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Passive volume reduction heart surgery using the Acorn Cor Cap Cardiac Support Device



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”Ask and it will be given to you;
seek and you will find;
knock and the door will be opened to you.

For everyone who asks receives;
he who seeks finds;
and to him who knocks the door will be opened.”

Matthew 7:7-8

To Lena, Nils and Sofia.

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ABSTRACT

Heart failure is a growing health problem, affecting an increasing number of patients with rapidly increasing costs for the health care system. In spite of recent improvements in pharmacological, non-pharmacological and surgical treatments the prognosis for patients with severe heart failure is still poor.

Heart failure is associated with numerous processes and changes in left ventricular structure and function often referred to as left ventricular remodelling.

The Acorn Cor Cap Cardiac Support Device is a mesh-like polyester device designed to arrest and reverse these processes thereby facilitating left ventricular reversed remodelling in heart failure.

We have explored the effect of passive containment surgery using the Acorn Cor Cap Cardiac Support Device in heart failure patients with ischemic or idiopathic dilated cardiomyopathy. Following application of the Acorn Cor Cap Cardiac Support Device reduced cardiac dimensions, increased functional capacity, decreased levels of circulating plasma levels of Endothelin-1 and improved quality of life was demonstrated.

Furthermore, the possible beneficial effect on reduction on left ventricular dilatation with application of the Acorn Cor Cap Cardiac Support Device concomitant with aortic valve replacement in patients with longstanding aortic regurgitation and left ventricular dilatation was evaluated. No additive beneficial effects of application of the Acorn Cor Cap Cardiac Support Device were found in these patients when compared to patients with chronic aortic regurgitation and left ventricular dilatation undergoing aortic valve replacement as the sole procedure.

The acute effects of application of the Acorn Cor Cap Cardiac Support Device in experimental porcine myocardial infarction were investigated. No acute effect on hemodynamics, coronary vasomotor function, Endothelin-1 levels or infarction size was demonstrated following application of the Acorn Cor Cap Cardiac Support Device at induction of acute experimental myocardial infarction.

Based on the findings in these studies it is concluded that application of the Acorn Cor Cap Cardiac Support Device is safe, simple and without apparent negative effects. In heart failure patients with ventricular dilatation the Acorn Cor Cap Cardiac Support Device represents a novel and interesting amendment to current surgical treatment options with likely beneficial effects.

Key words; Acorn Cor Cap Cardiac Support Device, acute myocardial infarction, aortic regurgitation, dilated cardiomyopathy, heart failure, heart failure surgery, passive containment surgery, ventricular remodelling.

LIST OF ORIGINAL ARTICLES

This thesis is based on the following papers, which will be referred to by their Roman numerals.

- I. Franco-Cereceda A, Lockowandt U, Olsson A, Bredin F, Forssell G, Öwall A, Runsiö M and Liska J. Early results with cardiac support device implant in patients with ischemic and non-ischemic cardiomyopathy. *Scand Cardiovasc J* 2004;38:159-63.
- II. Olsson A, Bredin F and Franco-Cereceda A. Echocardiographic findings using tissue velocity imaging following passive containment surgery with the Acorn Cor Cap™ cardiac support device. *Eur J Cardiothorac Surg* 2005;28:448-53.
- III. Bredin F and Franco-Cereceda A. Reversed remodelling in dilated cardiomyopathy by passive containment surgery is associated with decreased circulating levels of endothelin-1. *Eur J Cardiothorac Surg* 2006;29:299-303.
- IV. Bredin F, Olsson A and Franco-Cereceda A. No additive effect of passive containment surgery in patients with aortic regurgitation and left ventricular dilatation. *Ann Thorac Surg* 2007;84:510-3.
- V. Bredin F and Franco-Cereceda A. Midterm results of passive containment surgery using the Acorn Cor Cap™ Cardiac Support Device in dilated cardiomyopathy. Submitted.
- VI. Bredin F, Lockowandt U and Franco-Cereceda A. Passive ventricular remodelling using the Acorn Cor Cap™ Cardiac Support Device does not influence porcine acute myocardial infarction. Submitted.

LIST OF ABBREVIATIONS

ACE	Angiotensin Converting Enzyme
ADO	Adenosine
AHA	American Heart Association
AR	Aortic Regurgitation
ARB	Angiotensin Receptor Blocker
AS	Aortic Stenosis
AVR	Aortic Valve Replacement
BRB	Beta Receptor Blocker
BP	Blood Pressure
CABG	Coronary Artery Bypass Grafting
CMF	Cardiomyopathy
CPB	Cardio Pulmonary Bypass
CRT	Cardiac Resynchronisation Therapy
CSD	Acorn Cor Cap™ Cardiac Support Device
DCMP	Dynamic Cardiomyoplasty
EF	Ejection Fraction
ET	Endothelin
HR	Heart Rate
IABP	Intra Aortic Balloon Pump
ICD	Implantable Cardiac Defibrillator
ICU	Intensive Care Unit
LAD	Left Anterior Descending coronary artery
LOS	Length Of Stay
LVAD	Left Ventricular Assist Device
LVEDD	Left Ventricular End Diastolic Diameter
LVEF	Left Ventricular Ejection Fraction
LVEDS	Left Ventricular End Systolic Diameter
LV	Left Ventricle
LVR	Left Ventricular Reconstruction
MR	Mitral Regurgitation
NYHA	New York Heart Association
PLV	Partial Left Ventriculectomy
RV	Right Ventricle
SD	Standard Deviation
SEM	Standard Error of the Mean
SP	Substance P
TVI	Tissue Velocity Imaging
TNF- α	Tumour Necrosis Factor- α
TTC	Triphenyl Tetrazolium Chloride

INTRODUCTION

In the ageing Western population heart failure is an increasing problem (Levy et al. 2002). Calculations show that in the year of 2040 as many as 75 million US citizens, or over 20 % of the population, will be over 65 years of age. Both the incidence and prevalence of heart failure increase exponentially with age (Masoudi et al. 2002). The prevalence of heart failure has been estimated to approximately 7.2% and 5.2% in men and women respectively between 60 to 79 years of age and to 11.6% and 12.4% after the age of 80 years, respectively. The direct and indirect cost of heart failure in the US for 2007 has been estimated to \$33.2 billion (Heart Disease and Stroke Statistics–2007 Update). Recent estimates suggest that more than 200,000 individuals in Sweden suffer from symptomatic heart failure and that there is approximately 30,000 new cases every year (Willenheimer et al. 2007). In spite of improvements in treatment, the prognosis of severe heart failure is still poor, with a one year mortality of over 50 % (Swedberg et al. 2005).

The failing heart undergoes numerous structural and functional changes referred to as ventricular remodelling (Konstam et al. 2003). Progressive ventricular dilatation is a frequently occurring component in this process and has also been shown to be an important prognostic factor (Lee et al. 1993). The Acorn Cor Cap™ Cardiac Support Device (CSD; Acorn Cardiovascular Inc.; St Paul, MN, USA) is a mesh-like polyester

fabric which is positioned around the dilated failing heart in order to reduce wall stress and facilitate a reversed remodelling of the heart, thereby reshaping the heart from a dilated spherical shape to an ellipsoidal shape.

This thesis presents our experiences and results regarding CSD application in heart failure patients with ischemic or idiopathic cardiomyopathy (CMP; Paper I, II, III and V), in patients with aortic regurgitation (AR) and ventricular dilatation (Paper IV), and in an animal model of acute myocardial infarction (Paper VI).

HEART FAILURE

Definition and classification

Heart failure is a clinical syndrome that is characterised by specific symptoms i.e. dyspnea and fatigue in the medical history and signs (oedema, rales) on examination (Hunt et al. 2005). Traditionally heart failure patients have been classified by the New York Heart Association (NYHA) according to functional capacity.

NYHA class I; No limitations; ordinary physical exercise does not cause undue fatigue, dyspnea or palpitations.

NYHA class II; Slight limitation of physical activity; comfortable at rest but ordinary activity results in fatigue, dyspnea or palpitations.

NYHA class III; Marked limitation of physical activity; comfortable at rest but less than ordinary activity results in symptoms.

NYHA class IV; 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.

The NYHA functional classification is based upon a subjective assessment and can frequently change over time. To address these problems, and due to the progressive nature of heart failure, the American Heart Association (AHA) has presented an additional classification of heart failure (Hunt et al. 2005.).

Stage A; Patients with high risk for development of heart failure but no apparent structural abnormality of the heart.

Stage B; Patients with structural abnormality of the heart but never had symptoms of heart failure.

Stage C; Patients with structural abnormality of the heart and current or previous symptoms of heart failure.

Stage D; Patients with end stage symptoms of heart failure that are refractory to standard treatment.

It is important to understand that patients can only progress in one direction from A to D and to realise that this classification system is intended as a complement to the NYHA classification only.

Etiology

Heart failure can be caused by myocardial dysfunction, valve abnormalities, pericardial disease, rhythm disturbances or by extra cardiac abnormalities. It is crucial to establish the etiology since this has important implications on the treatment. In the Western World coronary artery disease is the most common cause of heart failure in patients under the age of 75 years and systolic dysfunction is usually present. In older patients the etiology is more often unclear and a diastolic dysfunction is often present (Swedberg et al. 2005).

Pathophysiology

During the last decades the knowledge and understanding of the pathophysiology behind heart failure has greatly increased. This has

had huge impact on the treatment of heart failure (Opie et al. 2006). The development of heart failure is usually preceded by a so called index event that either can be easily identified such as an acute myocardial infarction or an infectious myocarditis, or in other cases a gradually evolving process such as a pressure overload in arterial hypertension or volume overload in valve regurgitation. Depending on the etiology this index event initiates numerous processes. Myocardial ischemia by coronary artery disease results in down regulation of myocardial contractile function called myocardial hibernation. Following a large myocardial infarction there is a loss of contractile tissue with chamber dilatation and fibrosis. Pressure overload results in concentric hypertrophy with initially well preserved systolic function while volume overload results in ventricular dilatation and earlier dysfunction (Braunwald et al. 2000). Following the index event there is a gradual development with variable speed that results in a number of adaptive mechanisms such as neurohormonal activation, changes in gene expression, energy depletion, apoptosis and increased levels of cytokines. An ongoing “auto inductive process” with multiple components such as increased myocyte size, increased fibrosis and further ventricular dilatation results in progressive deterioration. These changes of the failing heart are often called ventricular remodelling. Eventually this development will result in symptoms of heart failure such as oedema and congestion (Francis. 2001).

