Management of patients treated with left ventricular assist devices

A clinical and experimental study

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Linköping 2001
Diseases desperate grown
By desperate appliance are reliev´d
Or not at all

(Hamlet, act IV, scene 3)
William Shakespeare

To Qina, Viktor and Anton
This thesis describes the management of patients treated with mechanical circulatory support devices for short- or long-term use. Twenty-four patients suffering from postcardiotomy heart failure were treated with a minimally invasive axial flow pump. The device was effective in unloading the failing left ventricle and in maintaining an adequate systemic circulation. The principles of perioperative monitoring, and pharmacological therapy are outlined. The pump was also used as an alternative to the heart-lung machine in conjunction with coronary artery bypass surgery. Together with a short-acting β-blocker, esmolol, the heart was decompressed and heart motion was reduced, facilitating bypass surgery on the beating heart. The anesthesiological considerations using this method are described.

An implantable left ventricular assist device was used as a bridge to heart transplantation in 10 patients. We were interested in assessing the possibility to establish such a treatment program at a non-transplanting center. A multidisciplinary approach was enabled thanks to the organization of our Heart Center and due the close collaboration with our transplant center at Lund University. As one of the first centers in Europe, we established a well-functioning program with good results. Nine out of 10 of the bridge patients, with treatment times varying between 53 to 873 days, survived pump treatment and were eventually transplanted. The device proved to be powerful enough to support the failing heart and enable rehabilitation of the patients. Outpatient management became simpler when using the electrical device with belt-worn batteries. The uncertain durability and the high risk of device-related complications are shortcomings that limit its potential for more permanent treatment of heart failure.

A new generation of small implantable axial blood flow pumps has therefore been developed. The principles of these pumps are based on the first generation axial flow pumps evaluated in this thesis. After several years of basic research and experimental studies, the first human implants have been performed. In the thesis, the hemodynamic effects of such a novel axial flow pump have been evaluated in an acute heart failure model. This technology holds great promise, both as a bridge to heart transplantation, and as a permanent circulatory support system.
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This thesis is based on the following papers, which will be referred to in the text by their Roman numerals:

I. Postoperative management of patients with Hemopump support after coronary artery bypass grafting.

II. Anesthetic management of patients undergoing coronary artery bypass grafting with the use of an axial flow pump and a short-acting β-blocker.
    Peterzén B, Lönn U, Babić A Carnstam B, Rutberg H, Casimir-Ahn H.

III. Management of patients with end-stage heart disease treated with an implantable left ventricular assist device in a non-transplanting center.
     Peterzén B, Granfeldt H, Carnstam B, Nylander E, Dahlström U, Rutberg H,
     Casimir-Ahn H.

IV. Long term follow-up of patients treated with an implantable left ventricular assist device as an extended bridge to heart transplantation.
    Submitted for publication.

