-converting enzyme inhibitors

Angiotensin-converting enzyme inhibitors are recommended as first-line therapy in patients with a reduced left ventricular systolic function expressed as a subnormal ejection fraction, i.e. 40-45% with or without symptoms [1, 5].

The original hypothesis behind the investigation of angiotensin-converting enzyme inhibitors in patients with heart failure was that these agents would reduce the progression of clinical heart failure through vasodilatation. Clinical trials have demonstrated reduction in morbidity and mortality [12]. Since the inception of these trials, the rationale for treatment has expanded substantially, and it is now understood that angiotensin-converting enzyme inhibitors directly affect the cellular mechanisms responsible for progressive myocardial pathology.

Beta-blockers

Beta-blockers should be considered for the treatment of all patients with stable heart failure and reduced ejection fraction. Beta-blocking therapy reduces hospitalizations, improves the functional class and leads to less worsening of heart failure [1]. In addition, beta-blockers can reduce the risk of death and the combined risk of death or hospitalization [5, 13, 14].

The initial report [15], and subsequent case series [16, 17] from Sweden of beta-blockers in heart failure was met with considerable scepticism which persisted for 15 years. The concept of administering a negative inotrope was thought to be contraindicated in heart failure. Eventually, large multicenter trials could demonstrate significant reduction in mortality and morbidity when beta-blockers were added to angiotensin-converting enzyme inhibitors therapy [14, 18-20].

Spironolactone

Elevated aldosterone levels have several adverse consequences, including increased sodium retention, potassium and magnesium loss, myocardial collagen production, ventricular hypertrophy, myocardial norepinephrine release, and endothelial dysfunction.

Aldosterone antagonists are recommended in addition to angiotensin-converting enzyme inhibitors, beta-blockers and diuretics in advanced heart failure (NYHA III-IV) with systolic dysfunction to improve survival and morbidity. Aldosterone antagonists are also recommended in addition to standard treatment after myocardial infarction with left ventricular systolic dysfunction and signs of heart failure to reduce mortality and morbidity [1, 5]. Spironolactone reduced the risk of death from all causes, death from cardiac causes, and hospitalization for cardiac causes, among patients who had severe heart failure as a result of left ventricular systolic dysfunction, and who were receiving standard therapy including an angiotensin-converting enzyme inhibitor [21].

Statins

Statins have been proven to effectively reduce cardiovascular events in patients with
coronary artery disease, and all patients undergoing coronary artery bypass grafting should receive statin therapy [22].

Observational studies have consistently shown that patients with heart failure who take statins seem to do better than similar patients who do not [23-26]. For example, in a large cohort study of patients with chronic heart failure, those who started taking statins had a lower risk of death or hospitalization for heart failure than those who did not. [23].

Heart failure patients have been systematically excluded from randomized, controlled clinical cholesterol-lowering trials [24, 27]. Therefore, the effect of statin therapy in these patients remains to be established. Several randomized, placebo-controlled statin trials are under way to evaluate the efficacy of statin treatment in terms of reducing clinical endpoints in heart failure [28].

Heart failure treatment options

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<th>NYHA III</th>
<th>NYHA IV</th>
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<td><strong>Interventions</strong></td>
<td><strong>End stage</strong></td>
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<tr>
<td>ACE-inhibitors</td>
<td>Cardiac resynchronization therapy</td>
<td>Heart transplantation</td>
</tr>
<tr>
<td>Beta-blockers</td>
<td>Coronary artery bypass grafting</td>
<td>Left ventricular assist device</td>
</tr>
<tr>
<td>Spironolactone</td>
<td>Mitral valve repair</td>
<td>Total artificial heart</td>
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</table>

**Figure 3. Heart failure treatment options.**
Heart transplantation

Heart transplantation remains the “gold standard” for the treatment of end-stage heart failure. In 1981, the introduction of the immunosuppressive drug cyclosporine dramatically increased patient survival and marked the beginning of the modern era of successful cardiac transplantation. Cardiac transplantation is reserved for a select group of patients with end-stage heart failure refractory to optimal medical therapy or other surgical procedures. Prognosis for one year survival without transplantation should be less than 50%. The number of transplants worldwide is strictly limited by donor availability and has changed little over the past decade, despite a trend toward using older donors. For younger patients, without serious co-morbidity, who are prepared to endure a lifetime of immunosuppressive drugs, heart transplantation is an outstanding alternative [29]. Today, transplant recipients have 87% probability of surviving the first year after transplantation, a median survival over 10 years, and a high probability of an excellent quality of life [30]. Results, however, are worse in ischemic heart disease. Further, results in patients with uncomplicated diabetes mellitus are not significantly different compared to non-diabetics, but survival is compromised in patients with more severe diabetes [31].

The International Society for Heart and Lung Transplantation (ISHLT) provide concise and clear guidance to transplant centers [32]. According to the ISHLT database [30], the primary indication worldwide for adult heart transplantation during the last five years was almost evenly distributed between ischemic and non-ischemic cardiomyopathy (42% and 46%, respectively). Causes of death after heart transplantation were graft failure, which accounted for 40% of deaths within the first 30 days post-transplant, and multiple-organ failure (14%).

After five years, cardiac allograft vasculopathy and late graft failure (likely due to allograft vasculopathy) together accounted for 30% of deaths, followed by malignancies (23%).

Mechanical circulatory support devices

Over the last two decades, mechanical circulatory support devices have been developed at a rapid pace. The goal has been to support patients with advanced heart failure as a bridge to cardiac transplantation, a bridge to recovery, and an alternative to transplantation, also called destination therapy. The current generation of devices vary from short-term to intermediate-term and long-term duration. Also, partial left ventricular support, more complete left ventricular support, right ventricular support, and biventricular support options are available to fill the need in a particular patient. Devices can be positioned as paracorporeal pumps or intracorporeal pumps with transcutaneous drivelines or completely implantable systems. The major current limitations are infection, coagulopathies, and device dysfunction [33]. The term left ventricular assist device or left ventricular assist system indicates left ventricular support, the broader term mechanical circulatory support device has been adopted to include left ventricular, right ventricular, and biventricular devices, and complete heart replacement devices.

The International Society for Heart and Lung Transplantation (ISHLT) initiated the ISHLT Mechanical Circulatory Support Device database because of the evolving important role of device therapies in the temporary and permanent treatment of advanced heart failure. The registry has collected voluntary data from 60 international centres since 2002 and the most recent report was published in 2005 was based on analysis of 655 patients entered into the database between January 1, 2002 and December 31, 2004 [33]. In the database, bridge to transplantation therapy represents about 80% of all device therapy. Bridge to transplantation is particularly successful in
Figure 4. Orthotopic cardiac transplantation with bicaval technique.
Hunt. N Engl J Med 2006;355:231-5. Copyright © 2006 Massachusetts Medical Society. All rights reserved.

Figure 5. Components of the left ventricular assist device in the REMATCH study. The inflow cannula is inserted into the apex of the left ventricle, and the outflow cannula is anastomosed to the ascending aorta. Blood returns from the lungs to the left side of the heart and exits through the left ventricular apex and across an inflow valve into the prosthetic pumping chamber. Blood is then actively pumped through an outflow valve into the ascending aorta. The pumping chamber is placed within the abdominal wall or peritoneal cavity. A percutaneous drive line carries the electrical cable and air vent to the battery packs (only the pack on the right side is shown) and electronic controls, which are worn on a shoulder holster and belt, respectively.
Rose et al. N Engl J Med 2001;345:1435-43. Copyright © 2001 Massachusetts Medical Society. All rights reserved.
younger adults, for whom successful support to transplantation is possible in nearly 75% of cases. Destination therapy presently represents only 12% of cases and one year survival among these is 40% in patients younger than 65 years.

The conclusion of the Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure (REMATCH) trial was that the use of a left ventricular assist device in patients with advanced heart failure resulted in a clinically meaningful survival benefit and an improved quality of life. In selected patients who are not candidates for cardiac transplantation, a left ventricular assist device can thus be an acceptable alternative therapy [34] (Figures 5 and 6). Prolonged, near-complete unloading of the left ventricle with the use of a left ventricular assist device has been shown to be associated with structural reverse remodeling and can be accompanied by functional improvement [35]. Furthermore, in selected patients without acute myocarditis, severe heart failure secondary to nonischemic cardiomyopathy can be reversed with the use of a left ventricular assist device and pharmacologic therapy [36].

In patients with severe biventricular failure, cardiac replacement with a total artificial heart (Figure 7) can be an alternative as a bridge to transplantation therapy. The CardioWest Total Artificial Heart was successfully used as bridge to cardiac transplantation in 81 patients with heart failure in whom inotropic therapy had failed and who were not candidates for the use of a left ventricular assist device. Implantation of the total artificial heart helped to restore hemodynamic function, and promoted end-organ recovery. The rate of survival to transplantation was 79% and the one and five year post-transplant survival was 86% and 64%, respectively [37].

Partial left ventriculectomy

Partial left ventriculectomy, or the Batista procedure [39], aims to treat dilated cardiomyopathy by reducing cardiac volume and left ventricular wall tension through the resection of a portion of the left ventricle. It is often accompanied by a mitral valve procedure to treat preoperative mitral regurgitation or to prevent postoperative mitral regurgitation. Variations of the technique for partial left ventriculectomy include lateral partial left ventriculectomy and anterior partial left ventriculectomy. In lateral partial left ventriculectomy, an incision is made at the apex of the left ventricle and extended towards the base. A wedge-shaped portion of the left ventricle is resected, leaving the papillary muscles intact where possible. Extended partial left ventriculectomy additionally excises the papillary muscles and the mitral valve. In anterior partial left ventriculectomy, the area between the left anterior descending artery and the attachment of the left anterolateral papillary muscle is resected and closed as in lateral partial left ventriculectomy.

When the initial experience of the procedure was presented in 1997, it received much attention due to the positive early results with remarkable improvement in a group of patients with advanced heart failure and dilated cardiomyopathy, previously facing death within a year unless transplanted. Although early mortality was 22% in the first report, several institutions around the world, including Huddinge University Hospital, Stockholm, started to perform partial left ventriculectomy [40].

The early experience of the Cleveland Clinic [41] was carefully optimistic, and concluded that the operation could serve as a biologic bridge to transplantation and it might be an alternative to transplantation for patients who are not candidates for transplantation.

However, the main findings of the long-term follow-up and analysis of the Cleveland Clinic experience [42] were less encourag-
Figure 6. Kaplan-Meier analysis of survival in the group that received left ventricular assist devices and the group that received optimal medical therapy in the REMATCH study.
Rose et al. N Engl J Med 2001;345:1435-43. Copyright © 2001 Massachusetts Medical Society. All rights reserved.

Figure 7. Total artificial heart. An artificial heart (Abiocor), shown implanted in a recipient’s mediastinum. The prosthesis replaces the right and left ventricles of the recipient.
ing. In 62 patients with almost exclusively idiopathic dilated cardiomyopathy (95% transplant candidates), early mortality was 3.2% and survival was 80% and 60%, and event-free survival was 49% and 26%, at one and three years respectively. Furthermore, it was hard to identify reliable preoperative patient characteristics associated with outcome, and thus difficult to determine which patients who would benefit from the operation. Event-free survival was defined as freedom from all cause mortality, implantation of a left ventricular assist device, return to NYHA class IV heart failure, relisting for transplantation, or use of an implantable cardioverter-defibrillator. The discrepancy between the survival and event-free survival at one year postoperatively could partly be explained by the safety-net provided at a specialized heart failure centre, with left ventricular assist device or transplantation therapy readily available.

These findings, and reports of poor results from other institutions, dampened the interest in partial left ventriculectomy, and consequently many centers abandoned the procedure.

However, some institutions still perform partial left ventriculectomy in carefully selected patients with impressive results [43, 44].

Cardiac Support Device

The Acorn CorCap™ Cardiac Support Device (Acorn Cardiovascular Inc., St. Paul, MN, USA) is a biocompatible support jacket placed around the right and left ventricles to prevent further dilatation (Figure 8). The cardiac support device provides end-diastolic ventricular support to reduce wall stress and myocardial stretch which promotes reverse remodeling.

Early clinical studies have shown that the device is safe and treatment is associated with improvements in left ventricular structure and function and patient symptoms [45, 46]. The device is now being evaluated in an international randomized clinical trial [47]. Results from the mitral valve procedure stratum of the trial, with mostly patients with idiopathic dilated cardiomyopathy, showed a further benefit in patients who received the device in addition to a mitral valve procedure [48].

Cardiac resynchronization therapy

Cardiac resynchronization therapy alone or in combination with an implantable defibrillator improves quality of life, exercise capacity, and survival in patients with moderate or severe heart failure and systolic dysfunction [49-56].

Reverse remodeling is induced by cardiac resynchronization therapy [57]. However, the reverse remodeling process is less extensive in patients with ischemic heart disease compared with patients with non-ischemic etiology [58].

Cardiac resynchronization therapy can be considered in patients with reduced ejection fraction and ventricular electrical dysynchrony (QRS width more than 120 ms) and who remain symptomatic (NYHA III–IV) despite optimal medical therapy [1].