Endothelins

The endothelins (ET) constitute a family of four closely related peptides (ET-1; ET-2; ET-3; ET-4) derived from the respective precursor forms big endothelins 1-4 by ET converting enzymes. Heart failure is associated with increased levels of plasma ET-1 and a role for ET-1 has been postulated in structural and functional changes in the failing remodelling heart (Moe et al. 2003).

ET-1 exerts its action through binding to two specific receptors called type A (ET_A) and type B (ET_B). ET_A is expressed in vascular smooth muscle cells and cardiac myocytes, its interaction with ET-1 mediates vasoconstriction and cell proliferation. ET_B is expressed on vascular endothelial cells and its interaction with ET-1 results in nitric oxide induced vasodilatation and prostacyclin release. The ET_B receptor plays a determinant role in the clearance of ET-1 (Attina et al. 2005).

Treatment

Pharmacological treatment

Angiotensin-converting enzyme (ACE) inhibitors: Early on the ACE inhibitors were shown to have beneficial effects on mortality in heart failure (CONSENSUS.1987, SOLVD.1991). Additional studies in patients with reduced Left Ventricular Ejection Fraction (LVEF) or overt heart failure after acute myocardial infarction have all shown reduced mortality in patients treated with ACE inhibitors (SAVE. 1992, AIRE. 1993, TRACE. 1995). Current US and European guidelines recommend ACE inhibitors as first line therapy in all patients with reduced LVEF irrespective of symptoms.

Angiotensin receptor blockers (ARB): In the CHARM–Alternative Study patients with heart failure intolerant to ACE inhibitors were shown to have a trend towards lower mortality. In the CHARM-Added Study patients with heart failure treated with ACE inhibitors and ARB were similarly shown to have a trend toward lower mortality (CHARM. 2003). ARB is currently recommended for patients intolerant to ACE inhibitors and as an addition to ACE inhibitors in the case of persistent symptoms.

Beta receptor blockers (BRB): Use of the BRB bisoprolol, metoprolol succinate or carvedilol in heart failure patients have all shown to reduce mortality (CIBIS-II.1999, MERIT-HF. 2000, COPERNICUS. 2001). Furthermore, an additive beneficial effect of

BRB in combination with ACE inhibitors is the rationale for BRB being recommended for all patients with mild, moderate or severe heart failure (Swedberg et al. 2005).

Aldosterone receptor blockers: In patients with severe heart failure treated with ACE inhibitors a reduction of mortality with addition of spironolactone has been seen (RALES.1999). Eplerenone, an aldosterone blocker, has been shown to reduce mortality in patients with reduced LVEF after myocardial infarction (EPHESUS. 2003). Aldosterone blockade is currently recommended in addition to ACE inhibition and BRB in patients with severe heart failure suffering from symptoms (Swedberg et al. 2005, Hunt et al. 2005).

Statins: Inhibitors of 3-hydroxy-3-methyl glutaryl coenzyme A reductase are prescribed to patients with hyperlipidemia. In addition to a potent cholesterol lowering effects statins have effect on endothelial function, antioxidants and inflammatory response that makes them of great interest for patients with heart failure. However, the beneficial effect of statins in heart failure beyond the lipid lowering effect remains to be established (Toussoulis et al. 2006).

Diuretics: Diuretics are used in heart failure patients to eliminate signs of fluid retention. No long term studies of diuretic therapy in heart failure patients have been performed (Adorisio et al. 2006).

Non-pharmacological treatment

Cardiac Resynchronisation Therapy (CRT): CRT as the sole procedure or in combination with Implantable Cardiac Defibrillator (ICD) improves symptoms, quality of life and reduces complications and risk of death in heart failure patients (COMPANION. 2004, CARE-HF. 2005). In a recent systematic review of randomized trials with CRT, the frequency of hospitalizations was reduced by 37% and death by 22% (McAllister et al. 2007). Furthermore, CRT treatment appears to reverse ventricular remodelling (Donal et al. 2006). Consequently CRT using bi-

ventricular pacing in heart failure patients with NYHA functional class III-IV with reduced LVEF, ventricular dyssynchrony and presenting symptoms despite optimal pharmacological treatment is recommended in the US and European guidelines (Hunt et al. 2005, Swedberg et al. 2005).

Surgical treatment

Coronary Artery Bypass Grafting (CABG)

Knowledge regarding the pathophysiology behind the development of heart failure with hibernating myocardium in coronary artery disease has increased the interest in referring these patients for revascularisation. CABG operations have been advocated as an important part in the treatment of these patients (Mitropoulos et al. 2001). Studies of midterm outcomes following CABG operations in patients with severe left ventricular dysfunction have shown excellent results (Shapira et al. 2006).

Valve surgery

Mitral valve surgery in patients with heart failure has been performed with outstanding results (Bolling et al. 1998). In the multicenter Acorn Clinical Trial the results showed a beneficial effect of surgical elimination of mitral regurgitation (MR) alone, with additional beneficial effect of application of the Acorn Cor Cap™ CSD (The Acorn Clinical Trial. 2006).

For the majority of patients with symptomatic aortic stenosis (AS), aortic valve replacement (AVR) is the treatment of choice (Asch et al. 2006). A recent study has shown the importance of early surgical intervention in patients with aortic regurgitation (AR) that shows ventricular dilation and/or decreased LVEF (Tornos et al. 2006).

Heart transplantation

Heart transplantation was introduced as a therapeutic option in the sixties, although initially with questionable results. The introduction of the immunosuppressive drug cyclosporine in 1981 led to dramatically

improved results. Further drug and surgical development has led to current excellent results with a one year survival of >85% and a median survival of more than 10 years (Taylor et al. 2005). Thus, heart transplantation is a well established treatment that could be described as the “gold standard” for the treatment of end-stage heart failure. However, this option is possible only to a limited number of patients primarily due to lack of donor organs but also because of contraindications to the procedure.

Left Ventricular Assist Devices (LVAD)

A scientific basis for implantable left ventricular assist devices (LVAD) in patients with end-stage heart failure was shown in the REMATCH study (REMATCH. 2001). Extended follow-up have confirmed the earlier findings of the patients included in the REMATCH study and also demonstrated an improvement in the survival among the patients subjected to LVAD implantation over the course of the trial (Park et al. 2005). In heart failure patients LVADs can be used as a bridge to transplant or as a destination therapy. However, LVADs are for different medical and non-medical reasons not a viable option for all patients with end-stage heart failure.

Partial Left Ventriculectomy (PLV)

This procedure was explored by Randas Batista and is based on the hypothesis that a raise in ventricular diameter results in increased wall tension with augmented metabolic demands that can not be met resulting in progressive heart failure (Batista. 1997). Initial positive outcomes could not be confirmed and further studies revealed a significant early failure rate and a poor long time event free survival with the procedure (Franco-Cereceda et al. 2001). The interest in and use of this procedure has therefore declined.

Left Ventricular Reconstruction (LVR)

One rationale for LVR in ischemic CMP is the finding that left ventricular size strongly

correlates with prognosis (Lee et al. 1993). Several variations of LVR have been described and they often include other procedures such as coronary artery bypass surgery, mitral valve surgery and/or interventions to reduce ventricular arrhythmias (Lee et al. 2004). The potential role of LVR in ischemic heart disease has recently been explored (Sartipy. 2007). The ongoing STICH trial will hopefully further clarify the role of LVR in ischemic CMP (Menicanti et al. 2004).

Dynamic Cardiomyoplasty (DCMP)

This procedure was originally described in 1985 by Carpentier and Chachques. It is performed by wrapping the Latissimus Dorsi muscle around the failing heart and with the following use of a pacing device stimulating the muscle to contract in synchrony with cardiac contractions (Jessup. 2000). The C-SMART study was planned to compare the effect of DCMP versus medical therapy. The study was stopped due to slow patient recruitment. It showed no significant difference in survival 12 months postoperatively (Voss et al. 2001). Currently this procedure is no longer practiced.

Passive containment surgery using the Acorn Cor Cap™ Cardiac Support Device (CSD)

Early findings demonstrated that an important contribution to the initial beneficial effect of DCMP could be attributed to the girdling effect of the muscle wrap around the failing, remodelling heart (Patel et al. 1997). Based on these findings the Acorn Cor Cap™ CSD was developed. The CSD consists of a mesh-like polyester fabric. The device has a bidirectional compliance with greater circumference support compared to the base to apex support thus facilitating a reshaping of the heart from a spherical to a more ellipsoidal shape. The design and features of the CSD have been thoroughly described (Walsh. 2005; see cover page).

Numerous animal studies have confirmed the potential beneficial effects of CSD application in heart failure. Several important

and interesting findings were reported in an experimental animal model with dogs subjected to coronary microembolization induced heart failure. CSD application to these animals prevented progressive ventricular enlargement and reversed ventricular shape (Sabbah. 2005). Reversal of maladaptive gene program and down regulation of cytokines were also observed (Rastogi et al. 2005). Furthermore, CSD treatment resulted in attenuation of cardiomyocyte hypertrophy and improvement of cardiac sarcoplasmic reticulum calcium cycling (Gupta et al. 2005). In an ovine model of high rate pacing induced heart failure application of the CSD resulted in improved cardiac function, reduced left ventricular volume and reduced mitral regurgitation (Power et al. 2005).

Implantation of the CSD one week after induction of experimental acute myocardial infarction has in an ovine model been correlated to infarct size reduction and attenuation of ventricular remodelling (Blom et al. 2005).

Early human studies in patients with dilated CMP showed amelioration of symptoms, improved cardiac function and improved functional performance (Konertz et al. 2001).

AIMS OF THE STUDY

Based on the early reports of the potential beneficial effects of the CSD, we initiated studies with the CSD in the summer of 2001 in different settings of heart failure and/or LV dilatation. The aims of these studies were:

1. To evaluate the echocardiographic findings, functional and quality of life effects of passive containment surgery using the Acorn Cor Cap™ Cardiac Support Device in heart failure patients with dilated cardiomyopathy (Paper I and V).
2. To investigate changes following passive containment surgery using the Acorn Cor Cap™ Cardiac Support Device with echocardiography including pulsed wave tissue velocity imagining in patients with dilated cardiomyopathy and heart failure (Paper II).
3. To explore the effects on circulating plasma levels of endothelin-1 and big endothelin-1 following passive containment surgery using the Acorn Cor Cap™ Cardiac Support Device in heart failure patients with dilated cardiomyopathy (Paper III).
4. To study the effect of concomitant application of the Acorn Cor Cap™ Cardiac Support Device on reduction of ventricular dilatation in patients with aortic regurgitation and ventricular dilatation undergoing aortic valve replacement (Paper IV).
5. To explore the acute effects of application of the Acorn Cor Cap™ Cardiac Support Device on hemodynamics, coronary vasomotor function and infarct size at induction of porcine acute myocardial infarction (Paper VI).