V. Hemodynamic evaluation of the Jarvik 2000 Heart during heart failure in a calf model.
   Peterzén B, Gregoric IM, Myers TM Lönn U, Träff S, Hübbert L, Lindström L,
   Wårdell K, Frazier OH, Jarvik RK, Casimir-Ahn H.
   Manuscript.
# ABBREVIATIONS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>ACT</td>
<td>Activated clotting time</td>
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<tr>
<td>ALT</td>
<td>Alanine aminotransferase</td>
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<tr>
<td>AST</td>
<td>Aspartate aminotransferase</td>
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<tr>
<td>AV</td>
<td>Atrio-ventricular</td>
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<tr>
<td>A-V O₂</td>
<td>Arterio venous oxygen difference</td>
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<tr>
<td>BIVAD</td>
<td>Biventricular assist device</td>
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<tr>
<td>CI</td>
<td>Cardiac index</td>
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<td>CO</td>
<td>Cardiac output</td>
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<tr>
<td>CPB</td>
<td>Cardiopulmonary bypass</td>
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<tr>
<td>CVP</td>
<td>Central venous pressure</td>
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<tr>
<td>DAP</td>
<td>Diastolic arterial blood pressure</td>
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<tr>
<td>ECG</td>
<td>Electrocardiography</td>
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<tr>
<td>HM</td>
<td>HeartMate™</td>
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<tr>
<td>HP</td>
<td>Hemopump™</td>
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<tr>
<td>HR</td>
<td>Heart rate</td>
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<tr>
<td>Htx</td>
<td>Heart transplantation</td>
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<tr>
<td>IABP</td>
<td>Intra-aortic balloon pump</td>
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<tr>
<td>ICU</td>
<td>Intensive care unit</td>
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<tr>
<td>LAP</td>
<td>Left atrial pressure</td>
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<tr>
<td>LIMA</td>
<td>Left internal mammary artery</td>
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<tr>
<td>LV</td>
<td>Left ventricle</td>
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<tr>
<td>LVAD</td>
<td>Left ventricular assist device</td>
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<tr>
<td>LVDD</td>
<td>Left ventricular end diastolic dimension</td>
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<tr>
<td>MAP</td>
<td>Mean arterial blood pressure</td>
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<tr>
<td>MCS</td>
<td>Mechanical circulatory support</td>
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<tr>
<td>MHz</td>
<td>Mega Hertz</td>
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<tr>
<td>NO</td>
<td>Nitric oxide</td>
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<tr>
<td>OR</td>
<td>Operating theatre</td>
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<tr>
<td>PA</td>
<td>Pulmonary artery</td>
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<tr>
<td>PAPm</td>
<td>Mean pulmonary arterial blood pressure</td>
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<tr>
<td>PCWP</td>
<td>Pulmonary capillary wedge pressure</td>
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<tr>
<td>PDE</td>
<td>Phosphodiesterase</td>
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<tr>
<td>PVRI</td>
<td>Pulmonary vascular resistance index</td>
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<tr>
<td>RER</td>
<td>Respiratory exchange ratio</td>
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<tr>
<td>RIMA</td>
<td>Right internal mammary artery</td>
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<tr>
<td>rpm</td>
<td>Revolutions per minute</td>
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<tr>
<td>RV</td>
<td>Right ventricle</td>
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<tr>
<td>RVAD</td>
<td>Right ventricular assist device</td>
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<tr>
<td>RVDD</td>
<td>Right ventricular end diastolic dimension</td>
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<tr>
<td>RVEDV</td>
<td>Right ventricular end diastolic volume</td>
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<tr>
<td>RVEF</td>
<td>Right ventricular ejection fraction</td>
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<tr>
<td>RVSD</td>
<td>Right ventricular end systolic dimension</td>
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<tr>
<td>RVESV</td>
<td>Right ventricular end systolic volume</td>
</tr>
<tr>
<td>RVFS</td>
<td>Right ventricular fractional shortening</td>
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<tr>
<td>SAP</td>
<td>Systolic arterial blood pressure</td>
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<tr>
<td>SD</td>
<td>Standard deviation</td>
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<tr>
<td>SV</td>
<td>Stroke volume</td>
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<tr>
<td>SvO₂</td>
<td>Mixed venous oxygen saturation</td>
</tr>
<tr>
<td>SVRI</td>
<td>Systemic vascular resistance index</td>
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<tr>
<td>TAH</td>
<td>Total artificial heart</td>
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<tr>
<td>TI</td>
<td>Tricuspid insufficiency</td>
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<tr>
<td>TRP-T</td>
<td>Troponin T</td>
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<tr>
<td>TEE</td>
<td>Transesophageal echocardiography</td>
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<tr>
<td>TTE</td>
<td>Transthoracic echocardiography</td>
</tr>
<tr>
<td>VCO₂</td>
<td>Carbon dioxide elimination</td>
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<tr>
<td>VE</td>
<td>Pulmonary ventilation</td>
</tr>
<tr>
<td>VO₂</td>
<td>Oxygen uptake</td>
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<tr>
<td>VTI</td>
<td>Velocity time integral</td>
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INTRODUCTION

There is a vast amount of reports dealing with surgical principles of treating acute and chronic heart failure with a variety of mechanical circulatory support systems. Principally these devices have been used either for short-term treatment of postcardiotomy heart failure, or as long-term support in patients with untractable congestive heart failure. There is less written about the perioperative management of such patients, i.e. principles for anesthesia, monitoring and postoperative therapy.

The incidence of postcardiotomy heart failure has decreased over recent years due to improved care of patients prior to surgery, better drugs, refined surgical techniques, better equipment and improved perioperative management of the patients (1-3). However, myocardial dysfunction after cardiac surgery, with the use of cardiopulmonary bypass (CPB), remains a clinical problem. Before weaning from CPB, care must be taken to achieve adequate body temperature, proper oxygenation with correct acid-base balance, optimal pre- and afterload of both ventricles and atrial-ventricular pacing if needed. If weaning cannot take place following these attempts during optimal conditions, three options are available: 1) reinstitute CPB and allow the heart to further recover; 2) employ pharmacological means of manipulating the inotropic state of the heart and the vasculature; or 3) reinstitute CPB and employ mechanical circulatory support (MCS) (4). These principles must frequently be used in combination.