Implantable cardioverter-defibrillator

According to the American College of Cardiology/American Heart Association/European Society of Cardiology Guidelines [59], implantable cardioverter-defibrillator therapy is recommended for primary prevention to reduce total mortality by a reduction in sudden cardiac death in patients with left ventricular dysfunction due to prior myocardial infarction who are at least 40 days post-myocardial infarction, have an left ventricular ejection fraction less than or equal to 30% to 40%, are NYHA functional class II or III, are receiving chronic optimal medical therapy, and who have reasonable expectation of survival with a good functional status for more than one year. (Class of recommendation: I, level of evidence: A).
Figure 8. CorCap™ Cardiac Support Device. Mann et al. J Card Fail 2004;10:185-92. Copyright © 2004 Elsevier B.V. All rights reserved.

Figure 9. Biventricular pacing for cardiac resynchronization therapy. Two leads allow pacing of the right atrium and right ventricle. The third lead, which is advanced through the coronary sinus into a venous branch that runs along the free wall of the left ventricle, allows early activation of the left ventricle, which would otherwise be activated late during conduction. Hare. N Engl J Med 2002;346:1902-5. Copyright © 2002 Massachusetts Medical Society. All rights reserved.
Left ventricular reconstruction

History and evolution

Surgical repair of a left ventricular aneurysm was first performed by Charles Bailey in 1954 [61], and the first resection under cardiopulmonary bypass was reported by Denton Cooley in 1958 [62]. In 1985, Vincent Dor described a surgical technique, the endoventricular circular patch plasty [63, 64] built on prior contributions by Cooley and Jatene [65, 66]. Left ventricular reconstruction by the Dor procedure was originally developed as a more physiological left ventricular aneurysm repair technique as compared to simple linear repair. Dor have reported the effects on hemodynamics, functional class and electrophysiology in large single-centre series of patients [67]. The effects of additional nonguided endo-cardiectomy and cryoablation to the Dor procedure in patients with ischemic ventricular arrhythmias was presented in 1994 [68]. Di Donato later demonstrated that outcome in a large series of left ventricular reconstruction, was more strongly linked to the extent of asynergy than to the type of asynergy (akineti vs. dyskinetic) [69]. The operation has subsequently been applied on patients with ischemic dilated cardiomyopathy and regional asynergy without discrete left ventricular aneurysm [70, 71].

Currently, left ventricular reconstruction is an established text-book procedure for aneurysm repair. Ongoing investigations aim to delineate its role in heart failure surgery.

Indications

Generally accepted indications for left ventricular reconstruction (adapted from Menicanti [72]):

1. Anteroseptal infarction and dilated left ventricle (end-diastolic volume index more than 100 mL/m²)
2. Depressed ejection fraction
3. Left ventricular regional asynergy, either dyskinesia or akinesia, greater than 35% of the ventricular perimeter
4. Symptoms of angina, heart failure, arrhythmias, or a combination of the three, or inducible ischemia on provocative tests in asymptomatic patients.

Relative Contraindications

1. Systolic pulmonary artery pressure more than 60 mmHg (when not associated with severe mitral regurgitation).
2. Severe right ventricular dysfunction
3. Regional asynergy without dilation of the ventricle

Enhanced hemodynamics, cardiac performance and excellent short- and long-term survival has been demonstrated after left ventricular reconstruction [67, 69-71, 73-77]. Moreover, left ventricular reconstruction results in left ventricular volume reduction [78], changes in left ventricular shape, and decreased left ventricular wall stress and mechanical dyssynchrony, which improves systolic and diastolic function [79, 80].

Surgical technique

Left ventricular reconstruction can be performed by a number of closely related methods as described in more detail in the Discussion, page 53.

The surgical technique, corresponding to the procedure used at the Karolinska University Hospital, is richly illustrated by Menicanti [81], and the online version of the article (available at http://mmcts.ctsnetjournals.org) includes video content which describes the procedure in great detail.

Ventricular tachycardia

Postinfarction cardiac remodeling with progressive left ventricular dilation and deteriorating function is associated with increasing risk for ventricular arrhythmias [82]. Surgical techniques to treat ventricular tachycardia secondary to myocardial infarction were first described in patients in 1978 [83, 84].
The effects of nonguided endocardiectomy and cryoablation combined with left ventricular reconstruction in patients with ischemic ventricular arrhythmias was presented by Dor in 1994 [68]. Other authors have reported on various surgical techniques for aneurysm repair with or without intraoperative mapping in patients with ventricular arrhythmias [85-90].

Mitral regurgitation
Left ventricular dilatation induces geometric changes that can lead to mitral valve incompetence by several mechanisms: displacement of papillary muscles, tethering of the leaflets, and annular dilatation. Ischemic mitral regurgitation is associated with worse survival independently of baseline characteristics and degree of ventricular dysfunction [91]. There is a graded association between the severity of ischemic mitral regurgitation and the development of heart failure after myocardial infarction. Even mild ischemic mitral regurgitation is associated with an increase in the risk of heart failure [92].

Mitral valve repair can be performed either by a conventional atrial approach or by the transventricular approach during left ventricular reconstruction.

Figure 10. The Alfieri edge-to-edge technique for mitral valve repair.

Figure 11. Postinfarction left ventricular dilatation (left) and restored left ventricular shape and volume by left ventricular reconstruction (right).
From Menicanti [81]. Copyright © 2005 European Association for Cardio-Thoracic Surgery.
The overall aim of this thesis was to evaluate left ventricular reconstruction on the aspects of survival, functional status and quality of life in patients with ischemic heart disease and heart failure.

The specific aims were:

1. To review a single institution ten year experience with left ventricular reconstruction regarding safety (early mortality and morbidity) and long-term survival. (Study I)

2. To evaluate left ventricular reconstruction including surgery for ventricular tachycardia in patients with preoperative spontaneous or inducible ventricular tachycardia. (Study II)

3. To analyze risk factors for mortality and hospital re-admission for heart failure after left ventricular reconstruction. (Study III)

4. To prospectively investigate changes in functional status and quality of life after left ventricular reconstruction. (Study IV)

5. To prospectively investigate changes in biomarkers for heart failure (BNP and NT-pro-BNP) in relation to functional status after left ventricular reconstruction. (Study V)
PATIENT POPULATION

In Study I and II, all patients were operated on at former Huddinge University Hospital. In 2004, the two University Hospitals providing cardiac surgery in Stockholm; Karolinska Hospital and Huddinge University Hospital, were merged into the new Karolinska University Hospital. Study III includes all patients who underwent left ventricular reconstruction in Stockholm between May, 1994 and August, 2005. In Study IV and V, the first ten patients were operated at former Huddinge University Hospital, and the rest of the patients were operated at Karolinska University Hospital.

In total, 143 patients contributed to these studies, and eight patients were included in all five studies (Figure 12).

PATIENT SELECTION

Left ventricular aneurysm or ischemic dilated cardiomyopathy

Dyskinetic left ventricular aneurysm is commonly defined as a segment of left ventricular wall protruding from the expected outline of the ventricular chamber during systole, displaying paradoxical motion on left ventriculogram. However with increasing size of the left ventricular aneurysm, paradoxical movement becomes more difficult to identify and the distinction of the two separate entities, namely left ventricular aneurysm or large akinetic ventricle, may be hard to make. Di Donato demonstrated that outcome in a large series of left ventricular procedures was more strongly linked to the extent of asynergy than to the type of asynergy; akinetic vs. dyskinetic [69]. The three silhouette types (Figure 13) were described by Di Donato, and may be more useful in selecting patients most likely to benefit from surgery. These silhouettes were inspired by the centerline method which is used by some groups to model regional wall motion in the ventricle.

Common criteria for Study I-V

Patients were considered suitable for left ventricular reconstruction if they demonstrated an enlarged, either dyskinetic or akinetic, left ventricle accompanied by left ventricular dysfunction after myocardial infarction, and had symptoms of angina, congestive heart failure, ventricular tachycardia or a combination of these.

Particular criteria for Study II

All patients had spontaneous or inducible ventricular tachycardia.

Particular criteria for Study IV and V

Patients who had previously undergone cardiac surgery or who had non-anterior dyskinesia/akinesia were excluded.

Patients and Methods
Preoperative investigations

Coronary angiography
Coronary angiography was performed in all patients to reveal coronary artery pathology. Qualitative assessment of left ventricular volume and geometry was made by ventriculography in all patients.

Echocardiography
Transthoracic or transesophageal echocardiography was used to assess left ventricular dimensions and function, as well as valvular function. The mitral valve function was assessed preoperatively by transthoracic echocardiography. Intraoperative transesophageal echocardiography was used in all patients to confirm preoperative findings and to assess valve morphology and postoperative results after weaning from extracorporeal circulation.

Programmed electrical stimulation
Programmed electrical stimulation was performed before surgery and ½ to six months after surgery using a standard protocol including double or triple extra stimuli, three stimulation rates, and two locations. The protocol was terminated if sustained VT was induced. Sustained ventricular tachycardia was defined as a tachycardia lasting more than 30 seconds or clinically requiring intervention before that.

Detailed stimulation protocol
One 6F quadripolar electrode catheter was introduced percutaneously through the right femoral vein under fluoroscopic guidance and alternately positioned in the apex and in the right ventricular outflow tract. Ventricular extrastimuli were delivered using a Biotronic UHS 20 stimulator and recorded on a Recor Electrophysiology System (Siemens-Elema). The stimulation protocol included drive trains of 8 ventricular extrastimuli at cycle lengths of 600, 450 and 333 ms followed by a single or double extrastimuli from both the apex and the right ventricular outflow tract. In cases where ventricular tachycardia was not induced by this protocol, triple extrastimuli were used regardless if ventricular tachycardia had been clinically documented or not. The first extrastimulus was placed at a coupling interval 50 ms beyond the refractory period and brought to refractoriness in decrements of 10 ms. This extrastimulus was then placed 20 ms beyond the effective refractory period and a second extrastimulus was delivered at 50 ms beyond the refractory period and brought to refractoriness in decrements of 10 ms. Following this scheme the third extrastimulus was introduced. Ventricular refractoriness was calculated during each different pacing rate and position in the ventricle.

Radionuclide ventriculography
Left ventricular ejection fraction was assessed by radionuclide ventriculography (Study IV-V).

Cardiac magnetic resonance imaging
Left ventricular volumes were assessed by cardiac magnetic resonance imaging in most patients operated on since November 2003 (Study IV-V).

PATIENT CHARACTERISTICS

Study I
From May 1994 to July 2004, 101 consecutive patients underwent the Dor procedure for postinfarction dyskinetic left ventricular aneurysm or large non-aneurysmal akinetic left ventricle. Follow-up was completed on October 15, 2004. There were 77 men and 24 women, with a mean age of 64 years. Seventy-four patients were in NYHA functional class III or IV. Multi-vessel disease was present in 80 patients. The mean preoperative left ventricular ejection fraction was 27% (7-50%). All patients except one were operated electively. Fifty-three patients had a confirmed diagnosis of ventricular tachycardia preoperatively and 25 of these had spontaneous ventricular tachycardia.
**Figure 12.** Study population. Number of patients in Study I-V

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**Type I**

**AKINETIC/DYSKINETIC WITH DUAL BENDING**
- Preserved contraction of the anterobasal and inferobasal segments.
- Significant bending in the anterior and inferior walls.

**Type II**

**AKINETIC/DYSKINETIC WITH ONE BENDING**
- Preserved contraction in the inferobasal segment and weaker contraction of anterobasal segment.
- Loss of bending in anterolateral segment with detectable bending in the inferior area.

**Type III**

**AKINETIC/DYSKINETIC WITHOUT BENDING**
- Diffuse hypokinesis in the anterobasal and inferobasal regions with diffuse akinesia in other segments.
- No inferior or lateral bending.

**Figure 13.** Postinfarction left ventricular silhouettes suitable for left ventricular reconstruction. The three silhouette types can be evaluated with echocardiography, angiography, or cardiac magnetic resonance imaging.
Study II

From July 1997 to December 2003, 53 consecutive patients underwent the Dor procedure including ventricular tachycardia surgery for postinfarction dyskinetic left ventricular aneurysm and ventricular tachycardia. Follow-up was completed on October 15, 2004. All patients were operated on electively, although 14 patients with spontaneous ventricular tachycardia were hospitalized before the operation owing to life-threatening arrhythmias. All patients had a confirmed diagnosis of ventricular tachycardia preoperatively, and 24 of these had spontaneous ventricular tachycardia. Eight patients with spontaneous ventricular tachycardia were survivors of sudden cardiac death. Forty-six patients underwent preoperative programmed electrical stimulation, and of these, 45 had inducible ventricular tachycardia. Medication at preoperative programmed electrical stimulation was amiodarone (n=4), sotalol (n=1), other beta-blockers (metoprolol, atenolol, or carvedilol, n=27), digoxin (n=3), no antiarrhythmic medication (n=9), and unknown in one case. In total, this study included 53 patients of which 24 had spontaneous ventricular tachycardia and 29 had inducible-only ventricular tachycardia. Postoperative programmed electrical stimulation data were presented separately for these two groups.

Study III

Between May 1994 and August 2005, 136 consecutive patients underwent left ventricular reconstruction by the Dor procedure for postinfarction dyskinetic left ventricular aneurysm or large non-aneurysmal akinetic left ventricular. Follow-up was completed on September 21, 2005. There were 104 men and 32 women, with a mean age of 64 years. Ninety-four patients (69%) were in NYHA functional class III or IV. Multi-vessel disease was present in 108 patients (79%). The mean preoperative left ventricular ejection fraction was 26% (7-50). All patients except one were operated electively. Fifteen patients with spontaneous ventricular tachycardia were hospitalized before the operation due to life-threatening arrhythmias. Sixty patients underwent preoperative programmed electrical stimulation and 52 patients had inducible ventricular tachycardia preoperatively. Spontaneous ventricular tachycardia was present in 33 patients.