MATERIALS AND METHODS

All studies were approved by the Ethical Committee at the Karolinska University Hospital or the Ethics Committee for Animal Research at Karolinska Institutet. Patients were included after informed, written and signed consent.

In vivo studies in heart failure patients (I, II, III, V)

Between June 2001 and October 2006 twenty patients (18 males, 2 females) with idiopathic (n=10) or ischemic (n=10) cardiomyopathy (CMP) were subjected to application of the CSD either as the sole procedure (n=3) or in conjunction with other open heart surgery. The first five of the patients were part of an initial Limited Market Release Study. Patients included in study I-III and V are presented in Table I. Inclusion criteria which all had to be fulfilled included (I) left ventricular end-diastolic diameter (LVEDD) > 60 mm or indexed to > 30 mm/m² body surface area, (II) an ejection fraction (EF) of 10-45%, (III) NYHA class III-IV or when in class II only if a history of at least one previous class III or IV episode, (IV) stable and optimal drug therapy and (V) mitral regurgitation < 2+ (unless accepted for MR surgery). Exclusion criteria included end-stage heart failure requiring inotropic support, hypertrophic CMP, cardiac re-operations, myocardial infarction < 90 days or systemic disease (pulmonary, renal or hepatic dysfunction). The patients' preoperative and perioperative characteristics are presented in

Table II and III, respectively.

Anaesthesia: All patients received their routine daily cardiac medications on the morning of surgery. All standard American Society of Anesthesiologists non invasive monitors and peripheral intravenous and intra-arterial catheters were placed before induction. Anesthesia was induced using fentanyl (5-15 µg/kg) and midazolam (0.03-0.05

Table I. Patients included in paper I-III and V.

Patient	Paper I	Paper II	Paper III	Paper V
1	X	X	X	X
2	X	X	X	X
3	X	X	X	X
4	X	X	X	X
5	X	X	X	X
6	X	X	X	X
7	X	X	X	X
8	X	X	X	X
9			X	X
10				X
11		X	X	X
12		X	X	X
13		X	X	X
14		X	X	X
15				X
16				X
17				X
18				X
19				X
20				X

mg/kg). Intubation was facilitated with atracurium. Patients were ventilated to achieve normocapnia (PaCO₂ 35–45 mm Hg). A flow directed pulmonary artery catheter and a transesophageal echocardiography probe were inserted after induction. Anaesthesia was maintained with intermittent fentanyl and isoflurane or sevoflurane before Cardio Pulmonary Bypass (CPB) and an infusion of propofol (1–4 mg/kg/h) during and after CPB. Based on our preliminary experience with levosimendan (Simdax; Orion Corp.; Espoo; Finland) in patients with low EF undergoing cardiac surgery, all patients received levosimendan as an inotrope starting with a loading dose of 12 µg/kg prior to skin incision, followed by a continuous infusion of 0.1 µg/kg/min during 24 hours.

Surgery: All patients were operated on through a midline sternotomy by the same surgeon. Cardiopulmonary bypass was initiated using a centrifugal pump (BP 80, Biomedicus Biomed, Houston, TX, USA) and a membrane oxygenator (Affinity, Medtronic Inc., Minneapolis, MN, USA) primed with acetated Ringers solution. During CPB the temperature was allowed to drift to 34°C. The cardioplegia solution was mixed 1:4 with blood and delivered at a temperature of 4°C. The cardioplegia contained (mmol) KCl 100, MgSO₄ 8, glucose 28, tris(hydroxymethyl)aminomethane (THAM) 20 and saline 0.9% to a volume of 1000 ml. Before applying the Acorn Cor Cap™ Cardiac Support Device (CSD), the heart dimension was measured to select proper sizing. With the

Table II. Preoperative characteristics of patents in paper I–III and V.

Pat (nr)	Age (years)	Sex (F/M)	LVEDD (mm)	MR (grade 1–4/4)	EF (%)	NYHA (class)	6 min walk (m)	Quality of life (0–10)	Etiology (ISCH/IDIOP)
1	66	M	67	1	15	3	452	5.2	ISCH
2	69	M	60	1	30	3	480	4.9	ISCH
3	50	F	70	1	32	2	312	3.0	IDIOP
4	58	M	73	2	20	4	288	1.5	IDIOP
5	44	M	73	2	28	3	384	1.1	IDIOP
6	61	M	67	1	30	2	411	4.7	ISCH
7	78	M	62	2	10	3	274	7.0	IDIOP
8	72	M	80	1	15	3	358	4.4	ISCH
9	72	M	60	1	20	3	400	8.4	ISCH
10	42	M	81	1	20	4	398	2.3	IDIOP
11	32	M	67	3	42	2	480	3.8	IDIOP
12	56	F	80	3	14	3	432	4.9	IDIOP
13	51	M	68	1	29	2	226	6.4	ISCH
14	58	M	77	3	25	2	507	5.3	IDIOP
15	66	M	77	3	15	3	410	7.6	IDIOP
16	59	M	82	3	25	3	235	5.3	IDIOP
17	72	M	69	1	20	3	246	5.9	ISCH
18	70	M	85	1	18	3	312	2.7	ISCH
19	63	M	72	1	25	3	440	4.5	ISCH
20	65	M	69	1	20	3	332	3.8	ISCH

EF=ejection fraction; F=female; IDIOP=idiopathic; ISCH=ischemic; LVEDD=left ventricular end diastolic diameter; M=male; MR=mitral regurgitation; NYHA=New York Heart Association.

CSD hemline positioned adjacent to the atrio-ventricular groove the device was stabilized by interrupted 3-0 Prolene sutures (Ethicon, Somerville, NJ, USA) and final adjustment was done on the beating heart to ensure a snug fit. Transesophageal echocardiography was used to ensure that the final fit did not reduce LVEDD by more than 10%.

Follow-up: Before surgery all patients were evaluated by transthoracic echocardiography (System 5, GE Vingmed, Hortem, Norway). All examinations were performed with the subjects in left lateral decubitus position by the same physician.

Functional status was assessed by NYHA class and 6-min walk (Enright. 2003, Olsson et al. 2005, Shah et al. 2001). Quality of life was evaluated using the Uniscale questionnaire (Spitzer et al. 1981).

At follow up 3, 6 and 12 months postoperatively and thereafter once every year these examinations and evaluations were repeated.

In study II pulsed wave tissue velocity imaging (TVI) in the apical four-chamber, apical two chamber and apical long axis views the mitral annular velocities were recorded at six sites corresponding to the septal, lateral, anterior, inferior, antero-septal and infero-lateral left ventricle (LV) wall. Tricuspid annular velocities were recorded at the free right ventricle (RV) wall (Fig. 1). The analysis included measurements of systolic annular velocities (S_m), early diastolic (E_m) and late diastolic (A_m) annular velocities (Fig. 1). Peak systolic, early diastolic and late diastolic mitral and tricuspid velocities respectively from the above sites were used as mea-

Table III. Perioperative characteristics and postoperative follow-up of patients in paper I-III and V.

Patient Nr.	Surgical procedure in addition to CSD	Date of surgery (year-month)	Follow-up time (months)
1	ITA-D1	01-06	24
2	ITA-LAD; SVG-RPD	01-06	60
3	-	01-07	60
4	C-E Physioring 28 mm	01-08	60
5	C-E Physioring 30 mm	02-02	60
6	ITA-LAD; SVG-M2	02-04	60
7	-	02-09	48
8	ITA-LAD; SVG-M1, RPD	02-10	48
9	ITA-LAD; SVG-D1, RPD	03-04	48
10	-	03-04	-
11	C-E Physioring 28 mm	03-06	36
12	C-E Physioring 26 mm	03-11	12
13	ITA-LAD; SVG-RPD, M1	03-12	36
14	C-E Physioring 30 mm	04-02	36
15	C-E Physioring 30 mm	05-02	24
16	C-E Physioring 30 mm	05-10	12
17	ITA-LAD; SVG-M1, M2	05-12	3
18	ITA-LAD, SVG-RPD	06-06	6
19	ITA-LAD; SVG-D1, RPD	06-08	6
20	ITA-LAD; SVG-M1, RPD	06-10	6

C-E = Carpentier-Edwards; D = Diagonal branch of the LAD; ITA = Internal thoracic artery; LAD = Left anterior descending artery; M = Marginal branch of the circumflex artery; RPD = Right posterior descending artery; SVG = Saphenous vein graft.

surement of global LV systolic (LV S_m) and diastolic (LV E_m and LV A_m) respectively RV systolic (RV S_m) and diastolic (RV E_m and RV A_m) function (Waggoner et al. 2001).

In study III plasma for analysis of ET-1 and big endothelin-1 was obtained from a peripheral

vein before surgery and at patient follow up 3, 6 respectively 12 months postoperatively. All samples were collected from non fasting patients in the afternoon into EDTA vacuum tubes, kept in ice slush and centrifuged. The patients plasma was then frozen at -70°C and stored until analysis. The content of ET-1 and big ET-1 like immunoreactivity was determined by radioimmunoassay.

In vivo studies in patients with aortic regurgitation and ventricular dilatation (IV)

Between April 2003 and March 2006 ten male patients with aortic regurgitation (AR) graded as 3-4/4, ventricular dilatation with LVEDD > 70 mm and normal coronary angiograms were accepted for AVR. Five of the patients received the Cor CapTM Cardiac Support Device in addition to a mechanical valve prosthesis. The following five patients meeting the inclusion criteria underwent AVR without device implantation and served as controls. Preoperatively bicuspid valves were diagnosed in 6 patients (3 in each group). The patients' preoperative and operative characteristics are presented in Table IV.

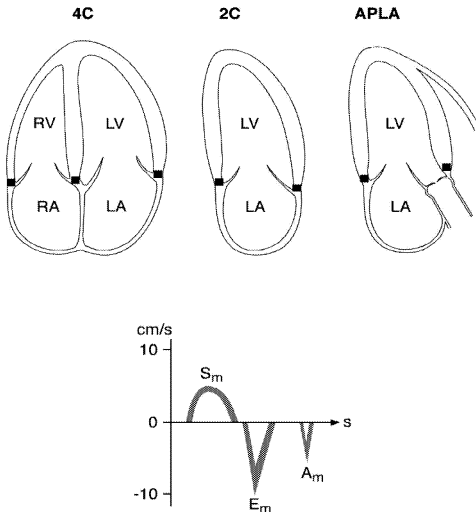


Fig. 1. Myocardial velocity measurements sites (■) in the apical four-chamber (4C), two chamber (2C) and apical long axis (APLA) views. The annular measurement principle of systolic velocity (S_m) and early (E_m) respectively late (A_m) diastolic velocities are also shown.