Around 200 000 people in Sweden suffer from symptomatic congestive heart failure (CHF) (5), most of them above 65 years of age. The vast majority can be treated pharmacologically. However, despite intense pharmacological treatment, a few patients deteriorate and become candidates for heart transplantation. Due to the shortage of donor organs, only 20 to 40 heart transplantations are performed per year in Sweden. The lack of donor organs is increasing in Sweden, as it is in other countries. International results indicate that around 30% of the patients on the waiting list, die prior to transplantation (6). Today some of these patients can be treated with MCS, as a “bridge” to transplantation. Research efforts are also directed towards producing MCS systems for long-term use, or for permanent cardiac replacement (7).

MCS was first used clinically in 1953 with the implementation of cardiopulmonary bypass (8). This breakthrough led to surgical treatments for a variety of cardiac disorders. The
success of CPB stimulated research into other innovative techniques for supporting the circulation.

In the 1960s, CHF patients were occasionally supported by CPB (9), ventricular assist device (10), or total artificial heart (11). Although the overall success rate was limited, this early experience did show that MCS could adequately sustain a patient’s circulation until cardiac function recovered or a donor heart for transplantation could be obtained (7). Throughout the years, several different assist devices have been developed.

The current mechanical circulatory support can be divided into five groups, based on different operating principles: 1) intra-aortic balloon pump, 2) centrifugal pumps, 3) displacement pumps, 4) axial blood flow pumps, and 5) total artificial hearts.

In this thesis, the principles used for management of patients treated with a minimally invasive axial flow pump for short-term use, and an implantable left ventricular assist device for long-term use, are outlined. Evaluation of the hemodynamic effects of a novel implantable axial blood flow pump was also performed in an acute heart failure model.

I. Postcardiotomy heart failure

Pathophysiology of cardiac failure after heart surgery

In the perioperative period, the heart must cope with the acute insult of surgical intervention and CPB. The heart has to endure the ischemic insult of cardioplegic arrest and reperfusion injury. This might increase the likelihood of postoperative myocardial dysfunction. It is generally accepted that contractile dysfunction not only results from myocardial infarction, it may also be a result of myocardial stunning and hibernation.

In 1982, Braunwald and Kloner (12) described delayed recovery of myocardial contractile function as a result of reperfusion injury after an ischemic event and called it “myocardial stunning”. In 1985, Rahimtoola (13) introduced the term “hibernating myocardium”, characterizing persistently depressed ventricular function caused by chronic myocardial hypoperfusion and ischemia. Finally, in 1986 Murry (14) described the most recently discovered consequence of ischemia, “ischemic preconditioning”, i.e. the paradoxical phenomenon that myocardium reversibly injured by ischemia is more tolerant to subsequent episodes of ischemia, see Fig 1.
Areas of stunned myocardium may be present along with areas of ischemic and hibernating myocardium. The crucial difference between the stunned and hibernating myocardium is that in the stunned myocardium, coronary blood flow has been fully restored, in contrast to the hibernating myocardium, which is associated with reduced coronary blood flow. The effects of stunning are abnormalities of both systolic and diastolic function.

**Figure 1** Consequences of myocardial ischemia include: 1) myocardial infarction with permanent contractile dysfunction, caused by long-lasting ischemia; 2) hibernating myocardium as a result of chronic hypoperfusion; 3) stunned myocardium after reperfusion of ischemic myocardial tissue; and 4) preconditioned myocardium after brief ischemic insults. The preconditioned myocardium may in turn offer protection during a subsequent ischemic event and has been demonstrated to limit infarct size in animal models. It is unclear whether the preconditioned myocardium is capable of enhancing the recovery of stunned myocardium. Redrawn from Vroom MB, van Wezel HB. J Cardiothorac Vasc Anesth 1996;6:789-99.

The subendocardium is at the highest risk for ischemic injury, since increases in intracavity systolic pressure compress subendocardial vessels, allowing coronary blood flow to the LV only in diastole. Increase in diastolic ventricular filling pressures will impede blood flow to the endocardium as well as increase the ventricular wall tension. Increases in heart rate will shorten the diastolic perfusion period for the endocardium. The increase in ventricular filling pressures and heart rate will increase the myocardial oxygen demands.