Study IV

During two years, beginning March, 2003, 23 patients with postinfarction dyskinetic left ventricular aneurysm or large non-aneurysmal akinetic left ventricular were included. There were 16 men and 7 women, with a mean age of 65 (44-80) years. Seventeen patients (74%) were in NYHA functional class III or IV. Multi-vessel disease was present in 20 patients. The mean preoperative left ventricular ejection fraction was 26% (10-45%). All patients were operated electively. All patients but one underwent preoperative programmed electrical stimulation and 17 patients had inducible ventricular tachycardia preoperatively. Two patients had preoperative episodes of spontaneous ventricular tachycardia.

Study V

Between March 2003 and May 2006, 29 patients with postinfarction dyskinetic left ventricular aneurysm or large non-aneurysmal akinetic left ventricular were included. There were 20 men and 9 women, with a mean age of 65 (44-80) years. Twenty-two patients (76%) were in NYHA functional class III or IV. Multi-vessel disease was present in 26 patients. The mean preoperative left ventricular ejection fraction was 26% (10-45%). All patients were operated electively. Twenty-four patients underwent preoperative programmed electrical stimulation and 18 patients had inducible ventricular tachycardia preoperatively. Three patients had preoperative episodes of spontaneous ventricular tachycardia.
SURGICAL TECHNIQUE

Left ventricular reconstruction

The operation was performed using cardiopulmonary bypass and moderate systemic hypothermia. Standard cardiac anesthesia was used. A transesophageal echocardiography probe was used to evaluate preoperative and postoperative left ventricular and mitral valve function, filling and de-airing. Cardiopulmonary bypass was instituted in a routine fashion. In all cases, but three, the aorta was cross-clamped, and myocardial protection was achieved with intermittent cold antegrade and retrograde blood cardioplegia. The aneurysm was incised parallel to the interventricular septum and the left anterior descending artery, and clots were removed. Endocardectomy was performed in some patients with a severely calcified left ventricular aneurysm, to facilitate closure of the left ventricular incision. A purse-string suture (2-0 Prolene) was placed around the circumference of the scar at the transition zone (usually near the base of the papillary muscles) and tied down to determine the size of the new ventricular opening (the Fontan stitch). A bovine pericardial patch (Periguard; Synovis Life Technologies, Inc., St Paul, MN, USA) or a dacron patch (SVR™ System, Chase Medical, Richardson, TX, USA) was then secured over the ventricular opening with a running 2-0 Prolene suture. The edges of the ventricular free wall were then closed over the patch with a running 2-0 Prolene suture. The distal coronary anastomoses were performed. The cross-clamp was removed and the proximal anastomoses to the ascending aorta were done with a sidebiting clamp. The patient was then weaned from cardiopulmonary bypass in a standard fashion.

Surgery for ventricular tachycardia

In patients with preoperative inducible or spontaneous ventricular tachycardia, a subtotal nonguided endocardectomy was conducted on the septum and anterior wall of the left ventricle. Linear cryo lesions (Frigitronics CCS-200, CooperSurgical, Inc., Trumbull, CT, USA) were applied at the edge of the endocardial resection [68].

Mitral valve procedures

In all patients with preoperative grade III-IV mitral regurgitation and in about half of the patients with grade II mitral regurgitation, a mitral valve procedure was done. All patients who underwent a mitral valve procedure (n=37) had ischemic mitral regurgitation, defined as mitral regurgitation in patients with a prior myocardial infarction, and with normal mitral leaflets. Thirty-one patients with functional ischemic mitral regurgitation underwent mitral valve repair solely by the Alfieri edge-to-edge technique [93] without annuloplasty. Mitral valve repair was accomplished in two patients with a rigid ring annuloplasty, which in one patient was combined with an edge-to-edge plasty. In three patients the edge-to-edge technique was associated with a posterior annuloplasty without a ring as described by Menicanti [94]. One patient received a mechanical prosthesis [95].

DATA COLLECTION AND FOLLOW-UP

National registers

A national registration number is allocated to every Swedish citizen. Using this personal identity number, data extraction from several national registers is possible. Swedish national registers were used in the individual studies as follows; Total Population Register, Statistics Sweden (Study I-V), Cause of Death Register, Centre for Epidemiology at the National Board of Health and Welfare (Study I-III), and Inpatient Register, Centre for Epidemiology at the National Board of Health and Welfare (Study III-IV)

Study I

All patients were followed until October 2004. Follow-up consisted of review of
patients' charts and our institutional database, as well as data from national registers. No patient was lost to follow-up.

**Study II**
All patients were followed until mid-October 2004. Follow-up consisted of review of patients’ records (including interrogation of implantable cardioverter-defibrillators when applicable) and our clinic’s database and data from national registers. No patient was lost to follow-up.

**Study III**
In September 2005, all patients were followed up with respect to survival by use of a continuously updated national population register. By this procedure all patients could be assigned a date of death or identified as being alive on September 21, 2005. Data collection consisted of review of patients’ records and our institutional database and data from national registers. The date for the first readmission for heart failure was established by using hospital records and a national hospital discharge register. The In-patient Register records all in-patient care in Sweden. The validity of the diagnosis of heart failure in the Swedish Inpatient Register has recently been examined and found to be very high (96%) in patients treated at an internal medicine or cardiology department or when heart failure was the primary diagnosis [96]. The cause of death was determined by use of the Cause of Death Register, and hospital records. The expected survival, which was used to calculate the relative survival, was derived from survival data of the total Swedish population, matched for gender, age and date of operation [97].

The primary end point was all-cause mortality. Secondary end points were early mortality and the combination of first re-admission for heart failure or cardiac death. Cardiac death was defined as death due to cardiac failure, ischemic events or sudden death.

**Study IV**

**Health-related quality of life**
All patients were asked to complete the Medical Outcome Study 36-item Short Form (SF-36) questionnaire one to two weeks before surgery, six months postoperatively, and at late follow-up. The primary outcome measures were the physical component summary and mental component summary scores from the SF-36, (Figure 14). SF-36 is a standardized, self-administered survey measuring health-related quality of life [98]. The validity and reliability of the Swedish version has been evaluated [99]. The questionnaire consists of 36 items and measures health using eight subscales with two to ten items per scale. The subscales and summary scores can be compared to the general population allowing for norm-based interpretation. Scoring of the SF-36 was performed according to the methods described in the Swedish version of the SF-36 Manual [98]. For each of the eight subscales, the score was summed and transformed to a scale of 0–100, representing the percentage of the highest possible score achieved. The scales are constructed in such a way that a higher score indicates better health. To estimate the summary measures, standard scoring algorithms was used. Several advantages of the physical component summary and mental component summary over the original eight scales of the SF-36 have been reported [98, 100]. For the physical component summary score, very high scores indicate no physical limitations, disabilities, or decrements in well-being as well as high energy level. Very low scores indicate substantial limitations in self-care, physical, social, and role activities, severe bodily pain, or frequent tiredness. For the mental component summary score, very high scores indicate frequent positive affect, absence of psychological distress and of limitations in usual social or role activities due to emotional problems. Very low scores indicate frequent psychological suffering, and substantial social and role disability due to emotional problems.
**Six minute walk test**
The six-minute walk test was administered one to two weeks before surgery, six months postoperatively, and at late follow-up by a standardized method [101] with a course length of 40 meters. Patients were instructed to walk at their own pace while attempting to cover as much distance as possible during the allotted time. The test was supervised and the time was called out every minute. No encouragement was offered. During the test, patients were allowed to rest or stop and then continue as soon as they could resume the walk. At the completion of six minutes, the patient was told to stop and the distance covered was recorded. The self-paced six-minute walk test assesses the submaximal level of functional capacity. Most patients do not achieve maximal exercise capacity during the six-minute walk test although the test may be more of a maximal exercise test in patients with severe heart failure. However, because most activities of day to day life are performed at submaximal levels of exertion, the six-minute walk test may be more representative of the functional status in daily life [102].

**New York Heart Association functional class**
The NYHA functional class was assessed one to two weeks before surgery, six months postoperatively, and at late follow-up.

**Survival and re-admission for heart failure**
Time to re-admission was defined as the time from the operation to either first hospital re-admission due to heart failure or death. The date for the first readmission for heart failure was established by using hospital records and a national hospital discharge register. The date for death was ascertained by use of a continuously updated national population register.

**Study V**
**Measurement of levels of BNP and NT-pro-BNP**
In the first ten patients, arterial blood samples were collected into chilled tubes, immediately centrifuged at 4 °C to separate the plasma. The plasma samples were preserved at -70 °C for later analysis. By this procedure, samples were obtained preoperatively and six months postoperatively. In the remaining patients, and in all patients at
late follow-up, venous blood samples were collected for same day analysis. Measurements of peptide levels were performed by the Department of Clinical Chemistry at the Karolinska University Hospital using commercially available kits (BNP: SHIONORIA BNP, CIS Bio International, France and NT-pro-BNP: Elecsys, Roche Diagnostics).

**New York Heart Association functional class**
The NYHA functional class was assessed one to two weeks before surgery, six months postoperatively, and at late follow-up.

**Left ventricular ejection fraction**
Ejection fraction was assessed by radionuclide ventriculography and/or echocardiography one to two weeks before surgery and repeated six months postoperatively.

**Cardiac magnetic resonance imaging**
Cardiac magnetic resonance imaging (1.5-T Symphony, Siemens, Erlangen, Germany) was performed one to four weeks before surgery and repeated six months postoperatively.

**Survival**
The date for death was ascertained by use of a continuously updated national population register.

**STATISTICAL ANALYSES**

**Study I**
Continuous variables were reported as mean, standard deviation and range. Cumulative survival rates were presented as Kaplan-Meier estimates [103].

**Study II**
Continuous variables were reported as mean, standard deviation or median and range. Cumulative survival rates were calculated by Kaplan-Meier estimation. Differences between survival curves were analyzed by using the log-rank test.

**Study III**
Continuous variables were reported as mean and standard deviation. Cumulative survival rates were presented as Kaplan-Meier estimates. Differences between survival curves were analyzed by using the log-rank test. Risk factors for early mortality were identified by bivariate analysis using contingency tables and the Fisher's exact test for categorical variables and Mann-Whitney U-test for continuous variables. Risk factors for long-term mortality were identified by using a Cox proportional hazards model [104]. Survival curves for all-cause mortality were estimated by Kaplan-Meier analysis, stratified by baseline characteristics, and were compared by use of log-rank tests. In this way, a set of potential explanatory variables were isolated and were then used for model fitting. Baseline characteristics considered clinically important were also included. A manual forward and backward variable selection procedure was used to select the final model. A p-value of less than 0.05 was chosen as the criterion for variable retention. Risk factors for the composite end-point of cardiac death or re-hospitalization due to heart failure in operative survivors were identified in a similar fashion as risk factors for long-term mortality.

**Study IV**
Data were presented as mean and standard deviation or number of patients. Pre- and postoperative intra-group comparisons were performed with parametric or non-parametric tests for dependent samples, as appropriate. The paired samples t test was used for the continuous variables physical component summary score, mental component summary score and six-minute walk test distance. The Wilcoxon signed ranks test was used for end-diastolic volume index and end-systolic volume index, and the marginal homogeneity test, which is an extension of the McNemar test, was used for categorical data (NYHA class). A two-tailed p-value of 0.05 was used to indicate statistical significance.
Study V
Data were presented as mean and standard deviation, median or number of patients. Pre- and postoperative intra-group comparisons were performed with non-parametric tests for dependent samples; the Wilcoxon signed ranks test or the marginal homogeneity test, as appropriate. Association between BNP, NT-pro-BNP, NYHA class, ejection fraction, and left ventricular volumes was estimated by Spearman’s correlation. Cumulative survival was estimated by the Kaplan-Meier method. A two-tailed p-value of 0.05 was used to indicate statistical significance.

Statistical software
Statistical analyses were performed using SPSS version 13 or 14 (SPSS Inc., Chicago, IL, USA).

ETHICAL CONSIDERATIONS
All studies were approved by the regional Human Research Ethics Committee in Stockholm, Sweden. Informed consent was obtained from all patients in Study IV and V.
Results
STUDY I

Objective
To review a single institution 10-year experience with left ventricular reconstruction regarding safety (early mortality and morbidity) and long-term survival.

Results
All patients underwent left ventricular reconstruction by the Dor procedure, and 99 patients had concomitant coronary artery bypass grafting with a mean of 2.4 ± 1.2 (1–5) grafts. In 92 patients, the left internal thoracic artery was used as a conduit to the left anterior descending artery or a diagonal branch. Of the two patients who did not have revascularization, one patient had previously undergone coronary artery bypass grafting and had patent grafts, and the other was the only urgent case with a contained rupture of a left ventricular aneurysm. Non-guided subtotal left ventricular endocardiectomy and cryoablation for ventricular tachycardia was performed in 53 patients. In another four patients, endocardiectomy was performed because of severe calcification of the aneurysm. Mitral valve surgery was performed in 29 patients, using predominantly the Alfieri edge-to-edge technique [93]. Operative data are summarized in Table 3.