Table IV. Preoperative and periooperative characteristics of patients in paper IV.

Pat nr	Age (years)	AR (grade 1-4/4)	Native valve	Procedure	Mechanical valve size (mm)	Root diameter (mm)	STJ diameter (mm)	Aorta ASC diameter (mm)
1	45	3-4	Bicuspid	AVR+CSD	29	44	35	36
2	44	3-4	Bicuspid	AVR+CSD	25	37	32	34
3	61	3-4	Tricuspid	AVR+CSD	29	42	32	40
4	48	3-4	Bicuspid	AVR+CSD	25	42	35	34
5	35	4	Tricuspid	AVR+CSD	25	33	29	33
6	36	3	Bicuspid	AVR	27	45	39	39
7	57	3	Tricuspid	AVR	23	35	24	29
8	62	3	Tricuspid	AVR	25	35	30	31
9	69	3-4	Bicuspid	AVR	25	34	30	31
10	43	3-4	Bicuspid	AVR	27	34	34	38

AR=aortic regurgitation; ASC=ascendens; AVR=aortic valve replacement; CSD= Acorn Cor CapTM Cardiac Support Device; STJ=sino tubular junction.

Anaesthesia: Induction of anaesthesia and maintenance of anaesthesia were performed as in study I-III and V but patients in study IV were not treated with levosimendan.

Surgery: Surgical technique and device implantation were identical with study I- III and V.

Follow-up: Prior to surgery, 3 months post-operatively and 12 months postoperatively all patients were evaluated by transthoracic echocardiography (System 5, GE Vingmed, Hortem, Norway).

In vivo animal studies (VI)

Animal preparation: Swedish farm pigs (weight 30-40 kg; n=20) of either sex were fasted overnight and given premedication with intra muscular tiletamin+zolazepam 15 mg/kg, medetomin 0.05 mg/kg and atropine

sulphate 0.04 mg/kg. Anaesthesia was induced with intravenous sodium penthobarbitone 10 mg/kg. The animals were intubated and mechanically ventilated. Anaesthesia was maintained with a continuous infusion of fentanyl 10-20 µg/kg/h and midazolam 100-200 µg/kg/h. The heart was exposed through a left sided thoracotomy. A vessel loop was passed around the left anterior descending coronary artery (LAD) at a position from which approximately the distal two thirds of the artery was occluded by tightening the snare. Proximal to the snare a 0.6 mm intravenous catheter was placed in the LAD for infusion of vasoactive substances. An ultrasonic flow probe connected to a flow monitor was placed immediately distal to the snare. In ten of the animals a CSD was positioned with a snug fit around the left ventricle (Fig. 2).

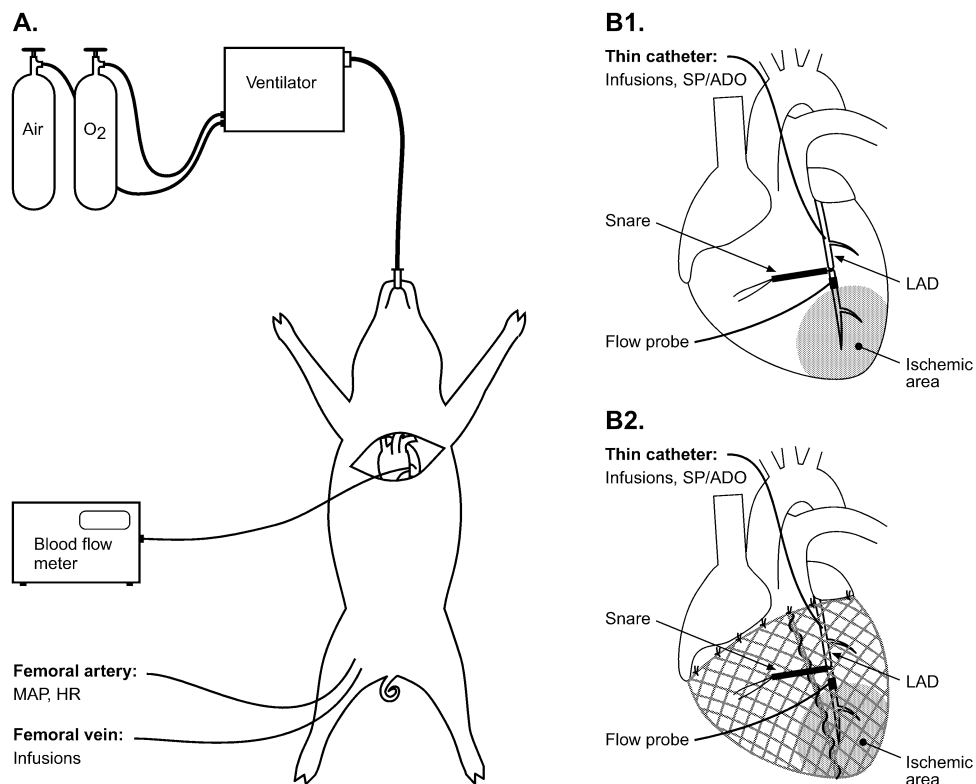


Fig. 2A+B. A; Schematic illustration of the model for the in vivo animal studies (VI). B 1; Control animals not subjected to CSD application. B 2; Animals subjected to CSD application.

Study protocol: The animals were randomised to the different protocols and after 30 minutes of stabilisation base line values for Heart Rate (HR) and Blood Pressure (BP) were recorded. Venous blood samples for analyses of ET-1 and Tumour Necrosis Factor- α (TNF- α) were obtained. The blood samples were drawn from the femoral catheters, centrifuged and frozen at -70°C until analysis. LAD flow was measured before and after injection of vasoactive substances. Adenosine (ADO) was given as a bolus injection of 40 μ g to evaluate the endothelium-independent coronary vasodilatation (Wilson et al. 1990). After a washout time, verified by flow measurements, substance P (SP), an endothelium dependent vasodilator, was injected as a bolus of 10 μ g (Franco-Cereceda et al. 1987).

The LAD was then occluded for 60 min by tightening the snare followed by 120 min of reperfusion, in animals with (n=5) or without (n=5) the CSD. Blood samples for analysis of ET-1 and TNF- α were drawn at 10 and 60 min of ischemia and at 60 and 120 min of reperfusion. HR and BP were simultaneously recorded. A separate set of control animals were subjected to the same study protocol excluding ischemia (n=5) or receiving the CSD alone (n=5). ADO and SP were administered as bolus doses in all pigs into the LAD before ischemia and after 120 min of reperfusion, accordingly in the controls.

After 120 min of reperfusion the LAD snare was tightened in all animals and 2 ml/kg of 2% Evans blue was injected into the right atrium. The animals were thereafter sacrificed by an intravenous injection of a high dose of pentobarbiturate.

The hearts were then sliced transversely in approximately 1 cm thick slices and the nonstained myocardium was outlined (i.e. area at risk). Incubation in 0.8 % solution of triphenyl tetrazolium chloride (TTC) at 37°C for 20 minutes stains necrotic myocardium red (Fishbein et al. 1981). The areas of necrosis, area at risk and total left ventricle area were determined by planimetry. In the

animals subjected to ischemia the extent of necrosis was expressed as percentage of the area at risk. In all animals the area at risk was expressed as percentage of the total left ventricle area. In the hearts subjected to ischemia, tissue samples for analysis of ET-1 and TNF- α were taken from necrotic areas and from stained areas (i.e. areas not subjected to ischemia) and in the hearts from the control group tissue samples were taken from non stained and stained areas, respectively.

Statistical analyses

Study II: Data are presented as mean \pm standard error of mean (SEM). For statistical analysis, repeated measures of variance (ANOVA) with Bonferroni comparison were used.

Study III: Data are presented as mean \pm SEM. ET-1 and big ET-1, NYHA functional class, the 6-minute walk and cardiac dimensions were compared by a Wilcoxon signed ranked test. The association between ET-1 levels and cardiac dimensions was evaluated by Pearson's correlation test

Study IV: Data are presented as mean \pm standard deviation (SD). Data were analysed according to a repeated measures analysis of variance (ANOVA), with time (from preoperative values to 12 months post-operatively) as the repeated measures factor and CSD (yes/no) as the between factor.

Study V: Data are presented as mean \pm SEM. For comparisons over time, an analysis of variance (ANOVA) for repeated measures was performed both for ordinal responses (variable NYHA) and for continuous responses (Procedure GENMOD and Mixed in SAS®, SAS Institute Inc., Cary, NC, USA). Group, Time and Group x Time were fitted as fixed effects. Group was the between factor and Time was the within factor. Comparison between pre operation and follow up time

points were performed if the time effect was significant.

Study VI: All values are given as mean \pm SEM. Data were analysed according to a repeated measures analysis of variance (ANOVA), with time (from pre-ischemia values through 120 min of reperfusion) as the repeated measures factor and CSD (yes/no) and Ischemia (no/yes) as the between factor. If the interaction between groups and time was significant, simple main effect were examined. The P-values were then corrected according to the Bonferroni procedure. Infarct size was analysed with one way ANOVA.

For all studies a P value < 0.05 was considered significant.

The assistance of Elisabeth Berg of the Medical Statistics Unit, Department of Medical Informatics and Educational Development, Karolinska Institutet, in the statistical evaluation of data is acknowledged.

RESULTS

***In vivo* studies of cardiac dimensions, cardiac function, functional capacity and quality of life in heart failure patients (I, V)**

Twenty patients meeting the inclusion criteria were subjected to application of the CSD. Ten patients with ischemic CMP underwent concomitant bypass surgery. Three patients out of the ten patients with idiopathic CMP received the CSD as the sole procedure, while seven patients in addition to the CSD application were subjected to mitral valve plasty. The Intensive Care Unit (ICU) time was 4 ± 1 days (mean \pm SEM). Two patients were re-operated within the first 24 postoperative hours due to suspected bleeding and tamponade. Four patients had an Intra Aortic Balloon Pump (IABP) in situ at the arrival to the ICU. These IABPs could all be successfully weaned within the first 3 postoperative days. At arrival to the ICU thirteen patients, seven

with ischemic CMP and six with idiopathic CMP, required inotropic drugs in addition to the levosimendan infusion all patients received. These drugs could be successfully weaned within the first 3 postoperative days, for all patients but two. One patient was treated for septicaemia verified by cultures and a second patient was treated for a suspected septicaemia. All patients could leave the ICU.

Hospital Length of stay (LOS) was 16 ± 2 days. One patient suffered a superficial wound infection and another patient was treated for a suspected pneumonia. All patients but one could leave the hospital and there were no deaths within the first 30 days.