The underlying pathology of stunning is still not clarified, but might be related to reduced high-energy phosphate levels, intracellular calcium overload, generation of superoxide
radicals, and disturbances in microcirculatory flow involving platelets and white blood cells (15, 16), see Fig 2.

Among the numerous mechanisms proposed, two appear to be most plausible: 1) generation of oxygen-derived free radicals (“oxyradical hypothesis”) and 2) impaired calcium homeostasis resulting in calcium overload, excitation-contraction uncoupling, and/or decreased myofibril sensitivity to calcium (“calcium-overload hypothesis”) (17). The recovery of myocardial metabolism after CPB and aortic cross clamp may be adversely affected by the combined effects of ischemia and neuroendocrine stress response to trauma (18). The myocardial ATP content is limited, and decreases further in the post ischemic myocardium. During normal condition glucose, lactate, and free fatty acids (FFA) are the major sources of energy for the heart and the choice of substrate is primarily determined by the availability of substrates. Ischemia leads to an increased consumption of the amino acid glutamate and hypoxia enhances the utilization of glucose and possibly the use of amino acids metabolites in the Krebs cycle (19). A decrease in coronary blood flow and oxygen supply, might lead to an impeded utilization of oxygen and substrates (20-22). Loss of Krebs cycle glucose intermediates has been proposed as a major explanation for this phenomenon (23). However, it has been shown that the stunned myocardium can respond to inotropic therapy, indicating that adequate ATP stores can be recruited to restore proper ventricular function (24, 25). Inotropes, however, will not have the same effect on the ischemic myocardium (26).

**POSTCARDIOPLEGIA DYSFUNCTION**

![Figure 2](image)

*Figure 2. A schematic representation of mechanisms leading to postischemic dysfunction in hearts damaged by ischemia-reperfusion injury. The generation of oxygen-derived free radicals triggers abnormalities in calcium homeostasis and kinetics of contraction, leading to dysfunction. Other perturbations may develop and extend the degree of dysfunction. Abbreviations: E-C, excitation-contraction uncoupling; SR, sarcoplasmatic reticulum; Sympath Neural, sympathetic neural activity; ATP, adenosine triphosphate. Redrawn from Vinten-Johansen and Nakanishi. J Cardiothorac Vasc Anesth 1993;4 (suppl 2):6-18.*
Pharmacological and metabolic treatment

When a low cardiac output develops, it is often difficult to know whether the contractile dysfunction is a consequence of ischemia, stunning, infarction or a combination of these abnormalities. In order to prevent the deleterious consequences of low flow, treatment usually involves the use of vasoactive agents, especially if ischemia appears less likely. Traditionally, the treatment of low cardiac output associated with cardiac surgery has focused on the left ventricular function. Efforts have been made to optimize LV function, by improving myocardial blood flow, the oxygen supply/demand ratio, and allow time for ventricular recovery. This has been achieved with the use of vasodilators and by increasing the contractile state of the myocardium.

Vasodilators

Multiple vasodilators are available to treat hypertension and/or to decrease the ventricular loading in order to improve diastolic function when attempting to discontinue CPB. The agents most commonly used are nitroglycerine and sodium nitroprusside, which by increasing cyclic guanosine monophosphate in the vascular cells, produce venodilatation and a varying degree of arterial vasodilatation affecting both preload and afterload (27). Vasodilator therapy, in combination with inotropic stimulation, is often required to alter ventricular loading conditions and to treat any diastolic dysfunction that may occur. Prostaglandin, prostacyclin and nitric oxide (NO) have been successfully used to treat pulmonary hypertension of various etiologies (28-30). However, D’Ambra et al. reported, that administration of norepinephrine in a left atrial line was needed in order to counteract the systemic vasodilatation induced by prostaglandin E1. Coyle et al. (31) found that when norepinephrine was administered this way, it was to a major part metabolized in the systemic circulation. If norepinephrine is ineffective, administration of angiotensin II could be an alternative (32).