Early findings
Early mortality, defined as death within 30 days of the operation or death before discharge from the hospital, was 8/101 (7.9%). Two patients died during surgery, both due to heart failure/low output syndrome. Six patients died in the intensive care unit 1-50 days after primary operation due to low output syndrome in five cases and severe anoxic brain injury in one case. Fourteen patients underwent early reoperation for various reasons. Inotropic support was needed for more than 24 hours in 25 patients. Intra-aortic balloon pumping was used postoperatively in 14 patients. Postoperative stroke occurred in seven patients, of whom three had complete regression of symptoms before discharge. A summary of postoperative data is presented in Table 4.

Long-term findings
Mean follow-up of operative survivors (n=93) was 4.4 ± 2.8 (0.1–10.4) years. The actuarial survival curve (including early mortality) is shown in Figure 15. Overall survival was 88% at one year, 79% at three years and 65% at five years. Late causes of death were cardiac in 14 cases, noncardiac in four cases (cancer, renal failure, stroke, pneumonia) and undetermined in six cases. There was no confirmed arrhythmia-related death and no sudden death. Four patients underwent reoperation, 3–13 months after the primary operation, all due to mitral regurgitation. Two of these did not undergo a mitral valve procedure at the primary operation. In one case there was also patch failure. All underwent mitral valve replacement. In one of these patients the cardiac function deteriorated and the patient subsequently underwent successful cardiac transplantation. Two patients received biventricular pacemakers/implantable cardioverter-defibrillators due to congestive heart failure.

Conclusions
Left ventricular reconstruction by the Dor procedure is a reproducible and safe surgical option in patients with left ventricular aneurysm or ischemic dilated cardiomyopathy. Early mortality was 7.9% and five year survival was 65%.
TABLE 3.

Perioperative data (mean ± SD (range) or number of patients)  

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<td>No. of distal anastomoses</td>
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<td>Reconstruction of the ascending aorta</td>
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<tr>
<td>Intraventricular thrombus</td>
<td>24</td>
</tr>
<tr>
<td>ECC mins</td>
<td>173 ± 65 (55-477)</td>
</tr>
<tr>
<td>XCL (min)</td>
<td>103 ± 31 (39-200)</td>
</tr>
</tbody>
</table>

CABG, coronary artery bypass grafting; LITA, left internal thoracic artery; LAD, left anterior descending artery; VT, ventricular tachycardia; AVR, aortic valve replacement; VSD, ventricular septal defect; ASD, atrial septal defect; ECC, extracorporeal circulation; XCL, cross-clamp time.

TABLE 4.

Postoperative data (mean ± SD (range) or number of patients)  

<table>
<thead>
<tr>
<th>Event</th>
<th>n = 101</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early mortality</td>
<td>8 (7.9%)</td>
</tr>
<tr>
<td>Heart failure/LOS</td>
<td>7</td>
</tr>
<tr>
<td>Acute/hypoxic brain injury</td>
<td>1</td>
</tr>
<tr>
<td>Mors in tabula/ICU</td>
<td>2/6</td>
</tr>
<tr>
<td>Reoperation</td>
<td>14/101</td>
</tr>
<tr>
<td>Bleeding</td>
<td>9</td>
</tr>
<tr>
<td>Hypotension/LOS</td>
<td>1</td>
</tr>
<tr>
<td>Patch failure on day 2</td>
<td>1</td>
</tr>
<tr>
<td>Mediastinitis</td>
<td>1</td>
</tr>
<tr>
<td>PA-catheter removal</td>
<td>1</td>
</tr>
<tr>
<td>Sternal rewiring</td>
<td>1</td>
</tr>
<tr>
<td>Inotropic support (h)</td>
<td>19 ± 34 (0-168)</td>
</tr>
<tr>
<td>&gt; 24 h</td>
<td>25</td>
</tr>
<tr>
<td>Time to extubation (h)</td>
<td>16 ± 25 (3-168)</td>
</tr>
<tr>
<td>Stay in ICU (days)</td>
<td>2.3 ± 2.3 (0-13)</td>
</tr>
<tr>
<td>IABP</td>
<td>14</td>
</tr>
<tr>
<td>Stroke</td>
<td>7</td>
</tr>
<tr>
<td>Infection</td>
<td>5</td>
</tr>
<tr>
<td>Mediastinitis</td>
<td>1</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>4</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>32 ± 9.3 (15-50)</td>
</tr>
</tbody>
</table>

LOS, low output syndrome; ICU, intensive care unit; IABP, intra-aortic balloon pumping.

Figure 15. Overall actuarial survival after left ventricular reconstruction in 101 patients. Dotted curves are upper and lower 95% confidence interval.
STUDY II

Objective
To evaluate left ventricular reconstruction including surgery for ventricular tachycardia in patients with preoperative spontaneous or inducible ventricular tachycardia.

Results

Early findings
Early mortality, defined as death within 30 days of the operation or death before discharge from the hospital, was 2 of 53 patients (3.8%). There were no intraoperative deaths, but two patients died in the intensive care unit (1 and 50 days after primary operation). Postoperative stroke occurred in one patient who had complete regression of symptoms in two months.

Long-term findings
Mean follow-up of operative survivors (n=51) was 3.7 ± 2.0 years (range, 0.1 to 7.0 years). Overall survival was 94% at one year, 80% at three years, and 59% at five years. There was no difference in survival between patients with preoperative spontaneous or inducible ventricular tachycardia. Late causes of death were cardiac in eight cases, non-cardiac in two cases, and undetermined in five cases. There was no arrhythmia-related death and no sudden death. There was no loss to follow-up.

Freedom from postoperative arrhythmia
Surgical success in terms of arrhythmia control was defined as freedom from postoperative spontaneous ventricular tachycardia in operative survivors. Five patients had spontaneous ventricular tachycardia postoperatively; thus overall success rate was 90% (46 of 51 patients). Postoperative programmed electrical stimulation was conducted in 35 patients and showed another five patients with inducible-only ventricular tachycardia. Two of the patients with postoperative inducible-only ventricular tachycardia were noted among the five patients with posterior aneurysm. Medication at postoperative programmed electrical stimulation was amiodarone (n=3), sotalol (n=9), other beta-blockers (metoprolol, atenolol or carvedilol, n=9), digoxin (n=2), no antiarrhythmic medication (n=10), and unknown in two cases.

Patients with preoperative spontaneous ventricular tachycardia
Detailed results in patients with preoperative spontaneous ventricular tachycardia are shown in Figure 16 and Table 5. Fifteen of 18 patients who underwent postoperative programmed electrical stimulation were non-inducible at the postoperative study (Figure 16). Further, four of five patients without postoperative programmed electrical stimulation were also considered cured from ventricular tachycardia (Table 5). Finally, two of three patients with inducible ventricular tachycardia at postoperative programmed electrical stimulation were considered cured because one of them was noninducible at repeat programmed electrical stimulation and the other did not have any ventricular tachycardia detected by the implantable cardioverter-defibrillator that was implanted postoperatively. The success rate in these patients was 91% (15+4+2=21 of 23).

Patients with preoperative inducible-only ventricular tachycardia
In the group of patients with inducible-only ventricular tachycardia (n=29), postoperative programmed electrical stimulation was performed in 17 of 28 operative survivors, and 12 patients were noninducible. Inducible ventricular tachycardia was found in five patients, and two of those also had postoperative spontaneous ventricular tachycardia. One patient who did not undergo postoperative programmed electrical stimulation had spontaneous ventricular tachycardia. Postoperative programmed electrical stimulation was not conducted in another ten patients for various reasons; none of these had spontaneous ventricular tachycardia. Four patients received an im-
plantable cardioverter-defibrillator. In conclusion, success rate in patients with preoperative inducible ventricular tachycardia was 89% (25 of 28 patients).

**Conclusions**

Left ventricular reconstruction by the Dor procedure including endocardiectionomy and cryoablation resulted in a very high (90%) freedom from spontaneous ventricular tachycardia.

**Figure 16.** Detailed results in patients with preoperative spontaneous ventricular tachycardia (n=24) undergoing left ventricular reconstruction including surgery for ventricular tachycardia. (ICD = implantable cardioverter-defibrillator; Med = antiarrhythmic medication; PES = programmed electrical stimulation.)

**Table 5.**

Results in patients with preoperative spontaneous ventricular tachycardia who did not undergo postoperative programmed electrical stimulation (n = 5).

<table>
<thead>
<tr>
<th>Patient Number*</th>
<th>Postoperative Spontaneous VT</th>
<th>ICD</th>
<th>Comment</th>
<th>Arrhythmia Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>No</td>
<td>Yes, postop</td>
<td>Refused postop PES, received ICD, no detection of VT postop</td>
<td>Yes</td>
</tr>
<tr>
<td>17</td>
<td>Yes</td>
<td>Yes, postop</td>
<td>Recurrent VT postop; ICD active</td>
<td>No</td>
</tr>
<tr>
<td>18</td>
<td>No</td>
<td>No</td>
<td>Alive. No VT during follow-up</td>
<td>Yes</td>
</tr>
<tr>
<td>19</td>
<td>No</td>
<td>No</td>
<td>Died 2.5 years postop of CHF. No VT during follow-up</td>
<td>Yes</td>
</tr>
<tr>
<td>21</td>
<td>No</td>
<td>Yes, preop</td>
<td>Frequent VT detected and treated preop. No detection of VT postop</td>
<td>Yes</td>
</tr>
</tbody>
</table>

* Patient number refers to the consecutive order among patients operated on for spontaneous VT.

CHF = congestive heart failure; ICD = implantable cardioverter-defibrillator; PES = programmed electrical stimulation; postop = postoperative; preop = preoperatively; VT = ventricular tachycardia.
Objective
To analyze risk factors for mortality and hospital re-admission for heart failure after left ventricular reconstruction.

Results
All patients underwent left ventricular reconstruction by the Dor procedure, and 129 (95%) patients had concomitant coronary artery bypass grafting with a mean of 2.5 ± 1.2 (1-5) grafts. A mitral valve procedure was performed in 36 (26%) patients, using predominantly the Alfieri edge-to-edge technique [93] by the transventricular approach.

Early findings
Early mortality, defined as death within 30 days of the operation or death before discharge from the hospital, was 10/136 (7.4%). Two patients underwent re-operation two days and two weeks after left ventricular reconstruction, respectively, because of patch failure. Postoperative stroke occurred in eight patients. In three of these, symptoms had resolved completely before hospital discharge.

Risk factors for early mortality
Previous cardiac surgery was significantly associated with an increased risk for early mortality. Bivariate analysis of pre- and perioperative risk factors for early mortality in all patients are presented in Table 6.

Long-term findings
Median follow-up of operative survivors (n=126) was 4.2 (interquartile range 1.7-6.7) years. Overall survival was 89% at one year, 80% at three years, 68% at five years and 62% at nine years with nine remaining patients at risk. Late causes of death were cardiac in 22 cases, non-cardiac in seven cases (cancer, renal failure, stroke, pneumonia) and undetermined in one case. There was no confirmed arrhythmia-related death and no sudden death. Four patients underwent reoperation, 3-13 months after the primary operation, all due to mitral regurgitation. Two of these did not undergo a mitral valve procedure at the primary operation. All four underwent a mitral valve replacement without early mortality. One of these patients underwent successful heart transplantation one year later.

Risk factors for late mortality
Increasing age, diabetes mellitus and mitral valve regurgitation grade III-IV were strongly and significantly associated with late mortality in the multivariable model (Table 7). Preoperative findings of either spontaneous or inducible ventricular tachycardia, or surgery for ventricular tachycardia, were not found to be associated with early or late mortality.

Hospital re-admission due to heart failure
Freedom from a composite endpoint of first postoperative hospital re-admission due to heart failure or cardiac death in operative survivors was 78% at one year, 72% at three years and 58% at five years. Increasing grade of mitral valve regurgitation was strongly and significantly associated with hospital re-admission due to heart failure in the age-adjusted multivariable model (Table 7).