Five of the patients have postoperatively been subjected to CRT treatment. One patient was re-operated one year postoperatively due to recurrent MR. Four patients died during the study period, data regarding these patients is presented in table V.

Data in the summary of this thesis is presented

Table V. Causes of death during follow-up.

Pat nr.	Time of death (Months postop.)	Cause of death
1	26	Rapidly deteriorated after gastrointestinal infection. Died in terminal heart failure.
10	2	Deteriorating heart failure postoperatively. Subjected to LVAD treatment, died on post op day 8.
11	20	Deteriorating heart failure. Underwent heart transplantation. Died in acute rejection on post op day 1.
16	3	Deteriorating heart failure postoperatively. Died in terminal heart failure.

LVAD: Left Ventricular Assist Device

ted as “end of follow-up” defined as the latest clinical control. Follow up is complete with a mean follow-up time of 32 ± 5 months.

Echocardiographic findings

Following passive containment surgery using the CSD, the cardiac dimensions measured as LVEDD in patients with idiopathic CMP and ischemic CMP were reduced from preoperatively 74 ± 2 mm and 69 ± 3 mm, to at end of follow-up time 65 ± 3 mm and 64 ± 5 mm, respectively (Fig. 3).

Left ventricular end systolic diameter (LVESD) was reduced from preoperatively 66 ± 2 mm and 61 ± 3 mm to at end of the follow-up time 56 ± 5 mm and 56 ± 5 mm in

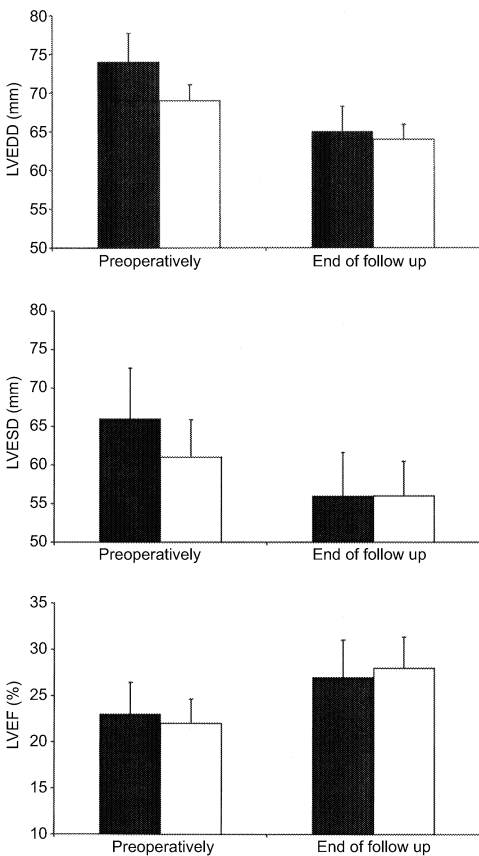


Fig. 3. LVEDD (top), LVESD (middle) and LVEF (lower) for patients with idiopathic CMP (filled bars) and ischemic CMP (open bars) preoperatively and at the end of follow up time. Results are presented as mean \pm SEM, n=19.

patients with idiopathic CMP and ischemic CMP respectively (Fig. 3). No differences in changes of cardiac dimensions were seen between patients with idiopathic versus ischemic CMP.

LVEF measurements revealed only minor changes in CMP patients. LVEF preoperatively was $23 \pm 3\%$ and $22 \pm 2\%$ and at end of follow-up time $27 \pm 5\%$ and $28 \pm 4\%$, respectively in patients with idiopathic and ischemic CMP, respectively (Fig. 3).

Functional assessment

There was an improvement in 6-minute-walk distance following CSD application. In patients with idiopathic and ischemic CMP, the 6-minute walk distance increased from preoperatively 372 ± 29 m and 366 ± 29 m to 479 ± 41 m and 413 ± 41 m, respectively, at the end of follow-up time (Fig. 4).

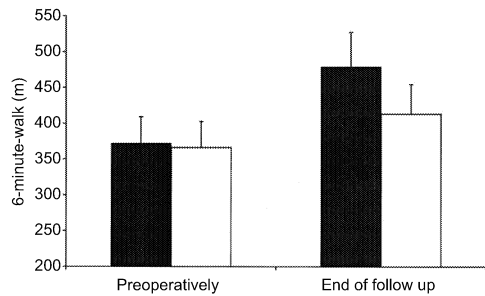


Fig. 4. 6-minute-walk for patients with idiopathic CMP (filled bars) and ischemic CMP (open bars) preoperatively and at the end of follow up time. Results are presented as mean \pm SEM, n=19.

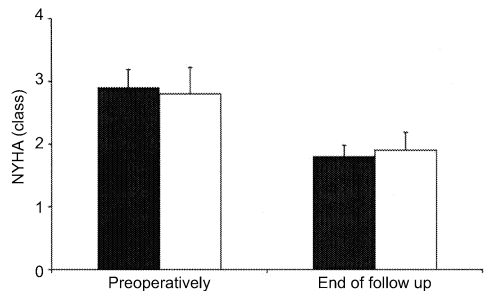


Fig. 5. NYHA classification for patients with idiopathic CMP (filled bars) and ischemic CMP (open bars) preoperatively and at end of follow up time. Results are presented as mean \pm SEM, n=19.

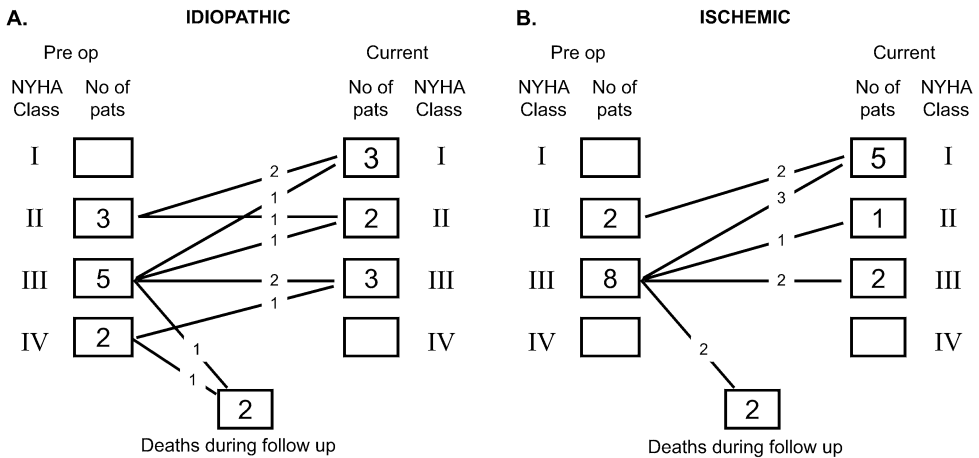


Fig. 6A+B. A; NYHA functional class for patients with idiopathic CMP preoperatively and currently. B; NYHA functional class for patients with ischemic CMP preoperatively and currently.

Functional capacity as evaluated by NYHA classification was improved following surgery. For patients with idiopathic CMP and ischemic CMP, NYHA class decreased from preoperatively 2.9 ± 0.2 and 2.8 ± 0.1 , respectively, to 1.8 ± 0.3 and 1.9 ± 0.4 , respectively at end of the follow-up time (Fig. 5). NYHA class preoperatively and currently for patients with idiopathic CMP and ischemic CMP are shown in Fig. 6 A+B.

No differences in functional capacity assessed with 6-minute-walk or with NYHA classification could be seen between patients with idiopathic versus ischemic CMP.

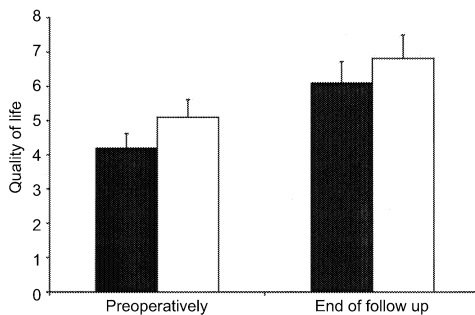


Fig. 7. Quality of life assessed by the Unscale Questionnaire for patients with idiopathic CMP (filled bars) and ischemic CMP (open bars) preoperatively and at end of follow up time. Results are presented as mean \pm SEM, $n=19$.

Quality of life

Quality of life assessed by the Unscale questionnaire improved following CSD application. For patients with idiopathic CMP and ischemic CMP, respectively quality of life improved from preoperatively 4.2 ± 0.7 and 5.1 ± 0.5 , to 6.1 ± 0.7 and 6.8 ± 0.4 , respectively, at the end of follow-up time (Fig. 7). No differences in the changes of quality of life could be seen between patients with idiopathic versus ischemic CMP.

In vivo echocardiography studies including pulsed wave tissue velocity (TVI) imaging in heart failure patients (II)

Cardiac dimensions

At the end of the TVI-study period (one year postoperatively, $n=12$) cardiac dimensions measured as LVEDD and LVESD significantly decreased from preoperatively 68 ± 2 mm and 60 ± 2 mm to 62 ± 3 and 53 ± 3 mm, respectively.

LV function

Systolic LV function measured as LVEF did not change significantly during the study period. This was confirmed using TVI de-

monstrating that neither LV systolic function measured as LV S_m nor LV diastolic function measured as LV E_m and LV A_m changed significantly during the study period.

RV function

A persistent RV dysfunction affecting systolic as well as diastolic function was detected using TVI. RV systolic function measured as RV S_m decreased from 9.5 ± 0.7 cm/s preoperatively to 7.4 ± 0.4 cm/s at the end of the study. RV diastolic function measured as RV E_m and RV A_m , respectively, decreased from 8.8 ± 1.1 cm/s and 14.1 ± 1.7 cm/s preoperatively to 6.3 ± 0.5 cm/s and 6.5 ± 0.9 cm/s, respectively at the end of the study (Fig. 8).

In vivo studies of circulating levels of Endothelin -1 and Big Endothelin-1 in heart failure patients (III)

Echocardiographic findings

Cardiac dimensions measured as LVEDD and LVESD decreased significantly from 69 ± 2 mm and 60 ± 2 mm preoperatively, to 62 ± 2 mm and 54 ± 3 mm, respectively at the end of the study (one year postoperatively, $n=13$). There were no statistically significant changes in LV systolic function measured as LVEF during the study period.

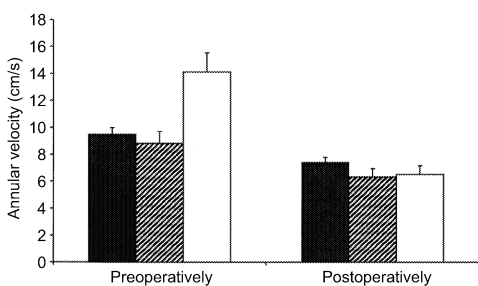


Fig. 8. RV systolic function (S_m , filled bars) and RV diastolic function (E_m , hatched bars; A_m , open bars), preoperatively and at the end of the study. Results are presented as mean \pm SEM, $n=9-11$.