Kieler-Jensen et al. found prostacyclin to be a more efficient dilator of resistance vessels and a less efficient venodilator (33), and that prostacyclin did not cause any coronary vasodilatation (34). Thereby, the “coronary steal” phenomenon, inducing myocardial ischemia could be diminished. Inhalation of prostacyclin and NO has been shown to be effective in reducing increased pulmonary artery pressures, with only a minor effect on the systemic pressures (30). Inhalation of NO has been widely used when treating right heart dysfunction both after LVAD implantation (35) and before and after heart transplantation (33,
Decrease in the outflow impedance should be beneficial for the failing right ventricle and for the pulmonary flow.

**Inotropic drugs**

Inotropic support is administered to reverse the systolic dysfunction that commonly occurs following cardiac surgery with the use of CPB. Beta-adrenergic agonists stimulate the $\beta_{-1}$- and $\beta_{-2}$- receptors and via activation of adenylate cyclase, intracellular cyclic adenosine monophosphate (c-AMP) levels can be elevated. c-AMP is the important second messenger in the heart that modulates intracellular calcium through the activation of protein kinases (37, 38). Subsequent binding of intracellular calcium to troponin C, leads to actin-myosin crossbinding and myocardial contraction. c-AMP also affects the diastolic relaxation of the heart through phosphorylation of sites on the sarcoplasmatic reticulum (37). Epinephrine is often the mainstay inotropic agent administered to patients following cardiac surgery in many institutions. However a major drawback with adrenergic $\beta$-stimulation is the more or less pronounced increase in heart rate that could be negative for myocardial blood flow and even induce myocardial ischemia. Vatner and Baig (39) showed the importance of heart rate in determining the effects of inotropes on regional myocardial dysfunction. They could demonstrate that when the increase in heart rate was controlled during administration of inotropes, myocardial blood flow increased and the contractile function improved. Several clinical studies stress the importance of tachycardia-related ischemia and its link to myocardial infarction (40-42). Another adverse effect of the inotropic drugs is the possibility of inducing peripheral vasoconstriction.

**Inodilators**

During the past decade, the specific phosphodiesterase-III (PDE-III) inhibitors such as enoximone, piroximone, milrinone, and amrinone have been increasingly considered for use in this setting (4, 43). They act via a selective inhibition of phosphodiesterase fraction III, a c-AMP- specific PDE- enzyme. PDE-III inhibition results in an increased accumulation of intracellular c-AMP (44). In vascular smooth muscle cells, the increase in c-AMP facilitates calcium uptake by the sarcoplasmatic reticulum and decreases calcium available for contraction, which leads to vasodilatation. Platelet PDE III is potently inhibited by these drugs (45).
Agents that increase c-AMP in the myocardium can both increase the contraction and enhance the relaxation. In combination with dilatation of the vascular bed, it can lead to reduction in both after- and preload which should be favourable for the failing ventricle. PDE-III inhibitors have little or no effect on increase in heart rate (46). PDE-III inhibitors have been suggested to affect the β-adrenergic agonists in a synergistic manner (47).

Metabolic intervention
Metabolic intervention might reduce the duration and extent of myocardial stunning (20, 48, 49), and some authors have reported that metabolic intervention prior to administration of inotropic agents is beneficial for myocardial recovery (18, 50). At our institution intervention with glucose-insulin-potassium (GIK) is frequently used in patients with low cardiac output states. The administration of supraphysiological doses of insulin, 1 U/kg/hour, overcomes the stress induced insulin resistance in the myocardium, leading to a shift towards carbohydrate oxidation, which provides the heart with a better oxygen economy (21). High doses of insulin also induce a dilatation of the arterial vascular bed (51). These effects are beneficial for the failing left ventricle. Administration of amino acids, i.e. glutamate and aspartate, alone or in combination with GIK treatment can be used during the postischemic phase or when signs of myocardial ischemia exist (52).

II. Congestive heart failure

Pathophysiology of congestive heart failure
CHF is not a specific disease but rather a clinical syndrome of diverse etiologies. This syndrome is characterized by ventricular dysfunction leading to a decrease in cardiac output, neurohumoral activation, and a reduction in exercise capacity and longevity. There is also a “vicious circle” of blood flow maldistribution with hypoperfusion of vital organs. The most common underlying causes are ischemic heart disease and hypertension, resulting in ischemic dysfunction of the myocardium. Other important causes of CHF include valvular heart disease, primary myocardial disease (idiopathic, infiltrative, or inflammatory) and congenital cardiac malformations (7). The compensatory mechanisms in CHF involve both the myocardium and neurohumoral systems. Initial myocardial compensation consists of an increase in muscle mass. In states of myocardial hypertrophy, the number of capillaries per unit muscle mass decreases, making the diffusion distance for oxygen greater. The number of
mitochondria per unit muscle decreases, leading to a reduction in the energy production, but the number of myofibrils increases with an increase in energy demand (53). Reductions in c-AMP in combination with a decrease in ATP-ase activity result in abnormalities of systolic function. Prolongation of the action potential leads to a slowing down of biochemical pumps, that are necessary for calcium sequestration and, in turn, to a diastolic dysfunction (54). This implies both systolic and diastolic dysfunction (53). Over time, a ventricular dilatation occurs, with an increase in ventricular volume and wall stress (Law of Laplace) (55). To maintain cardiac output, the ventricle becomes dependent upon increased preload, while it becomes sensitive to variations in afterload (56), see Fig 3.