Conclusions
Left ventricular reconstruction by the Dor procedure resulted in good long-term survival and a high degree of freedom from re-admission for heart failure. We found a strong association between increasing grade of mitral regurgitation and both long-term mortality and re-admission for heart failure.
Left ventricular reconstruction

Table 6

Bivariate analysis of preoperative and surgical risk factors for early mortality in all patients (n = 136)

<table>
<thead>
<tr>
<th>Variables</th>
<th>Early mortality</th>
<th></th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean ± SD or percentage (n)</td>
<td>Yes (n = 13)</td>
<td>No (n = 126)</td>
</tr>
<tr>
<td>Preoperative variables</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>67.2 ± 9.2</td>
<td>61.7 ± 9.7</td>
<td>0.24</td>
</tr>
<tr>
<td>Female</td>
<td>30% (3)</td>
<td>23% (29)</td>
<td>0.76</td>
</tr>
<tr>
<td>Ejection fraction</td>
<td>23.5 ± 8.8</td>
<td>26.6 ± 9.8</td>
<td>0.38</td>
</tr>
<tr>
<td>NYHA class III–IV</td>
<td>90% (9)</td>
<td>68% (86)</td>
<td>0.28</td>
</tr>
<tr>
<td>MR grade III–IV</td>
<td>30% (3)</td>
<td>12% (15)</td>
<td>0.13</td>
</tr>
<tr>
<td>Left main stenosis</td>
<td>10% (1)</td>
<td>2.4% (3)</td>
<td>0.27</td>
</tr>
<tr>
<td>Inducible VT</td>
<td>20% (2)</td>
<td>48% (50)</td>
<td>0.32</td>
</tr>
<tr>
<td>Spontaneous VT</td>
<td>30% (3)</td>
<td>24% (30)</td>
<td>0.76</td>
</tr>
<tr>
<td>Triglyceride level</td>
<td>70% (7)</td>
<td>49% (62)</td>
<td>0.33</td>
</tr>
<tr>
<td>Anterior LVA</td>
<td>80% (8)</td>
<td>93% (116)</td>
<td>0.22</td>
</tr>
<tr>
<td>Posterior LVA</td>
<td>10% (1)</td>
<td>4.8% (6)</td>
<td>0.42</td>
</tr>
<tr>
<td>ICDMP</td>
<td>10% (1)</td>
<td>4.6% (5)</td>
<td>0.37</td>
</tr>
<tr>
<td>Previous cardiac surgery</td>
<td>30% (3)</td>
<td>3.2% (4)</td>
<td>0.09</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>24.4 ± 4.0</td>
<td>26.1 ± 3.8</td>
<td>0.24</td>
</tr>
<tr>
<td>Diabetes mellitus²</td>
<td>40% (4)</td>
<td>17% (21)</td>
<td>0.06</td>
</tr>
<tr>
<td>Impaired renal function³</td>
<td>40% (4)</td>
<td>18% (22)</td>
<td>0.09</td>
</tr>
<tr>
<td>EuroSCORE</td>
<td>9.2 ± 2.6</td>
<td>7.4 ± 2.8</td>
<td>0.02</td>
</tr>
<tr>
<td>Surgical variables</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surgery for VT</td>
<td>20% (2)</td>
<td>45% (57)</td>
<td>0.11</td>
</tr>
<tr>
<td>Mitral valve surgery</td>
<td>50% (5)</td>
<td>25% (21)</td>
<td>0.09</td>
</tr>
<tr>
<td>CPB duration (min)</td>
<td>263 ± 107</td>
<td>160 ± 49</td>
<td>0.02</td>
</tr>
<tr>
<td>Number of bypass grafts</td>
<td>1.9 ± 1.5</td>
<td>2.5 ± 1.2</td>
<td>0.13</td>
</tr>
<tr>
<td>Non-use of LITA</td>
<td>50% (5)</td>
<td>12% (15)</td>
<td>0.007</td>
</tr>
<tr>
<td>No graft to LAD</td>
<td>40% (4)</td>
<td>5.6% (7)</td>
<td>0.004</td>
</tr>
</tbody>
</table>

BMI: body mass index; CPB: cardiopulmonary bypass; ICDMP: ischemic dilated cardiomyopathy; LITA: left internal thoracic artery; LVA: left ventricular aneurysm; MR: mitral regurgitation; NYHA: New York Heart Association; SS: standard deviation; VT: ventricular tachycardia.

* Treated with insulin or oral anti-diabetics.

Table 7.

Risk factors for late mortality (n = 136) and composite endpoint of first postoperative hospital re-admission due to heart failure or cardiac death in operative survivors (n = 126) after surgical ventricular restoration by Cox proportional hazards analysis

<table>
<thead>
<tr>
<th>Outcome and variables</th>
<th>Level</th>
<th>HR</th>
<th>95% CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Late mortality (n = 136, number of events = 40)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>One year</td>
<td>1.05</td>
<td>1.01–1.1</td>
<td>0.02</td>
</tr>
<tr>
<td>Diabetes mellitus² (n = 25)</td>
<td>Yes/no</td>
<td>2.75</td>
<td>1.4–5.5</td>
<td>0.004</td>
</tr>
<tr>
<td>Mitral regurgitation grade III–IV (n = 18)</td>
<td>Yes/no</td>
<td>2.83</td>
<td>1.3–6.1</td>
<td>0.008</td>
</tr>
<tr>
<td>Hospital re-admission/death (n = 126, number of events = 49)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>One year</td>
<td>1.06</td>
<td>1.02–1.1</td>
<td>0.002</td>
</tr>
<tr>
<td>Mitral regurgitation grade</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 (n = 57)</td>
<td>Yes/no</td>
<td>1 (reference)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I (n = 24)</td>
<td>Yes/no</td>
<td>1.49</td>
<td>0.6–3.6</td>
<td>0.38</td>
</tr>
<tr>
<td>II (n = 30)</td>
<td>Yes/no</td>
<td>1.97</td>
<td>0.9–4.1</td>
<td>0.07</td>
</tr>
<tr>
<td>III (n = 14)</td>
<td>Yes/no</td>
<td>2.65</td>
<td>1.0–6.8</td>
<td>0.04</td>
</tr>
<tr>
<td>IV (n = 4)</td>
<td>Yes/no</td>
<td>4.59</td>
<td>1.2–17</td>
<td>0.02</td>
</tr>
</tbody>
</table>

CI: confidence interval; HR: hazard ratio.

* Treated with insulin or oral anti-diabetics.
STUDY IV

Objective
To prospectively investigate changes in functional status and quality of life after left ventricular reconstruction.

Results
There was no early mortality defined as death within 30 days of the operation or before hospital discharge. All patients underwent left ventricular reconstruction by the Dor procedure, and 22 (96%) patients had concomitant coronary artery bypass grafting with a mean of 2.5 ± 1.2 (1-5) grafts. Mitral valve repair was performed in four (17%) patients.

All patients were alive at follow-up six months postoperatively. However, three patients died later; one renal-transplant recipient died from renal failure 2.1 years after surgery, and two patients died 1.6 and 2.5 years after the operation at age 79 and 74, respectively, both due to heart failure. During a total follow-up of 43.7 patient years, survival at 24 months was 93% with ten patients remaining at risk.

Late follow-up for functional and quality of life assessment was performed at a mean of 22 months (standard deviation 9.5, range 9-38 months) postoperatively.

New York Heart Association functional class
There was a significant improvement in functional status judged by NYHA class. Before surgery 17 patients (74%) were in NYHA class III-IV and six months after the operation 20 (87%) patients were in NYHA class I-II (p=0.0001). At late follow-up, two of the three patients in NYHA class III at six months had died, and the third had improved to NYHA class II. Thus, all patients alive at late follow-up (n=20) were in NYHA class I-II.

Six-minute walk test
Six-minute walk test distance increased in 12 of 17 patients who completed a pre- and postoperative six-minute walk test and the results are shown in Figure 17 and Table 8. Mean walking distance increased by 41 meters six months after the operation (p=0.06). Fourteen patients were available for six-minute walk test at late follow-up. Mean walking distance increased by 57 meters at late follow-up compared to baseline (p=0.03).

Health-related quality of life
Pre- and postoperative SF-36 questionnaires were completed by 21 (91%) and 17 (85%) of the patients at six months and at late follow-up, respectively. The mean preoperative and postoperative SF-36 scores are shown in Table 9. We observed a 15% mean increase in the physical component summary score (p=0.02) and a 13% mean increase in the mental component summary score (p=0.06) six months postoperatively. At late follow-up, we observed a mean increase in the physical component summary score of 25% (p<0.001) and a 37% mean increase in the mental component summary score (p=0.003) compared to baseline (Table 10).

Conclusions
We found that functional status (NYHA functional class, six-minute walk distance) and quality of life improved six months after left ventricular reconstruction and the improvement was sustained at late follow-up.
Left ventricular reconstruction

Table 8.
Six-minute walk test before and after left ventricular reconstruction.

<table>
<thead>
<tr>
<th>6MWD, m (Mean Difference)</th>
<th>SD</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preoperative versus 6 months postoperative (n = 56)</td>
<td>41</td>
<td>78</td>
</tr>
<tr>
<td>Preoperative versus late postoperative (n = 13)</td>
<td>57</td>
<td>86</td>
</tr>
<tr>
<td>6 months postoperative versus late postoperative (n = 12)</td>
<td>29</td>
<td>56</td>
</tr>
</tbody>
</table>

6MWD = six-minute walk distance.

Figure 17. Six-minute walk test distance before and after left ventricular reconstruction.

Table 9.
Short Form-36 scores before and after left ventricular reconstruction.

<table>
<thead>
<tr>
<th>SF-36 Subscales</th>
<th>Preoperatively</th>
<th>Six Months Postoperatively</th>
<th>Late Postoperatively</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (n = 21)</td>
<td>SD</td>
<td>Mean (n = 21)</td>
</tr>
<tr>
<td>Physical functioning</td>
<td>39</td>
<td>25</td>
<td>50</td>
</tr>
<tr>
<td>Physical role functioning</td>
<td>21</td>
<td>35</td>
<td>40</td>
</tr>
<tr>
<td>Bodily pain</td>
<td>53</td>
<td>25</td>
<td>59</td>
</tr>
<tr>
<td>General health</td>
<td>45</td>
<td>20</td>
<td>52</td>
</tr>
<tr>
<td>Vitality</td>
<td>31</td>
<td>25</td>
<td>48</td>
</tr>
<tr>
<td>Social functioning</td>
<td>53</td>
<td>32</td>
<td>63</td>
</tr>
<tr>
<td>Emotional role functioning</td>
<td>30</td>
<td>43</td>
<td>46</td>
</tr>
<tr>
<td>Mental health</td>
<td>57</td>
<td>27</td>
<td>60</td>
</tr>
<tr>
<td>Physical component summary score</td>
<td>31.7</td>
<td>9.9</td>
<td>36.5</td>
</tr>
<tr>
<td>Mental component summary score</td>
<td>35.5</td>
<td>14.4</td>
<td>40.0</td>
</tr>
</tbody>
</table>

Table 10.
Short Form-36 scores before and after left ventricular reconstruction.

<table>
<thead>
<tr>
<th></th>
<th>PCS (Mean Difference)</th>
<th>SD</th>
<th>p Value</th>
<th>MCS (Mean Difference)</th>
<th>SD</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preoperative versus 6 months postoperative (n = 21)</td>
<td>4.8 (+15%)</td>
<td>9.1</td>
<td>0.02</td>
<td>4.5 (+13%)</td>
<td>10.2</td>
<td>0.06</td>
</tr>
<tr>
<td>Preoperative versus late postoperative (n = 17)</td>
<td>8.0 (+25%)</td>
<td>5.8</td>
<td>&lt; 0.001</td>
<td>12.6 (+37%)</td>
<td>14.8</td>
<td>0.003</td>
</tr>
<tr>
<td>6 months postoperative versus late postoperative (n = 17)</td>
<td>2.0 (+5%)</td>
<td>7.4</td>
<td>0.27</td>
<td>6.9 (+17%)</td>
<td>12.8</td>
<td>0.04</td>
</tr>
</tbody>
</table>

MCS = mental component summary; PCS = physical component summary.
STUDY V

Objective
To prospectively investigate changes in biomarkers for heart failure (BNP and NT-pro-BNP) in relation to functional status after left ventricular reconstruction.

Results
There was no early mortality defined as death within 30 days of the operation or before hospital discharge. All patients underwent left ventricular reconstruction by the Dor procedure, and 28 patients had concomitant coronary artery bypass grafting with a mean of 2.8, (1-5) grafts. Mitral valve repair was performed in four (14%) patients with preoperative grade III or IV mitral regurgitation.

All patients were alive at follow-up six months postoperatively. However, four patients died later, one renal-transplant recipient died from renal failure 2.1 years after surgery, and two patients died 1.6 and 2.5 years after the operation at age 79 and 74, respectively, both due to heart failure, and one patient died at age 79 due to disseminated bladder cancer 2.8 years after surgery. During a total follow-up of 51 patient-years, survival at 24 months was 93% with 11 patients remaining at risk. Early follow-up for functional assessment and peptide measurements was performed at six months postoperatively. Late follow-up was performed at a mean of 21 (standard deviation 9.0, range 12-38) months postoperatively. Preoperative medication included angiotensin converting enzyme inhibitors in 97%, beta-blockers in 93% and spironolactone in 28%. Postoperative medication included angiotensin converting enzyme inhibitors in 97%, beta-blockers in 86% and spironolactone in 34%.

New York Heart Association functional class
There was a significant improvement in NYHA functional class. Before surgery 22 patients (76%) were in NYHA class III-IV and six months after the operation 25 (86%) patients were in NYHA class I-II (p<0.001). At late follow-up, all patients alive (n=25) were in NYHA class I-II. Pre- and postoperative NYHA class for all patients is shown in Figure 18.

Changes in BNP and NT-pro-BNP
There was a marked and significant reduction of NT-pro-BNP levels (2406 pg/mL vs. 1510 pg/mL; p=0.03 and 975 pg/mL; p=0.03) at six months postoperatively, and at late follow-up, respectively. The reduction of BNP levels (312 pg/mL vs. 228 pg/mL; p=0.12 and 191 pg/mL; p=0.20) at six months postoperatively, and at late follow-up, respectively, was not statistically significant. Changes in B-type natriuretic peptide levels are shown in Table 11. Three patients still in NYHA class III six months after surgery were excluded from the statistical analysis at this time-point, since they were non-responders without clinical improvement. In these three patients, there was a six-fold increase in mean BNP and a five-fold increase in mean NT-pro-BNP.