Functional assessment

Functional capacity assessed by NYHA classification and 6-minute walk, improved significantly from 2.8 ± 0.2 and 384 ± 24 m preoperatively to 1.8 ± 0.2 and 465 ± 33 m at the end of the study, respectively.

Endothelin-1 and Big Endothelin-1 levels

Basal preoperative plasma levels of ET-1 and Big ET-1 were 5.9 ± 0.6 and 0.52 ± 0.08 pM, respectively. Following surgery there was a significant decrease in circulating plasma levels of ET-1 at follow up 12 months postoperatively to 4.3 ± 0.3 pM. No statistically significant changes were observed in circulating plasma levels of big ET-1 which were 0.50 ± 0.1 pM at follow up (Fig. 9). There was a correlation between the decrease in circulating plasma levels of ET-1 and the reduction in LVEDD ($R=0.56$; $P<0.05$).

In vivo echocardiographic studies in patients with aortic regurgitation and ventricular dilatation (IV)

Postoperative ICU time was 2 ± 1 days. One patient had to be re-operated in the first postoperative night due to bleeding; he then developed acute renal failure and required renal replacement therapy for four days. Thereafter the postoperative course was uneventful for this patient. All other patients included in

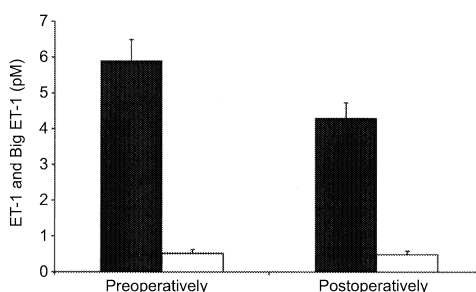


Fig. 9. Plasma levels of ET-1 (filled bars) and Big ET-1 (open bars) preoperatively and at the end of the study in CMP patients. Data is presented as mean \pm SEM, $n=13$.

the study had an uncomplicated postoperative course. Mean LOS was 10 ± 1 days, all patients could be discharged from the hospital and are all doing well at follow-up.

Echocardiographic/ET findings

Following AVR there was a significant reduction in cardiac dimensions measured as LVEDD and LVESD. However, there was no significant difference in the changes in cardiac dimensions between patients subjected to AVR+CSD and patients undergoing AVR only.

LVEDD was reduced from 74 ± 1 mm and 72 ± 4 mm preoperatively to 54 ± 6 mm and 53 ± 9 mm postoperatively in patients subjected to AVR+CSD and AVR as the sole procedure, respectively (Fig. 10). LVESD decreased from 56 ± 5 mm and 54 ± 8 mm preoperatively to 39 ± 8 and 35 ± 6 mm postoperatively in patients undergoing AVR+CSD and AVR alone (Fig. 10). There were no significant changes in LVEF in the two groups of patients (Fig. 10). TVI echocardiography revealed that patients undergoing AVR+CSD had unchanged LV systolic and diastolic function while an influence similar to that observed in heart failure patients was noted on the RV function (Fig. 11). The AVR+CSD patients had basal plasma ET-1 and Big-ET-1 levels of 4.5 ± 0.2 and 0.27 ± 0.07 fmol/ml, respectively remained unchanged during follow-up.

In vivo studies of the acute effects of the CSD in porcine acute myocardial infarction (VI)

Hemodynamics

There were no differences in baseline hemodynamics in any of the four groups of animals studied. During the experimental procedure a significant increase in HR over time was seen without any differences between the groups. The MAP remained unchanged in the non ischemic pigs while at 10 and 60

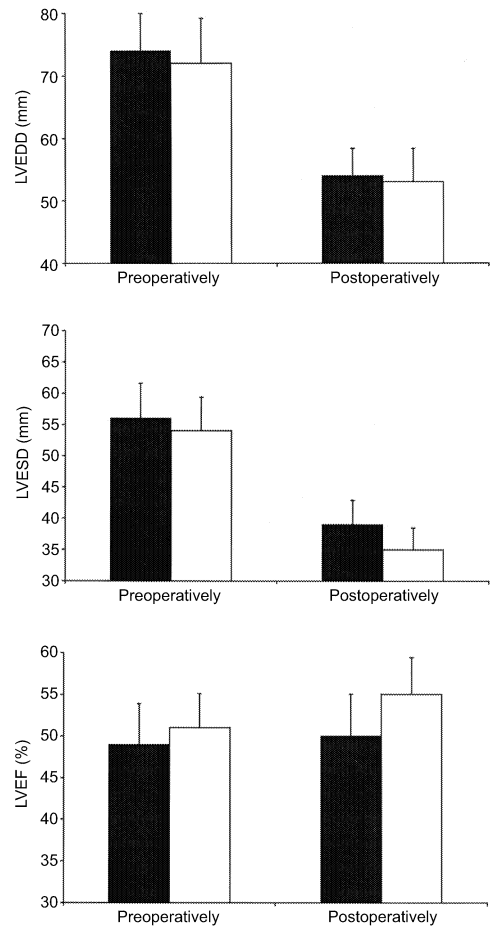


Fig. 10. LVEDD (top), LVESD (middle) and LVEF (lower) in patients subjected to AVR+CSD (filled bars) and control patients undergoing AVR as the sole procedure (open bars) preoperatively and at the end of the study. Results are presented as mean \pm SD, $n=5+5$.

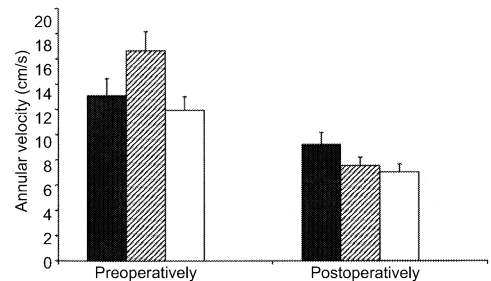


Fig. 11. RV systolic function (Sm, filled bars) and RV diastolic function (Em, hatched bars; Am, open bars), preoperatively and at the end of the study for patients undergoing AVR+CSD. Results are presented as mean \pm SD, $n=5$.

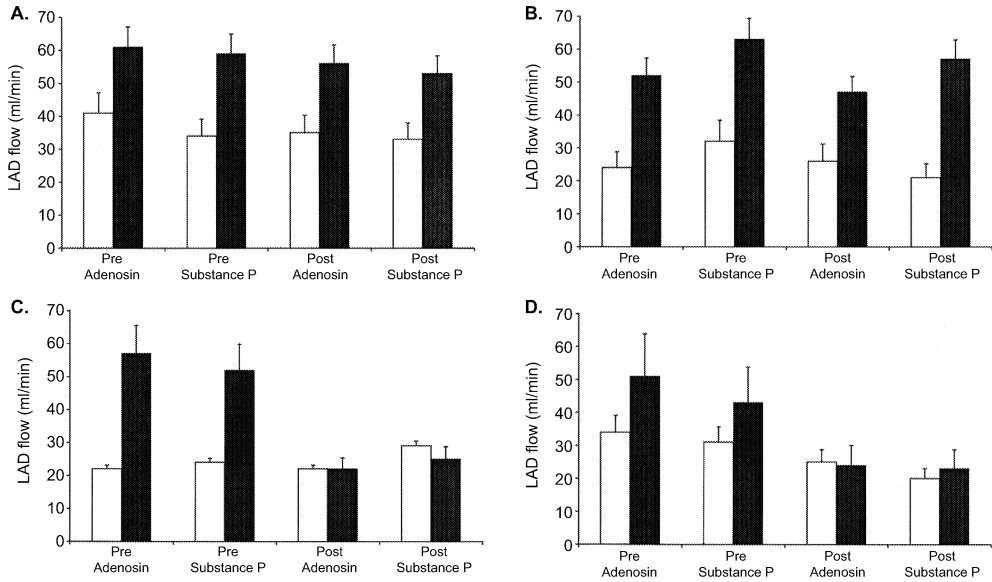


Fig. 12 A-D. LAD flow measured before (open bars) and after (filled bars) injection of ADO or SP. Measurements were made after stabilisation (Pre) and at the end of the experiment (Post). Results are presented as mean \pm SEM. A; Control group not subjected to CSD. B; Control group subjected to CSD. C; Ischemic group not subjected to CSD. D; Ischemic group subjected to CSD.

min of ischemia there was a significant decrease in MAP. Application of the CSD had no effect on the MAP.

LAD flow

At baseline conditions bolus injections of

ADO and SP evoked a significant increase in LAD flow in all animals without any major changes in MAP. This response remained unchanged after CSD application but was completely abolished in all pigs subjected to ischemia (Fig. 12 A-D).

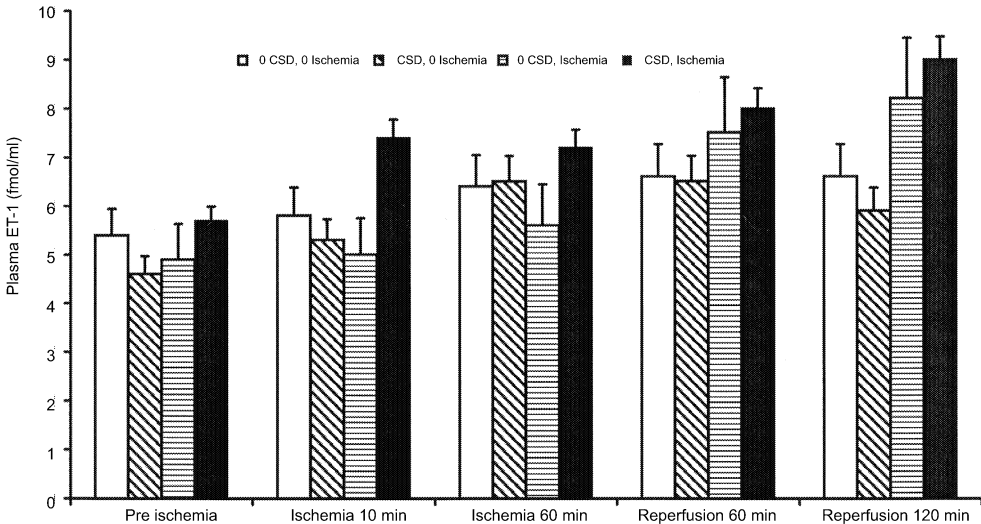


Fig. 13. Circulating plasma levels of ET-1 for each of the four groups of pigs throughout the experiment. Results are given as mean \pm SEM.