**Figure 3.** Schematic figure of left ventricular (LV) pressure volume loops, comparing the normal heart with that of a patient with end-stage cardiac failure. The heart with end-stage cardiac failure requires a greater preload for ejection, and its stroke volume (SV) at this preload is impaired. Small increases in LV afterload results in an increase in intracavity pressure, with a dramatic decrease in SV (arrow in dashed pressure volume loop), when compared to the maximum increase in intraventricular pressure rise in the normal heart. Redrawn form Dinardo J. Anesthesia for Cardiac Surgery (ed 2). New York, NY, Appleton and Lange, 1998, pp 201-239.

Neurohumoral compensatory mechanisms are caused by a reduction in tissue perfusion and involve the sympathetic nervous system and renin-angiotensin system (57). In an attempt to increase cardiac output via the Frank-Starling relationship, intravascular volume expansion and increased preload result from ADH and aldosterone secretion. Sympathetic stimulation leads to release of myocardial norepinephrine, which increases the contractility. The release of epinephrine supports both contractility and preload. Blood pressure is maintained by vasoconstriction caused by sympathetic stimulation and activation of the renin angiotensin system, see Fig 4. This is counteracted to some extent by the naturetic peptides, which
INTRODUCTION

promote diuresis and give rise to vasodilatation. All this compensatory activation of the sympathetic nervous system and the renin-angiotensin system might be beneficial in the short term, but in the chronic state it can be deleterious. The chronic sympathetic stimulation leads to a depletion of myocardial stores of norepinephrine (58). The increased serum level of catecholamines leads to a reduction in $\beta$-receptor density (59). This phenomenon, called down regulation, involves primarily $\beta_1$-receptors and not $\beta_2$-receptors (60). The normal ratio of $\beta_1/\beta_2$-receptors is 80/20, but is reduced in chronic heart failure to 60/40 (61). The degree of down regulation is directly related to the severity of ventricular dysfunction (60). This might reduce the effects of exogenous $\beta$-receptor stimulation (60). Growing evidence indicates that cytokines may play an important role in modulating the left ventricular dysfunction in patients with CHF (62). Increased levels of cytokines, such as IL-6, reflect worsening of the hemodynamic status and increasing heart failure symptoms (63).

Figure 4. Neurohumoral systems responsible for maintaining arterial blood pressure (ABP) through vasoconstriction by receptor stimulation: 1. Renin converts angiotensinogen to angiotensin I and angiotensin II. 2. Release of catecholamines from the adrenal medulla. 3. Release of vasopressin from the neurohypophysis. Abbreviations: $AT_1$, angiotensin receptor; $\alpha_1$ adrenergic receptor; AVP, arginine vasopressin; $V_1$, vasopressin receptor. Adapted from Mets B, et al. J Cardiothorac Vasc Anesth 1998;12:326-29.
Pharmacological treatment of congestive heart failure

The goal of the pharmacological therapy of CHF is to reduce mortality and morbidity, and to improve quality of life, by blocking the neurohumoral activation. Therapy with ACE inhibitors reduces both mortality and morbidity in patients with depressed LV systolic function (64). Inhibition of the chronic sympathetic stimulation with β-blockers is safe and well documented (65). The combined use of ACE inhibitors and β-blockers has improved functional status of the patients, improved LV function and reduced mortality and morbidity, more than each strategy alone (66). Spironolactone has, in addition to standard therapy, reduced mortality and morbidity in patients with CHF (67).