There was a close relationship between BNP and NT-pro-BNP at all time-points (r=0.85, n=21, p<0.001 preoperatively; r=0.84, n=24, p<0.001 six months postoperatively; r=0.93, n=20, p<0.001 late postoperatively).

Association between functional improvement and reduction of natriuretic peptides
Functional improvement (NYHA class reduction) correlated significantly with reduction in BNP (r=0.61, n=17, p=0.01) and NT-pro-BNP (r=0.58, n=24, p=0.003) levels six months after surgery.

Cardiac function
Left ventricular ejection fraction improved from 24% to 37% (p<0.001) at six months after surgery, assessed by radionuclide ventriculography in 22 patients and by echocardiography in seven patients. Left ventricular end-diastolic (110 mL/m² vs. 90 mL/m², p=0.009) and end-systolic
(75 mL/m$^2$ vs. 52 mL/m$^2$, p=0.006) volume decreased significantly, and cardiac index (2.0 L/min/m$^2$ vs. 2.5 L/min/m$^2$, p=0.003) improved six months after surgery, as shown in TABLE 12.

Association between ejection fraction, ventricular volumes and natriuretic peptides

Increasing ejection fraction correlated significantly with lower BNP (r=-0.58, n=15, p=0.02) and NT-pro-BNP (r=-0.51, n=16 p=0.04) levels six months after surgery (FIGURE 19). Decreasing left ventricular end-systolic volume correlated significantly with lower BNP (r=0.65, n=11, p=0.03) and NT-pro-BNP (r=0.62, n=12, p=0.03) levels six months after surgery (FIGURE 20).

Table 11.
Changes in B-type natriuretic peptide levels after surgical ventricular restoration

<table>
<thead>
<tr>
<th>Peptide levels (pg/mL)</th>
<th>Preoperative</th>
<th>6 months postoperative</th>
<th>Late postoperative</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>Mean (SD)</td>
<td>n</td>
</tr>
<tr>
<td>BNP</td>
<td>21</td>
<td>129</td>
<td>312 (466)</td>
</tr>
<tr>
<td>NT-pro-BNP</td>
<td>29</td>
<td>1088</td>
<td>2406 (4440)</td>
</tr>
</tbody>
</table>

SD = standard deviation

Table 12.
Left ventricular volumes and cardiac index by magnetic resonance imaging before and six months after surgical ventricular restoration

<table>
<thead>
<tr>
<th>Magnetic Resonance Imaging</th>
<th>Preoperative (n=18)</th>
<th>Postoperative (n=14)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
</tr>
<tr>
<td>EDVI (mL/m$^2$)</td>
<td>110</td>
<td>27</td>
</tr>
<tr>
<td>ESVI (mL/m$^2$)</td>
<td>75</td>
<td>28</td>
</tr>
<tr>
<td>CI (L/min/m$^2$)</td>
<td>2.0</td>
<td>0.4</td>
</tr>
</tbody>
</table>

CI = cardiac index, EDVI = end-diastolic volume index, ESVI = end-systolic volume index, SD = standard deviation

Conclusions
We found that severe heart failure secondary to post-infarction left ventricular remodeling can be reversed by left ventricular reconstruction. Clinical improvement was associated with reduced levels of B-type natriuretic peptides six months after surgery. Functional improvement was maintained and peptide levels were further reduced at late follow-up.
Figure 18. New York Heart Association functional class before and after left ventricular reconstruction.

Figure 19. BNP (upper graph) and NT-pro-BNP (lower graph) on the y-axis plotted against left ventricular end-systolic volume on the x-axis \((r=0.65, n=11, p=0.03; r=0.62, n=12, p=0.03, \text{ respectively})\) at six months after left ventricular reconstruction. Solid line = estimated regression line, dotted lines = 95% confidence interval.

Figure 20. BNP (upper graph) and NT-pro-BNP (lower graph) on the y-axis plotted against ejection fraction on the x-axis \((r=-0.58, n=15, p=0.02; r=-0.51, n=16, p=0.04, \text{ respectively})\) at six months after left ventricular reconstruction. Solid line = estimated regression line, dotted lines = 95% confidence interval.
The operative goal of left ventricular reconstruction by the Dor procedure is to achieve complete coronary revascularization, reduce left ventricular volume and to restore left ventricular shape. Mitral regurgitation and ventricular tachycardia are addressed when present.

Rationale
Post-infarction left ventricular dilatation is strongly linked to bad prognosis [2-4].

Hypothesis
Restored left ventricular size and form improves survival, functional status and quality of life.

LEFT VENTRICULAR RECONSTRUCTION

Aneurysm repair or treatment of heart failure?

According to the European Society of Cardiology Guidelines for the diagnosis and treatment of chronic heart failure [1], left ventricular aneurysmectomy is indicated in patients with large, discrete left ventricular aneurysms who develop heart failure (Class of recommendation I, level of evidence C). Other surgical procedures are mentioned in the Guidelines but are not recommended at this point for treatment of chronic heart failure.

In our opinion, left ventricular reconstruction should not be regarded as only an aneurysm repair technique but instead as a viable option in modern interventional treatment of heart failure. In selected cases, left ventricular reconstruction could be considered as an alternative to heart transplantation [71, 105-107].

Not a standardized technique

When comparing results from different studies, it is important to realize that left ventricular reconstruction is not a precisely defined operative procedure but rather a designation of a group of techniques aiming to restore normal left ventricular shape and volume. The endoventricular patch plasty, as described by Dor, always includes the use of a patch [64]. McCarthy, Cleveland Clinic, has described a double purse-string suture technique [108]. Mickleborough, Toronto, has developed a modified linear closure plus septoplasty, which sometimes includes the use of a patch [75]. Menicanti, Milano, has added the component of inferior plication of the left ventricle to the Dor procedure and also advocates the use of a mannequin in order to establish correct shape and volume and to avoid overcorrection [76]. The septal anterior ventricular exclusion (or Pacopexy) operation is another variant used in both ischemic [109] and idiopathic [110] dilated cardiomyopathy.
All patients in our series underwent left ventricular reconstruction by the Dor procedure, although a limited number of patients late in this series also underwent inferior plication, as described by Menicanti [94].

Sizing of the new ventricle

Dor [111] and Menicanti [76] advocates the use of a sizing balloon or mannequin in order to get a more objective assessment of postoperative left ventricular size. The value of a sizing device has yet to be determined. In most cases with thin-walled, fibrotic, dyskinetic left ventricular aneurysm, there is a clear transitional zone between dysfunctional tissue and viable contracting myocardium, which makes it easy to define the new ventricle. It is, however, conceivable that a sizing device could be beneficial in patients where a thin walled aneurysm has not yet developed. In our experience, the mannequin can be of help in these cases to guide the surgeon as to where the purse-string suture and patch should be placed to avoid overcorrection and consequently to ensure diastolic capacity. Leaving the patient with a too small ventricle is deleterious [112].

On or off clamp?

There is no general agreement on whether the reconstruction part of the operation should be performed with the heart beating or in cardioplegic arrest. Dor initially described the procedure on the arrested heart, but in the report from the Reconstructive Endoventricular Surgery returning Torsion Original Radius Elliptical shape to the left ventricle (RESTORE) group [70], in about half of the cases the ventricular portion of the procedure was done on the beating heart. The beating method was used more frequently in older patients, and those with lower ejection fraction, larger volume and more advanced heart failure. Five-year survival was comparable between the groups [113]. Another retrospective study showed no additional advantage of the beating heart approach over the continuous aortic cross-clamping method in a group of 53 patients undergoing the Dor procedure [114]. In our series, the operation was performed on the arrested heart in almost all patients.

Traditional linear repair

Traditionally a linear repair technique has been used on thin-walled left ventricular aneurysms. This technique does not allow for exclusion of the septal portion of the aneurysm. A recent retrospective study comparing simple linear repair and endoventricular patch plasty for left ventricular aneurysm has shown lower surgical risk and higher long-term survival after endoventricular patch plasty. The authors clarify that the differences in outcome should be interpreted with care due to study design [115].

Mickleborough has reported excellent results in a series of 285 patients, who had akinesia or dyskinesia and wall thinning, with a modified linear closure technique. In select cases (n=64, 22%) a patch septoplasty was performed due to dyskinetic septum [75]. Thus, different methods for aneurysm repair and septal exclusion have been described apart from simple excision and linear closure.

We believe that the patch plasty described by Dor is the method of choice after left anterior descending artery occlusion and anterior infarction since, in these cases, the septum is always affected, and the patch technique is a reproducible way to effectively exclude the septum and safely ensure diastolic capacity. Furthermore, the linear repair often makes grafting of the left anterior descending artery impossible.

Myocardial revascularization

Is the outcome a result of revascularization or ventricular reconstruction or both?

Complete revascularization is mandatory for a good outcome. Specifically, the left anterior descending artery should receive a graft, preferably the left internal thoracic artery [116], due to the fact that although the
distal part may be occluded, the proximal part supports the septal branches which are critical for the blood supply of the basal portions of the ventricle and septum [76].

Revascularization and ischemic cardiomyopathy

No randomized clinical trials have investigated the benefit of coronary artery bypass surgery in patients with advanced heart failure and ischemic cardiomyopathy.

Coronary artery bypass grafting alone usually does not lead to relief of heart failure symptoms or better left ventricular function in ischemic cardiomyopathy [117-119]. Recent reports [117, 118] support the speculation that revascularization alone is not sufficient in the dilated ventricle. Specifically, patients with ischemic cardiomyopathy and a substantial amount of viable myocardium and a high end-systolic volume due to left ventricular remodeling have a decreased likelihood of improvement of global function following myocardial revascularization [118]. Furthermore, patients with a large left ventricular end-systolic volume have a worse long-term prognosis as compared to patients with a smaller left ventricular end-systolic volume [117].

Nevertheless, coronary artery bypass surgery has an important role in patients with coronary artery disease and severe left ventricular dysfunction, with reported operative mortality of about 3-5% and five year survival of 60-70% in carefully selected patients [120, 121]. However, despite reasonably good early and late survival, late functional outcome after myocardial revascularization in ischemic cardiomyopathy remains unacceptable because of recurrence or persistence of heart failure [122].

Maxey performed a retrospective analysis of patients with ischemic cardiomyopathy, enlarged left ventricle (end-diastolic diameter more than 6.0 cm) and left ventricular dysfunction (ejection fraction less than 30%) who underwent operation between 1998 and 2002. Patients underwent either coronary artery bypass alone (n = 39) or coronary artery bypass with left ventricular reconstruction (n = 56) and outcomes were compared. The investigators found significantly better late outcome regarding mortality and freedom from heart failure in the group who underwent left ventricular reconstruction combined with coronary artery bypass surgery [123].

Better outcome when coronary artery bypass surgery was combined with ventricular reconstruction was demonstrated in a prospective, randomized study from Brazil [73]. The study included 74 patients who were randomized to either coronary artery bypass surgery (n=35) or coronary artery bypass surgery combined with left ventricular reconstruction by the Dor procedure (n=39). All patients had ischemic cardiomyopathy, left ventricular dysfunction with an ejection fraction less than 35%, left ventricular end-systolic volume index more than 80 mL/m$^2$, and anterior wall viability. Patients with mitral regurgitation more than grade II were excluded. Anterior wall motion was evaluated by angiographic examination and patients with akinetic anterior wall were included, and those who showed dyskinetic wall motion were excluded. Adverse events, defined as all causes of death, myocardial infarction, recurrent heart failure, and rehospitalization, were significantly less frequent after two years in the group that received a combined procedure. Six patients in the coronary artery bypass group developed grade III-IV mitral regurgitation late after surgery as compared to none in the combined procedure group. The patients who developed moderate to severe mitral regurgitation postoperatively had significantly larger preoperative end-systolic volume than the other patients in the same group [73].

The ongoing STICH Trial

The Surgical Treatment for Ischemic Heart failure (STICH) trial is an investigator-initiated clinical trial sponsored by the United States National Heart, Lung, and Blood Institute. It is an international, multicenter,
randomized clinical trial designed to test two hypotheses in patients with coronary artery disease and left ventricular dysfunction. The first hypothesis is that coronary artery bypass surgery combined with intensive medical therapy improves long-term survival compared with medical therapy alone. The second hypothesis is that left ventricular reconstruction combined with coronary artery bypass surgery and medical therapy improves survival free of hospitalization compared with coronary artery bypass surgery and medical therapy without left ventricular reconstruction [72].

### Table 13.
STICH trial inclusion criteria.

**STICH randomized clinical trial**
*(Surgical Treatment of Ischemic Heart Failure)*

**Inclusion Criteria:**
1. Left ventricular ejection fraction < 35%
2. Coronary anatomy suitable for revascularization.

**Exclusion Criteria:**
1. Aortic valvular disease clearly indicating the need for valve procedure
2. Patients with concurrent cardiogenic shock
3. Percutaneous coronary intervention planned for coronary artery disease treatment
4. Acute myocardial infarction as a cause of left ventricular dysfunction
5. More than one prior coronary bypass operation
6. Non-cardiac illness with life expectancy less than three years or imposing substantial operative mortality

![Flowchart](Figure 21. A total of 600 patients will be randomized between medical therapy (MED), coronary artery bypass surgery (CABG), and left ventricular reconstruction (LVR) + CABG. The 600 patients eligible for LVR but ineligible for medical therapy will be randomized between CABG and LVR + CABG. For the comparison of CABG + LVR vs. CABG alone, the primary endpoint is long-term survival free of cardiac hospitalization.)
Surgery for Ventricular Tachycardia

In our consecutive series of patients with preoperatively verified spontaneous or inducible ventricular tachycardia who underwent left ventricular reconstruction and nonguided endocardiectomy and cryoablation, freedom from postoperative spontaneous ventricular tachycardia was attained in 90% of operative survivors.