Endothelin-1 and Tumour Necrosis Factor- α levels

After stabilisation there were no significant differences in the circulating plasma levels of ET-1 between the four groups. Plasma levels of ET-1 remained unchanged in control animals throughout the experiment but increased significantly at 120 min of reperfusion in ischemic pigs (Fig. 13). Similarly, the cardiac tissue levels of ET-1 increased significantly following ischemia (Fig. 14). The CSD did not influence the plasma or tissue levels of ET-1 in control or ischemic pigs. Levels of TNF- α in plasma and tissues were not influenced by the experimental procedures in any of the groups of animals.

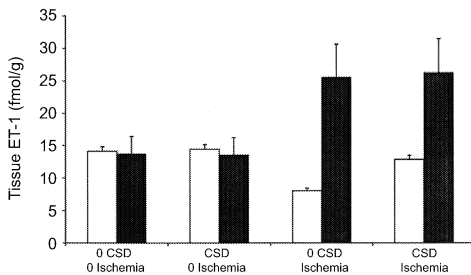


Fig. 14. Tissue levels of ET-1 for each of the four groups of pigs at the end of the experiment from stained areas (open bars) and non-stained areas (filled bars) of the myocardium. Results are given as mean \pm SEM.

Infarct size

The relation between the area at risk and total left ventricular area in the control group not subjected to CSD was $35 \pm 9\%$, in the control group with CSD $37 \pm 7\%$, in the ischemic group with CSD $41 \pm 7\%$ and in the ischemic group without CSD $46 \pm 4\%$. Application of the CSD did not significantly influence the relation between area at risk and total left ventricular area in neither control nor ischemic animals. CSD application did not influence the relation between the necrotic infarcted area and the area at risk.

DISCUSSION

Need for other treatment

In view of the increasing incidence and prevalence of heart failure there is a need for additional treatment options supplementing already existing pharmacological and surgical means of improving the problem (Hunt, 2004, Redfield, 2002). In the last decades the knowledge regarding the importance of surgical as well as non-surgical treatments to achieve reversed remodelling have improved substantially (Mudd et al. 2007). Surgical treatment in heart failure patients can be achieved either by dealing with the primary insult or cause alternatively by amelioration of the damaged heart thereby initiating reversed remodelling (Lange, 2007). We have therefore in these studies explored possible beneficial effects of passive containment surgery using the CSD in order to address the LV remodelling that often coincides with heart failure.

LV Remodelling

The mechanisms of LV remodelling in heart failure differs substantially depending on the cause of the heart failure. In a situation with pressure overload there will be an increase in wall stress. To compensate for this the myocytes grow in width with resulting increase in wall thickness thus reducing wall stress. Initially this process results in a hypertrophic heart with preserved systolic function. Eventually the compensatory increase in wall thickness will be insufficient and further pressure overload results in ventricular dilatation, reduced

systolic function and finally overt heart failure (Opie et al. 2006).

In volume overload there will be longitudinal growth initiating ventricular remodelling with changes in ventricular shape. Initially there is also an eccentric hypertrophy that combined with the ventricular dilatation can maintain forward flow. However, further ventricular dilatation that can not be compensated for results in progressive development of heart failure.

Subsequently, a vicious circle with volume overload and further dilation may be established resulting in signs and symptoms of heart failure (Opie et al. 2006).

Following acute anterior myocardial infarction, approximately 20% of patients develop structural LV dilatation that eventually will result in LV dysfunction (Gaudron et al. 1993). In remodelling after myocardial infarction there is a process with fibrosis and scar tissue followed by loss of contractile tissue and subsequent risk of ventricular dilatation. Modification of distending or deforming forces after myocardial infarction was early proposed as a target for therapeutic interventions in order to reduce ventricular dilatation (Pfeffer et al. 1990). Furthermore, LV dimensions have been established to correlate with poor survival in heart failure patients (Lee et al. 1993, Thohan, 2004). This increased understanding of the pathologic changes and processes resulting in progressive developments of heart failure has had important implications on heart failure therapies.

The Acorn Cor Cap CSD

In the early nineties findings indicated that increased mechanical load activates multiple signal pathways with resulting hypertrophic response from cardiomyocytes (Sadoshima et al. 1993). Results further suggested that the reversed remodelling seen after DCMP to a large extent was caused by the elastic constraining effect by the muscle wrap around the failing heart (Kass et al. 1995). These observations resulted in the subsequent development of the CSD.

Initial experimental studies in different heart failure models and with various species suggested that application of the CSD diminished the deterioration in LV function and improved reversed LV remodelling (Power et al. 1999; Chaudry et al. 2000). Numerous additional studies indicate reversed remodelling, reversal of chronic molecular and cellular abnormalities after CSD application in heart failure models (Saavedra et al. 2002; Sabbah et al. 2003; Raman et al 2003).

Based on the results and findings in previous experimental studies, human studies with the CSD were initiated by several groups worldwide. Follow-up 12 months postoperatively of patients with ischemic CMP subjected to CSD application demonstrated significantly reduced cardiac dimensions and improved functional capacity (Raman et al. 2001). Further studies where the majority of the patients had idiopathic CMP also demonstrated reduced cardiac dimensions, attenuated symptoms and

improved functional capacity (Konertz et al. 2001; Sabbah et al. 2001). All initial human studies of the CSD suffer from being small and non-randomised. To further explore the potential for the CSD in preventing further remodelling in heart failure patients the Acorn Clinical trial was therefore initiated in 2003 (Mann et al. 2004). Results from this multi-centre study regarding patients with MR and idiopathic CMP showed excellent results with a 30-day operative mortality of 1.6 %. Based on the findings from this study, trial investigators and study coordinators advocate a strong recommendation to consider mitral valve surgery in combination with the CSD to these patients (The Acorn Clinical Trial. 2006). However, this conclusion has been disputed due to the small differences between controls undergoing mitral valve surgery alone and patients subjected to mitral valve surgery and application of the CSD (Grossi et al. 2006). Our studies in heart failure patients demonstrate that the application of the CSD to patients with idiopathic or ischemic CMP is safe and simple. Following application of the CSD there is a significant reduction of cardiac dimensions, improved functional capacity and quality of life. Follow-up at the end of the study period showed no significant differences in the results between patients with idiopathic CMP and patients with ischemic CMP (V). This is in contrast to our initial observations (I). A summary of our principal findings following CSD application in the human studies are presented in table VI.

Table VI. Suggested effect of CSD application in the human studies in this thesis.

	LVEDD	LVESD	LVEF	NYHA	6-M-W	QoL	ET-1
Patients with idiopathic CMP (I-III, V)	↓	↓	→	↓	↑	↑	↓
Patients with ischemic CMP (I-III, V)	↓	↓	→	↓	↑	↑	↓
Patients with AR and LV dilatation (IV)	→	→	→				→

AR= aortic regurgitation; AVR= aortic valve replacement; CMP= cardiomyopathy; ET-1= endothelin-1; LV= left ventricle; LVEF= left ventricular ejection fraction; LVEDD= left ventricular end diastolic diameter; LVESD= left ventricular end systolic diameter; NYHA= New York Heart Association; QOL= quality of life.

→ = unchanged ↓ = decreased ↑ = increased

Asymptomatic patients with AR without LV dilatation or reduced LVEF have an excellent prognosis with conservative treatment (Bonow. 2000). Should LV dilatation and/or reduced LVEF appear, surgical treatment without delay is indicated (Dujardin et al. 1999, Tornos et al. 2006). Furthermore it has been demonstrated that early reduction of LV dilation in patients with AR following AVR correlates to short-term and long-term improvements in LV systolic function (Bonow et al. 1988). Based upon these facts the potential for the CSD in facilitation of reducing LV dimensions following AVR in patients with AR was evaluated (IV). Our results showed no additional beneficial effect of CSD application in this group of patients. Importantly, the study also revealed no negative effect on LV function by application of the CSD. However, a persistent RV dysfunction affecting both systolic and diastolic function was demonstrated in patients with AR undergoing AVR and CSD application. This RV dysfunction appears to be similar to the RV dysfunction demonstrated with TVI in heart failure patients following CSD application and also to the global RV dysfunction observed in non-failing cardiac surgery patients (Alam et al. 2003, Hedman et al. 2004).

Animal studies in a sheep model with CSD application 1 week post-induction of an anterior myocardial infarction demonstrated prevention of further remodelling (Pilla et al. 2003). Additional studies using the same model showed beneficial cellular and extra cellular effects following CSD application (Blom et al. 2005). To evaluate the acute effects of CSD application in immediate conjunction with induction of an anterior myocardial infarction, a porcine model of acute myocardial infarction that had earlier been found to be valid and reproducible was used (VI; Lockowandt et al. 2001). Although we could not demonstrate any clear-cut beneficial effect of CSD application in acute myocardial infarction, it is important to note that no negative effects were observed.

Our results clearly demonstrate that CSD application following induction of a large anterior infarction has no detrimental effects on hemodynamics, endothelin turnover, coronary vasomotor tone or endothelial function. Thus, others and our own experimental findings, combined with the evidence that ventricular dilatation following myocardial infarction correlates with poor prognosis indicate that CSD application is safe and could have a beneficial effect in patients following a large anterior myocardial infarction.

Importance of concomitant surgery

CABG

The CASS study demonstrated that patients with poor LV function undergoing CABG experienced a substantial symptomatic benefit compared with medically treated patients (Alderman et al. 1983). It has thereafter been shown that CABG surgery in patients with LV dysfunction significantly improves 3 year survival (Baker et al. 2004). Midterm results in patients with severe LV dysfunction undergoing CABG surgery with low mortality are of great interest (Shapira et al. 2006). All patients in our studies with ischemic CMP were subjected to CABG surgery and received at least the left internal thoracic artery to the anterior LV wall (LAD or diagonal). It may therefore be argued that the revascularization explains the beneficial effects observed in the patients. However, the heart failure patients likely to benefit from CABG usually receive more graft (>3; Elefteriades et al. 1997) than our patients. Additionally we have no knowledge of the graft patency in our patients excluding a possible evaluation of the importance of graft flow to the outcome. There was no correlation between extent of grafting and results in our studies suggesting that the increase in myocardial perfusion may not be the sole determinant for the postoperative outcome of our patients.