Indication for heart transplantation

Cardiac transplantation was introduced as a therapy for end-stage heart disease in 1967 (68). Since that time, there has been a marked improvement in the prognosis for patients after heart transplantation. The introduction of cyclosporine led to a reduction in rejection episodes and improvement in survival. These results have led to an expansion of this therapy (69, 70). Current selection criteria generally include New York Heart Association (NYHA) class IV heart failure with recurrent hospitalization despite aggressive medical therapy, and a risk for sudden death and with no firm contraindications to heart transplantation. Any systemic disease that will complicate recovery or reduce life expectancy contraindicates cardiac transplantation (71). Such conditions are immunodeficiency virus disease, degenerative neuromuscular disease, liver cirrhosis, severe renal failure, severe chronic obstructive pulmonary disease, and most cases of recent malignancy. Patients with a fixed high pulmonary vascular resistance are in general not candidates for heart transplantation. Diabetes mellitus, including insulin-dependent diabetes, does not appear to adversely affect the results after cardiac transplantation (72). However patients with diabetic end-organ dysfunction are excluded.
III. Mechanical circulatory support in the treatment of acute and chronic heart failure

Mechanical circulatory support (MCS) can be used for short- or long-term support. The incidence of MCS after open-heart surgery, is reported to be between 0.5% and 3% (1-3). The survival rate of patients with severe myocardial dysfunction treated with MCS after CPB has been reported to be from 30 to 60% (1, 73-75). The overall survival rate of patients treated with MCS for long-term use as a bridge to heart transplantation, is reported to be around 70 to 80% (76, 77).

The pump systems can be divided into five groups, based on different operating principles: 1) intra-aortic balloon pump, 2) centrifugal pumps, 3) displacement pumps, 4) axial blood flow pumps, and 5) total artificial hearts.

IABP as circulatory support for postcardiotomy heart failure

The IABP was first introduced in clinical practice in 1967 (78). The IABP affects cardiac function positively in several ways. It decreases myocardial oxygen demand (systolic unloading) and increases the supply of oxygen to the myocardium (diastolic augmentation) (79). This should favorably influence the myocardial oxygen/supply demand, which might improve the myocardial performance. The IABP does not, per se deliver energy to the systemic circulation and additional pharmacological support is therefore frequently required.

Centrifugal pumps

In the Bio-Medicus™ pump, the blood is accelerated in a pump house by centrifugal force and a nonpulsatile flow is generated. There is need for venous and arterial cannulae and an extracorporeal circuit. The tubings may be heparin coated and thereby systemic anticoagulation can be reduced. It can include an oxygenator and give full cardiopulmonary support. The system is flexible and can be used as an left ventricular assist device (LVAD), right ventricular assist device (RVAD), or biventricular assist device (BIVAD).

Displacement pumps

The principle is that blood enters the artificial pump from the heart and is ejected into the aorta by the movement of a diaphragm creating pressure variations in the pump. A pulsatile flow is created. They can be extracorporeal as the Thoratec™ and the AbioMed™, or
implantable as the Novacor™ and HeartMate™. Since we have used the HeartMate™ system it will be briefly reviewed in a following section.

The AbioMed BVS 5000™ is a pulsatile pump that can be used as LVAD, RVAD or BIVAD. The pump is extracorporeal, and functions entirely by gravitation. An arterial reservoir fills with blood, and a ventricular reservoir ejects blood (80).

**Axial blood flow pumps**

The principles of the axial flow pumps are based on the Hemopump™ (81), which is described in more detail in this thesis. A rotating impeller ejects blood from the LV to the systemic circulation with a continuous flow. An electromagnetic motor runs the impeller. The pumps are small, valveless, without compliance chamber. Compared to other MCS, they require less surgery for implantation. A variety of pumps for long-term use have been constructed, like the MicroMed DeBakey™, the HeartMate II™, and the Jarvik 2000 Heart™.

**Artificial hearts**

The CardioWest™ is a pulsatile biventricular cardiac replacement system. It is a displacement pump. It is a rigid polyurethane pump and contains a smooth, flexible polyurethane diaphragm that separates the blood and two air chambers. Mechanical valves provide unidirectional flow. Compressed air from an external drive console moves the diaphragm causing ejection of the blood (82).