Mechanisms of ventricular arrhythmia

The ability to reproducibly initiate an arrhythmia by programmed electrical stimulation is considered a characteristic of reentrant arrhythmia and is the mechanism of sustained uniform ventricular tachycardia associated with coronary artery disease [124]. Both nonsustained and sustained polymorphic arrhythmias, including ventricular fibrillation, can be induced even in persons without cardiac disease. In a person with cardiac disease, or a history of cardiac arrest, induction of polymorphic ventricular tachycardia can have a clinical significance because a cardiac arrest may be initiated by a polymorphic ventricular tachycardia. More importantly, the induction of a sustained uniform tachycardia only occurs in patients with spontaneous ventricular tachycardia or cardiac arrest or in the presence of a substrate known to be arrhythmogenic such as a left ventricular aneurysm or recent myocardial infarction [125]. The possibility of inducing ventricular tachycardia increases with decreasing left ventricular function, and patients with depressed left ventricular function and inducible sustained ventricular tachycardia have a higher risk of spontaneous ventricular tachycardia than those who do not have inducible ventricular tachycardia [126, 127]. The results of electrophysiologic testing can be used to assess the prognosis of patients with coronary disease, left ventricular dysfunction, and unsustained ventricular tachycardia, but the value of this information may diminish with time [128].

Revascularization for ventricular tachycardia

Does revascularization alone prevent recurrence of ventricular tachycardia?

In patients with inducible sustained monomorphic ventricular tachycardia and scars as a result of prior myocardial infarction, surgical revascularization alone will usually not be sufficient to prevent postoperative induction of the same arrhythmia, especially not in the presence of poor left ventricular function [124, 129-131].

Endocardiectomy and cryoablation

In 1994, Dor and associates [68] reported excellent results of nonguided subtotal endocardiectomy and left ventricular reconstruction in a series of 106 patients with spontaneous (n=49) or inducible (n=57) ventricular tachycardia. In 67 of those, cryoablation was also added. Early (n=96) and one year (n=37) postoperative programmed electrical stimulation showed freedom from inducible ventricular tachycardia at about 90%. Mickleborough and coworkers [75] recently published their large experience of left ventricular reconstruction in which 108 patients with preoperative ventricular tachycardia included visually directed endocardial excision and peripheral cryoablation. Postoperative freedom from ventricular tachycardia or sudden death was outstanding, and excluding patients receiving an implantable cardioverter-defibrillator (n=9), freedom from ventricular tachycardia or sudden death was 99%, 97%, and 94% at one, five, and ten years, respectively. The authors concluded that the combination of revascularization, left ventricular reconstruction, and visually directed ventricular tachycardia ablation appears to be very effective in preventing arrhythmias [75]. Other authors have reported good antiarrhythmic results after cryoablation or endocardial resection and various techniques for aneurysm repair with or without intraoperative mapping [86-90].
Is endocardectomy and cryoablation necessary in patients with ventricular tachycardia undergoing left ventricular reconstruction?

The goal of the Dor procedure is to achieve complete coronary revascularization, reduce left ventricular volume, and restore left ventricular shape to relieve ischemia and reduce wall tension. Given that it has been shown that myocardial stretch is arrhythmogenic [132], it is plausible that ventricular reconstruction, restoring near-normal left ventricular size and form and thus reducing wall tension, should have a beneficial effect on electrical stability. It has recently been reported that left ventricular reconstruction creates a mechanical intraventricular resynchronization in patients with ischemic cardiomyopathy and with no preoperative electrical conduction delay [79]. It has also been shown in patients with ischemic cardiomyopathy that cardiac resynchronization therapy reduces both inducibility of ventricular tachycardia [133] and frequency of ventricular tachycardia episodes [134-136]. Thus, it seems that intraventricular resynchronization, either by left ventricular reconstruction or biventricular pacing, reduces ventricular arrhythmias in the dilated heart. The mechanism for this improvement may be related to the beneficial effects on left ventricular synchrony, because improved synchrony will not only improve left ventricular hemodynamics but also homogenize regional wall stress and reduce regional prestretch, which is potentially arrhythmogenic [137]. In contrast to these theories, recent reports [138, 139] found a high incidence of sudden death late after surgery for left ventricular aneurysm without concomitant antiarrhythmic surgery.

However, according to Matthias Bechtel and coworkers [138], a limitation of their study was the lack of postoperative data on left ventricular dimensions. Mapping studies by Mickleborough and coworkers [140] in patients with recurrent ventricular tachycardia showed that ease of arrhythmia induction was related to mechanical loadings conditions. One possible explanation for late recurrences of ventricular arrhythmias after left ventricular reconstruction might therefore be progressive remodeling and left ventricular re-enlargement.

O'Neill reported on the Cleveland Clinic experience [139] in 217 consecutive patients who underwent left ventricular reconstruction as a nontransplant surgical strategy for patients with heart failure, with a focus on postoperative malignant arrhythmias. Primary end points were all-cause mortality and appropriate implantable cardioverter-defibrillator therapies, and median follow-up was 381 days. In addition to the left ventricular reconstruction, a small proportion of patients (13%) received a specific antiarrhythmic surgical procedure consisting of cryoablation, about half (46%) underwent a mitral valve procedure, and most patients (88%) were revascularized. The main findings were that patients remain at high risk of ventricular arrhythmias after left ventricular reconstruction and that the arrhythmias occur early postoperatively, in two thirds of the cases within 90 days. The authors recommend early implantation of a defibrillator or electrophysiology-guided cardioverter-defibrillator implantation before hospital discharge after left ventricular reconstruction [139]. In our opinion, patients scheduled for left ventricular reconstruction should be assessed for ventricular arrhythmias, and if present, specific arrhythmia surgery should be performed concomitantly, and the postoperative result should be verified by means of electrophysiology studies. With this protocol, implantation of an implantable cardioverter-defibrillator will not be needed in most patients after left ventricular reconstruction including surgical intervention for ventricular tachycardia [141].

Preferred treatment in case of antiarrhythmic surgical failure

In cases with postoperative confirmed spontaneous or inducible ventricular tachycardia, an implantable cardioverter-defibrillator is the recommended option. The Sudden Cardiac Death in Heart Failure
Trial demonstrated that amiodarone had no favorable effect on survival whereas implantable cardioverter-defibrillator therapy reduced mortality in patients with symptoms of heart failure and left ventricular dysfunction [142].

**Should all patients undergoing left ventricular reconstruction have a prophylactic implantable cardioverter-defibrillator postoperatively?**

Patients with coronary artery disease and previous acute myocardial infarction are at risk for recurrent coronary events such as development of heart failure, ventricular arrhythmias, and sudden cardiac death. The Multicenter Automatic Defibrillator Trial II (MADIT-II) reported that prophylactic implantation of a defibrillator improved survival in patients with a prior myocardial infarction and severe left ventricular dysfunction [143, 144]. It also showed that new or worsened heart failure requiring hospitalization was more frequent in the defibrillator group than in the conventional therapy group. The authors argue that patients saved from malignant ventricular arrhythmias by the implantable cardioverter-defibrillator live longer than conventionally treated patients and thus would have more time for heart failure to develop. Also, implantable cardioverter-defibrillator shocks might contribute to rehospitalization and myocardial injury, and backup ventricular pacing may impair left ventricular function [143, 144].

The CABG-Patch trial [145] found no evidence of improved survival among patients with coronary heart disease, a depressed left ventricular ejection fraction, and an abnormal electrocardiogram in whom a defibrillator was implanted at the time of elective coronary bypass surgery. However, a recent analysis [146] of the MADIT-II [143] study showed that implantable cardioverter-defibrillator therapy was associated with a significant survival benefit and reduction in sudden cardiac death risk after coronary revascularization. Notably, the improved survival was evident only when the implantable cardioverter-defibrillator was implanted more than six months after coronary revascularization. The authors speculate that the early period after coronary revascularization is dominated by nonarrhythmic mortality and this may explain the lack of defibrillator benefit in the CABG-Patch trial [146].

Because implantable cardioverter-defibrillator therapy does not address the problem of the substrate of ventricular tachycardia, merely the consequences, it is desirable to achieve abolishment of malignant ventricular arrhythmias. In our view, implantation of an implantable cardioverter-defibrillator after the Dor procedure including surgery for ventricular tachycardia is a surgical failure. It is our policy to only recommend cardioverter-defibrillator implantation for patients with documented antiarrhythmic surgical failure. There has been no arrhythmia-related death or sudden death during follow-up in our series, suggesting that over time, this treatment policy is valid.

**SURVIVAL AND HOSPITAL RE-ADMISSION**

We found that left ventricular reconstruction can achieve good long-term survival and a high degree of freedom from re-admission for heart failure in patients with advanced ischemic heart disease. We found a strong association between increasing grade of mitral regurgitation and both long-term mortality and re-admission for heart failure.

**Early and long-term survival**

Excellent single-center results of hemodynamic data and survival have been published by Dor [67] and Menicanti [76] and multi-center results published by the RESTORE team are equally satisfactory [70]. Our results regarding survival (68% at five years) are comparable to those previously reported (69-80% at five years) [70, 75, 111, 147].
However, the study populations differ slightly. Patients in our study had predominantly dyskinetic left ventricular aneurysms, whereas two thirds of the patients in the study by the RESTORE group [70] had akinetic rather than dyskinetic left ventricles. The authors also found that survival at five years were better in the group of patients that had dyskinetic as compared to akinetic morphology (80 vs. 65%; P<0.001). This finding is interesting, since Di Donato [69] demonstrated that outcome in a large series of left ventricular reconstruction patients was more strongly linked to the extent of asynergy than to the type of asynergy (akinetic vs. dyskinetic). However, it is our experience that the distinction between left ventricular aneurysm and enlarged akinetic non-aneurysmal ventricle is less clear the larger the akinetic area, thus there is a continuum between pure dyskinesia and pure akinesia.

A register study from the Society of Thoracic Surgeons National Cardiac Database included 731 patients operated during 2002-2004 at 141 centers [148]. The volume per site varied greatly. Only 20 centers performed more than nine procedures, and 110 centers performed five or fewer procedures during the study period. Approximately two thirds of all hospitals providing cardiac surgery in the United States participate in the National Cardiac Database. The study described contemporary performance of left ventricular reconstruction and the primary outcome measure, operative mortality, was 9.3%.

O’Neill reported on the Cleveland Clinic experience of 220 consecutive patients with excellent survival data of 1% operative mortality and 80% survival at five years in a population with somewhat worse left ventricular ejection fraction compared to ours [149]. Six patients underwent subsequent heart transplantation.

In our series, the overall survival in patients who underwent ventricular tachycardia surgery in addition to left ventricular reconstruction was not different from the group of patients who underwent left ventricular reconstruction alone.

Risk factors for mortality

Diabetes mellitus

Diabetes mellitus was associated with increased mortality in our study. This finding is in concordance with previous findings in patients with heart failure and ischemic cardiomyopathy [150].

Mitral regurgitation

Moderate and severe mitral regurgitation was associated with worse long-term survival. There was a tendency for negative impact of even mild mitral regurgitation on long-term mortality. Mild mitral regurgitation has been demonstrated to be an independent predictor of mortality after myocardial infarction [151]. Moderate ischemic mitral regurgitation does not resolve with coronary artery bypass surgery and is associated with worse survival [151]. Currently, most authors [94, 152, 153] recommend mitral valve repair in conjunction with left ventricular reconstruction for moderate to severe mitral regurgitation and it is still unclear if mild mitral regurgitation should be left uncorrected. The left ventricular reconstruction procedure may reduce mild mitral regurgitation by restoring left ventricular geometry and volume [75, 153].

Hospital re-admission for heart failure

The composite endpoint of re-hospitalization for heart failure or cardiac death is a very sensitive indicator of clinical efficacy of heart failure treatment. It combines two high prevalence, well defined endpoints that may be directly influenced by the therapy.

In the study by the RESTORE group, five year freedom from hospital re-admission for heart failure was 78% [70], however the authors state that the criteria for heart failure hospital admission may have varied among centers. Mickleborough [75] defined poor five year result as the need for transplantation or repeated (more than one) hospitalization for congestive heart failure or death and identified ejection fraction below 20%, presence of preoperative heart
failure, hypertension and ventricular tachycardia as predictors for poor five year result. Our study benefited from several national registers. The date and cause of death could therefore be accurately obtained in all patients. The date for re-admission for heart failure could likewise be ascertained in a national register where the diagnosis of heart failure has been validated [96]. Freedom from re-hospitalization for heart failure or cardiac death was 72% at three years and 58% at five years in our study and increasing age and increasing grade of mitral regurgitation were found to be associated with the composite end point of re-hospitalization for heart failure or cardiac death. We find it encouraging that at five years, 58% of the patients, of which 69% were in NYHA class III-IV preoperatively, were alive and had not been re-admitted to any hospital due to heart failure.