Mitral valve surgery

Results indicating that mitral valve surgery improves ventricular function in patients with long standing MR were presented in 1995 (Starling. 1995). Initial studies demonstrated improved survival and functional status and the interest in mitral valve reconstruction in patients with heart failure was enhanced (Bolling et al. 1998, Bolling. 2001). Other investigators have confirmed these initial results regarding both survival and symptomatic improvement (Bishay et al. 2000). However, other studies have been unable to detect significant results regarding mortality in patients with MR and LV systolic dysfunction undergoing mitral valve surgery (Wu. 2005). In our patients with idiopathic CMP, seven patients underwent mitral valve surgery. It is likely that correction of the MR is important for the outcome. In two of the patients a clinical deterioration and recurrent MR have been seen and one of these patients has after re-operation rapidly improved. Apart from these two cases there is no indication that return of the MR underlies the deterioration of the patients' functional capacity and quality of life at prolonged follow up. Based on the observed recurrence of MR combined with rapid deterioration it is likely that return/increased MR postoperatively predicts a poor outcome following the CSD application. Maintained minor MR (1+) was seen in patients doing excellent, as well as in patients doing poorly after surgery and probably has a small influence on postoperative outcome.

CRT

CRT is a well established treatment for patients with heart failure. Standard criteria for CRT treatment includes: NYHA class III or IV, LVEF less than 35%, QRS width equal or over 120 msec and optimal pharmacological therapy. Based on new findings regarding the selection criteria for patients treated with CRT it seems likely that the number of heart failure patients treated with CRT will increase (Bank et al. 2006).

In the heart failure patients studied, one patient was preoperatively treated with CRT (12 months prior to surgery) and in five additional patients CRT treatment was commenced during the follow up time with start at 2 weeks (n=1; when implanting an ICD due to ventricular arrhythmias), 6 months (n=1; patient died 26 months postop), or four years (n=3; after further deterioration). No clear-cut effects of the CRT treatment were observed in these patients and we can therefore not assess the role of the CRT following heart failure surgery using the CSD.

Endothelin-1

Circulating plasma levels of ET-1 are increased in patients with heart failure (Kinugawa et al. 2003). This increase in circulating plasma levels has been attributed to increased production as well as decreased clearance (Zolk et al. 1999, Parker et al. 2004). Early studies indicated a beneficial effect of endothelin receptor antagonism in heart failure patients (Bergler-Klein et al. 2004). However, a randomised, controlled study trial could not demonstrate additional beneficial effects on cardiac remodelling or clinical symptoms with addition of endothelin antagonism to other pharmacological heart failure treatment (EARTH. 2004). The circulating levels of ET-1 have been demonstrated to have a prognostic value in heart failure patients and to be a predictor of death in these patients (Pousset et al. 1997, Galatius-Jensen et al. 1996). ET levels decreased in our CMP patients following surgery with a correlation to LV size. Unchanged Big ET-1 levels suggest that changes in clearance rather than metabolism explain the decreased ET-1 levels. To what extent ET-1 could be an indicator of functional or anatomical status remains to be established. It is of interest to note that the circulating plasma levels of ET-1 in patients with AR and LV dilatation were unchanged although there was a reduction in cardiac dimensions indicating

that circulating plasma levels of ET-1 do not correlate to LV dimensions in non-failing patients.

Peri- and postoperative treatment

All the patients with CMP included in these studies had advanced heart failure, LV dilatation and depressed LVEF. These factors have all been demonstrated to predict use of inotropic drugs and generally this group of patients is considered to be a high risk population for peri- and postoperative complications (McKinlay et al. 2004). Optimal results are highly dependent upon proper surgical technique in combination with well planned and performed anesthesia and postoperative intensive care treatment. The peri- and postoperative strategies have been based on physiological aspects having as a primary aim and goal to do “what we can for the heart and not what the heart can do for us” (Håkanson et al. 1995). The beneficial effects of high-dose glucose-insulin-potassium treatment given to patients with severe cardiac dysfunction following cardiac surgery or with depressed LV function undergoing CABG has been demonstrated in earlier studies (Svedjeholm et al. 1995, Cimochoowski et al. 1997). Based on these findings and our own previous experience the majority of the patients received this form of metabolic support. Inotropic drugs are often necessary in the perioperative treatment following cardiac surgery in patients with compromised LV function (Muller et al. 2002). The intravenous inotropic drugs could be divided into drugs that increase the intracellular levels of cyclic adenosine monophosphat (cAMP) such as the β agonists and the PDE inhibitors and drugs acting independent of cAMP such as the digitalis glycosides and levosimendan (Lehtonen et al. 2004). Levosimendan is a calcium sensitizer that enhances contractility without increasing myocardial oxygen consumption in contrast to many other inotropic

drugs (Figgitt et al. 2001). Initial results regarding the use of levosimendan perioperatively to high risk patients undergoing cardiac surgery have been encouraging (Raja et al. 2006). In order to reduce the postoperative need for further inotropic drugs all patients were given levosimendan perioperatively (Bredin et al. 2007). The fact that there was no early postoperative mortality in this high risk group indicates that the physiological aspects regarding the perioperative treatment used in the studied patients could be applied to other high risk patients undergoing cardiac surgery. Furthermore, the results strongly indicate that the application of the CSD *per se* is safe.

Concerns with the CSD

RV dysfunction

Persistent RV dysfunction was found using TVI post operatively in patients undergoing CSD application. This dysfunction could be demonstrated in heart failure patients as well as patients with AR. These groups of patients showed a reduction of systolic and particularly diastolic RV function with no sign of improvement during the follow up time. Based on the fact that persistent depression of RV function following CABG surgery previously has been demonstrated in earlier studies it seems unlikely that this RV dysfunction could be attributed to the CSD application (Alam et al. 2003). Furthermore studies have demonstrated no effect on exercise performance by this RV dysfunction and therefore it has been proposed that the RV dysfunction probably has no clinical significance (Hedman et al. 2004). Interestingly, in contrast to our findings, electron-beam computed tomographic examination one month postoperatively of patients with idiopathic dilated cardiomyopathy (CMP) undergoing application of the CSD have shown reduced RV size and improved RV performance (Lembcke et al. 2004).

Re-operations

A major concern for patients undergoing treatment with the CSD is the potential difficulties in case of a later cardiac re-operation. Three patients, all with idiopathic CMP included in these studies have been re-operated. One patient was subjected to treatment with a LVAD two months after CSD application, a second patient underwent mitral valve surgery due to recurrent MR twelve months postoperatively and a third patient underwent heart transplantation 20 months postoperatively. Worldwide there have been 32 re-operations reported among the 424 patients subjected to CSD application up until 53 months postoperatively. The most frequent surgical procedures performed at re-operation were heart transplantation (n=15), LVAD implantation (n=8) and re-do mitral valve surgery (n=7). Although adhesions varied widely, all re-operations were successful and could be completed as planned (S. Kubo, Acorn Cardiovascular Inc., personal communication, 2007).

Local myocardial blood flow

Findings in our animal studies strongly indicate that the CSD has no detrimental effects on coronary vasomotor tone or endothelial function. Earlier studies have shown that 60 min of ischemia in a similar porcine model induces a reproducible AMI and attenuation of endothelium dependent as well as endothelium independent vasodilatation (Lockowandt et al. 2001). The lack of effects by the CSD already applied at induction of ischemia strongly supports that passive containment will not affect the endothelial vasomotor function following myocardial infarction.

Limitations of these studies

Studies performed in heart failure patients are restricted by the low number of patients and the lack of a control group. These limitations are due to the limited number of patients meeting the inclusion criteria at our

institution and therefore all eligible patients have been non-randomly included in the studies. Another possible confounding factor is the etiology; patients included had ischemic or idiopathic CMP. The later group could be further subdivided since several different etiologies to idiopathic CMP have been identified (Maisch et al. 2002). Moreover all patients had at least a one year history of heart failure and were on stable pharmacological therapy but there was a considerable variation in the duration of heart failure between patients. Another potential confounder is the fact that most of the patients underwent additional concomitant cardiac surgery. These limitations could be potential explanations to the variations in result following CSD application seen between individual patients. It would be of outmost interest to perform further, preferably, controlled studies in order to identify patient selection criteria as well as optimal timing of CSD application. Patients' quality of life was evaluated by Uniscale score. The Uniscale has been designed to assess the benefits of various treatments in serious illness (Spitzer et al. 1981). It has been demonstrated to be an appropriate tool to obtain a measurement of overall quality of life in patients with advanced cancer (Sloan et al. 1998). The Uniscale has however not been validated for the specific use of quality of life assessment in heart failure patients. This is in contrast to other forms such as the Medical Outcome Study 36-item Short Form (Sullivan et al. 1995). The first five CMP patients included in these studies were part of a Limited Market Release Study and the protocol of that study dictated the use of the Uniscale for evaluation of quality of life. In order to be able to include all eligible patients the decision was taken to use the Uniscale for evaluation of quality of life in all included patients.

SUMMARY AND CONCLUSIONS

1. In heart failure patients with dilated cardiomyopathy subjected to passive containment surgery using the Acorn Cor Cap Cardiac Support Device a significant reduction in cardiac dimensions (measured as left ventricular end diastolic diameter and left ventricular end systolic diameter), improved functional capacity (measured as NYHA class and 6-minute – walk) and improved quality of life (measured by the Uniscale score) were demonstrated.
2. Echocardiographic examinations including pulsed wave tissue velocity of heart failure patients with dilated cardiomyopathy following application of the Acorn Cor Cap Cardiac Support Device demonstrated significantly reduced cardiac dimensions, unchanged left ventricular systolic and diastolic function (measured as left ventricular ejection fraction, mitral annular peak systolic velocity and diastolic mitral annular velocities) and a significant, persistent reduction in right ventricular systolic and diastolic function (measured as tricuspid peak annular systolic velocity and tricuspid annular diastolic velocities, respectively).
3. Following passive containment surgery using the Acorn Cor Cap Cardiac Support Device in heart failure patients with dilated cardiomyopathy there was a significant reduction in circulating plasma levels of Endothelin-1, while circulating plasma levels of Big Endothelin-1 were unchanged.
4. Application of the Acorn Cor Cap Cardiac Support Device concomitant with aortic valve replacement in patients with aortic regurgitation and ventricular dilatation did not influence the magnitude or speed of reduction of ventricular dilatation.
5. Application of the Acorn Cor Cap Cardiac Support Device at induction of porcine acute myocardial infarction did not influence the hemodynamics, coronary vasomotor function or extent of infarct in size.

It is concluded that the Acorn Cor Cap Cardiac Support Device represents an interesting and likely beneficial adjuvant to the surgical arsenal in heart failure treatment. However, the timing of surgery and the optimal indications for its use needs to be further explored. The application of the Acorn Cor Cap Cardiac Support Device is safe, simple and without apparent negative effects.

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One of the major investigators in these studies (A F-C) served as member of the Acorn European Consultant Group between 2001-2003 but resigned to stand independent of any influence in the studies. The Acorn Cardiovascular Inc. neither has requested nor received any information or data from these studies prior to publication

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