MITRALVALVEREPAIR

Patients with ischemic cardiomyopathy and mitral insufficiency have lower life expectancy and poorer quality of life. At present, it is generally accepted that patients with mitral regurgitation, even of a moderate degree, undergoing coronary artery bypass surgery benefit from a concomitant mitral valve procedure [11, 154-156].

Ischemic mitral regurgitation

Functional ischemic mitral regurgitation is generally defined as a condition in which the mitral valve itself is normal but ischemic heart disease has led to changes in left ventricular volume, shape and function, causing mitral regurgitation. Therefore ischemic mitral regurgitation is considered to be a ventricular disease, rather than a valvular disease. Ischemic mitral regurgitation results from left ventricular remodeling (ventricular enlargement and increased sphericity) with annular dilatation and papillary muscle displacement with associated leaflet tethering and lack of coaptation. Ischemic mitral regurgitation cause left ventricular volume overload, resulting in further left ventricular remodeling with progressive mitral regurgitation, and thus a vicious circle is created [11].

Mitral regurgitation and prognosis

An important finding in Study III was the strong association between increasing grade of preoperative mitral regurgitation and both long-term mortality and re-admission for heart failure. This finding obviously raises the question whether the poor outcome in these patients was related to the complexity of the disease or to sub-optimal mitral valve repair or perhaps durability issues with recurrent mitral regurgitation.

Therefore, we performed a specific analysis of the long-term performance of mitral repair in our series of left ventricular reconstruction. The results will be published in a separate paper [95], and is presented in brief here.

Edge-to-edge mitral repair without annuloplasty in combination with left ventricular reconstruction

Thirty-one patients with functional ischemic mitral regurgitation underwent mitral valve repair solely by the edge-to-edge technique (Figure 10, page 25) [93] without annuloplasty in combination with left ventricular reconstruction. One further patient received a mechanical prosthesis and four additional patients had mitral valve repair with supportive annuloplasty. They were not included in this study, which specifically addressed the durability of edge-to-edge repair without annuloplasty. The mitral regurgitation grade at late follow-up is shown in Figure 22. Overall survival, including early mortality, was 77% at one year, 70% at two years, 55% at three years and 48% at five years with 13 remaining patients at risk. Two patients underwent reoperation, three and 13 months after the primary operation, respectively, due to recurrent grade III-IV mitral regurgitation. In one case, the Alfieri stitch had torn and the patient had a large mitral regurgitation. In
the other case the edge-to-edge plasty was intact and the mechanism for the mitral regurgitation was progressive annular dilation. Both underwent mitral valve replacement.

Correction of mitral regurgitation should preferably be done by repair [11, 157, 158] but occasionally replacement is necessary. Edge-to-edge repair [93, 159] is an attractive option for correction of functional ischemic mitral regurgitation and can readily be performed by a transventricular approach during left ventricular reconstruction. However, concerns have been raised regarding the durability of the edge-to-edge repair without annuloplasty, particularly in patients with ischemic cardiomyopathy [160, 161].

The Cleveland Clinic group described their experience of the edge-to-edge technique in 224 patients in a diverse clinical setting [160]. Indication for surgery was ischemic cardiomyopathy in 143 (64%) patients. Left ventricular reconstruction was performed in 48 patients and the mitral valve approach was transventricular in 20 patients. Most patients (84%) had an associated annuloplasty with a flexible partial band that extended from trigone to trigone and the most common size in ischemic mitral regurgitation was 26 mm, however 16 patients had no ring annuloplasty, usually patients who underwent left ventricular reconstruction. The authors reported good early term outcome but a disappointing late recurrence rate of moderate to severe mitral regurgitation at two years of 24%. Patients with ischemic cardiomyopathy did worse than patients with dilated cardiomyopathy. Interestingly, among patients with ischemic cardiomyopathy there was no difference regarding the recurrence of mitral regurgitation between patients who underwent left ventricular reconstruction and those who did not.

Figure 22. Mitral valve status (grade of mitral regurgitation) preoperatively (n=31), postbypass (n=26), predischarge (n=24) and late postoperatively (n=24) after edge-to-edge mitral valve repair without annuloplasty in combination with left ventricular reconstruction. Two patients who underwent reoperation due to recurrent severe mitral regurgitation are not included late postoperatively.

MR = mitral regurgitation, ECC = extra corporeal circulation, MVR = mitral valve replacement
In a study by Di Donato [162], mitral regurgitation was detected after the Dor procedure in 17/44 patients, and 14 of them did not have any preoperative mitral regurgitation. The patients who developed late mitral regurgitation had greater preoperative left ventricular volumes than the patients without late mitral regurgitation, suggesting a lower threshold for performing a direct valve procedure in patients with the largest left ventricular volumes. Mickleborough has presented a large series of left ventricular reconstruction by a modified linear closure technique [75]. In 129 patients with 2+ mitral regurgitation or more, no valve procedure was performed, and in 74 (57%) patients there was an improvement of mitral regurgitation by at least one grade. The authors proposed possible mechanisms for improvement including decreased annular dilatation caused by decreased ventricular size, improved papillary muscle function due to revascularization, and realignment of papillary muscles related to improved left ventricular geometry.

Thus, there is evidence of poor outcome in mild or moderate ischemic mitral regurgitation, not resolved by coronary artery bypass grafting alone. On the other hand, there are some, less solid, data describing a beneficial effect of left ventricular reconstruction on severity of mitral regurgitation [75, 153], theoretically based on improved left ventricular and papillary muscle geometry.

Our results and the reports by other institutions [159, 160] of sub-optimal long-term durability have convinced us to change our policy, and since 2003 we add annuloplasty to mitral valve repair during left ventricular reconstruction, usually as a posterior plication suture [94].
or heart transplantation, quality of life was assessed after surgery and was found to be better after left ventricular reconstruction in psychological and social relation scores. Heart transplant recipients scored higher in the physical capacity domain. There was, however, no quality of life comparison before and after surgery in this study [106]. The patients in our study reported a significant and clinically relevant improvement in the physical component summary score of the SF-36 six months after left ventricular reconstruction. There was a further improvement which was demonstrated at late follow-up, and the improvement was more pronounced in the mental domain. In a large cohort study, lower preoperative physical component summary score was associated with higher mortality at six months after coronary artery bypass surgery [163]. In another study [164], undertaken to investigate changes in quality of life following coronary artery bypass surgery, an average improvement of 16% in physical health status and an average improvement of 4% in mental health status was found. It was also found that patients with lower preoperative physical component summary and mental component summary scores were most likely to have an improvement in quality of life. Preoperative health status was the major determinant of change in quality of life after surgery. A 10-12% increase is generally accepted as a clinically relevant improvement after an intervention in cardiac patients [164, 165].

Cardiac resynchronization reduces the risk of death among patients with moderate or severe heart failure, and a QRS interval of at least 120 ms, and has favorable effects on the quality of life [54]. The effects on quality of life, is however small in comparison to other surgical strategies in heart failure such as implantation of an assist device [34, 166] or transplantation [106, 167].

Another aspect of functional and quality of life assessment after surgery, which needs to be recognized, is the patient's inclination not to disappoint the surgeon at follow-up. Many patients feel indebted and thankful to the surgeon and are reluctant to disclose their true functional status and tend to exaggerate their physical capability in order to please the surgeon. One way of possibly minimizing this effect is of course to leave the follow-up to another doctor, not affiliated with the surgical team. In our opinion, the SF-36 may partly solve this problem. The patient will fill out the form by him- or herself. The questionnaire is quite short and only takes a few minutes to fill out but yet it is complex enough to prohibit immediate interpretation. This setting may provide the patient with sufficient confidence to express a more honest or genuine view of their physical and mental health status.

Six-minute walk test

In a systematic review of the six-minute walk test as an outcome measure for treatment assessment in heart failure intervention trials [102] it was observed that there was a weak relationship between the six-minute walk test distance and symptom severity, judged by NYHA class. The authors concluded that the six-minute walk test has not yet been proven to be a robust test for pharmacological treatment effects but it appears useful for the assessment of cardiac resynchronization therapy. However, the results of the six-minute walk test were concordant with changes in symptoms, suggesting that it may be used as supportive evidence for symptom benefit [102]. One possible drawback with the six-minute walk test is that in patients who have little disability at baseline, measurement of exercise capacity may be an inadequate tool to assess response to treatment.
**B-type natriuretic peptides**

We found that severe heart failure secondary to post-infarction left ventricular remodeling can be reversed by left ventricular reconstruction. Significant clinical improvement in these patients was associated with reduced levels of B-type natriuretic peptides six months after surgery. Clinical improvement was maintained and peptide levels were further reduced at late follow-up.

**BNP levels after heart failure surgery**

A study from the Cleveland Clinic investigated the effect of left ventricular reconstruction on the level of neuroendocrine activation [168]. Ejection fraction increased by 51% and left ventricular end-diastolic and end-systolic volumes decreased by 36% and 46%, respectively. NYHA class improved in 13 patients and two patients had no change. In five patients, plasma levels of BNP were measured before and three months after the operation, and mean BNP decreased by 46% from 776 pg/mL to 417 pg/mL, (p=0.04) [168].

In another study, 37 patients with idiopathic dilated cardiomyopathy underwent septal anterior ventricular exclusion procedures and mitral valve procedures for heart failure. Ejection fraction increased from 20.9% to 27.5%, left ventricular dimensions decreased, cardiac index increased, and BNP levels decreased from 975 ± 866 pg/mL to 404 ± 366 pg/mL (p<0.05) in 31 hospital survivors one to six months after the operation [110].

Due to differences in analytical procedures, direct numerical comparisons between peptide levels found in the above mentioned studies [110, 168] and ours are not possible. However, it should be reasonably acceptable to compare the overall reduction in peptide levels. In our study, NT-pro-BNP was reduced by 37% and 51%, and BNP by 20% and 34% six months after surgery and at late follow-up, respectively. Thus, natriuretic peptide levels were reduced by about the same magnitude in our study as previously reported after left ventricular reconstruction. Further conclusions are precluded due to differences in patient selection (idiopathic vs. ischemic cardiomyopathy) and sampling times.

Baseline BNP is an important and independent prognostic marker in patients with heart failure and it has also been demonstrated that changes in BNP over time are associated with corresponding changes in mortality and morbidity [169]. Our results of a consistent decrease in peptide levels were closely correlated to reduction of heart failure symptoms after left ventricular reconstruction. Further studies are required to investigate if reduced levels of natriuretic peptides after left ventricular reconstruction are associated with better long-term survival.

**Coronary artery bypass surgery**

In a study of 31 patients with coronary artery disease, depressed ejection fraction and myocardial viability assessed by stress echocardiography undergoing coronary artery bypass surgery, BNP levels were found to decrease significantly at follow-up ten months after surgery. The difference between pre- and postoperative BNP levels correlated well with differences in pre- and postoperative left ventricular ejection fraction [170]. Thus, successful coronary artery bypass surgery in patients with impaired left ventricular function was found to improve symptoms and cardiac performance, in correlation with reduced BNP levels.

**Factors affecting natriuretic peptide levels**

Previous studies have shown that BNP and NT-pro-BNP are related to age and gender, with higher values in older individuals and in females. Peptide levels are also increased in patients with reduced renal function, and NT-pro-BNP is more affected than BNP by impaired renal function [8]. There were eight patients in our study with impaired renal function, but the majority only had mild impairment. Renal function was stable during follow-up, and therefore we do not consider our results to be confounded by changes in renal function before and after surgery.
LIMITATIONS

Study I-III
The major limitation is the lack of a control group. The combination of left ventricular reconstruction and coronary artery bypass surgery did not allow for evaluation of the specific role of each procedure. Another important limitation is the lack of postoperative invasive studies or cardiac magnetic resonance imaging in most patients, which are needed for detailed analysis of left ventricular volume, geometry, and performance. We had not complete follow-up of concurrent medication, but all patients have had regular contact with a cardiologist and/or family physician. The use of beta-blockers and angiotensin-converting enzyme inhibitors for patients with left ventricular dysfunction was common during the study period. Among the strengths of these studies are that most patient data have been prospectively collected, patients are consecutive, and that follow-up is complete.

Study IV and V
Study limitations include small sample size and the lack of a control group. Some patients, for different reasons, declined or could not participate in all parts of the study protocol which impose restrictions in the analysis of important potential associations between patient parameters and outcome measures.
Left ventricular reconstruction
Ulrik Sartipy
Conclusions

1. Left ventricular reconstruction by the Dor procedure is a reproducible and safe surgical option in patients with left ventricular aneurysm or ischemic dilated cardiomyopathy. Early mortality was 7.4% and five year survival was 68%. (Study I and III)

2. Left ventricular reconstruction including endocardiectomy and cryoablation resulted in a very high (90%) freedom from spontaneous ventricular tachycardia. (Study II)

3. Left ventricular reconstruction resulted in a high degree of freedom from readmission for heart failure. We found a strong association between increasing grade of preoperative mitral regurgitation and both long-term mortality and re-admission for heart failure. (Study III)

4. Functional status and health-related quality of life improved six months after left ventricular reconstruction and the improvement was sustained at late follow-up. (Study IV+V)

5. Severe heart failure secondary to post-infarction left ventricular remodeling can be reversed by left ventricular reconstruction. Clinical improvement was associated with reduced levels of B-type natriuretic peptides six months after surgery. Clinical improvement was maintained and peptide levels were further reduced at late follow-up. (Study V)
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