**An axial flow pump for temporary use**

An axial flow pump, the Hemopump™, was developed by Richard Wampler (81, 83). In 1988, Frazier et al. (84) performed the first clinical application with this pump. They presented this system as an alternative to the traditional treatment for patients suffering from post-cardiotomy shock. A small impeller is mounted at the end of a metallic wire surrounded by a polyurethane sheet. A 21F tube is positioned so that its proximal part covers the impeller. The tube is placed across the aortic valves into the left ventricle. The impeller is positioned distal to the aortic valves, see Fig 5. At the other end of the wire, a magnet is attached, which is placed in an electromagnetic motor. The electromagnetic motor, located paracorporeally, is able to make the wire and impeller rotate. A purge set assembly provides blood seal integrity and hydrodynamic lubrication for the pump and wire, and a console provides power to the
pump and purge set. When the impeller rotates, blood will be sucked from the left ventricle and ejected into the ascending aorta with a continuous flow. The capacity of the pump is 3 to 4.5 L/min, depending on the type of device. The pump has the possibility to decompress the failing left ventricle, increase myocardial blood flow and maintain adequate systemic perfusion (85).

**Figure 5.** The axial flow pump for temporary use. The pump is inserted through a graft anastomosed to the ascending aorta, with the tube in the left ventricle (LV). Redrawn from Peterzén B, et al. Ann Thorac Surg 1996;62:495-500.
An implantable assist device as a bridge to heart transplantation

Our HeartMate™ program was initiated as a result of the need for a LVAD in patients who were deteriorating while on the waiting list for heart transplantation. In 1993 the University Hospitals in Linköping and Lund embarked on a cooperative HeartMate™ LVAD program. The patients in this region are transplanted in Lund, but treated before and after the transplantation in Linköping. The HeartMate™ was chosen mainly due to the low incidence of thromboembolic complications with the system (86).

The HeartMate™ is a displacement pump, and is implanted through a median sternotomy with the use of CPB. The pump can be placed intraabdominally or in a preperitoneal pocket (87, 88). The LVAD inflow cannula is brought through the diaphragm and plugged into a Teflon cuff in the left ventricular apex. An outflow graft is sutured to the proximal end of the ascending aorta (Fig 6). The driveline is tunneled to the lower left or right abdominal quadrant. Biological valves are present in the inflow and outflow parts to ensure unidirectional flow. When the LVAD is operational, the left atrium and the left ventricle act as conduits for blood which drains through the ventricular apex into the LVAD. The device can be operated in a fixed or automatic mode. In the latter mode, which is more physiological, the pump fills passively to 90% capacity and is then activated by an electrical motor or pneumatically. Blood is ejected by a pusher plate mechanism and the pump delivers a pulsatile flow into the ascending aorta and the systemic circulation. The pump made of titanium measures 11.2 cm x 4.0 cm, with a weight of 1 and 1.5 kg for the pneumatic and electrical devices, respectively. It is lined with a textured polyurethane surface, and a diaphragm divides the pump house into two halves. The pump delivers a stroke volume of 85 mL, and has a maximal flow capacity of 10 to 12 L/min. The textured surface reduces the need for long-term anticoagulation (89). The initial LVAD design was based on the pneumatic system that required recovering patients to push a console. The current electrical device with belt worn batteries is more versatile, and allows patients to leave the hospital. This might improve the quality of life until heart transplantation (90).

Due to the shortage of available donor organs for transplantation, the duration of pump support can be long (91). The drawbacks of current LVADs are limited durability and an increasing number of complications over time (76, 92).
Figure 6. Schematic view of the TCI-HeartMate left ventricular assist device plugged into the left ventricular apex, located either intraabdominally or in a preperitoneal pocket, and connected to the ascending aorta. The diagram shows the use of a battery pack, containing rechargeable belt worn batteries, providing 4 to 6 hours of charge. Redrawn from Thermo Cardiosystems Inc.
A novel axial flow pump for long-term support

Contemporary implantable LVADs have been beneficial for numerous patients with end stage heart disease. However the LVADs are relatively large and extensive surgery is required for the implantation. Potential lethal complications, infection and thromboembolism, can occur which limit the long-term use of these pumps (92). A new generation of implantable pumps has been designed, with the hope of reducing the incidence of serious complications and in order to facilitate the implantation (93). Axial flow pumps offer several theoretical advantages over conventional LVADs. They are small, the foreign material has less contact with blood, and they should not move relative to the surrounding tissue. The novel pumps´ function is principally similar to the above mentioned Hemopump™. A rotating impeller is located within an outer housing. Axial flow pumps do not require valves, an external vent, or an internal compliance chamber. The critical design issue is the long-term reliability of the impeller bearings. One of the new prototypes attempts to avoid this problem, by using an electromagnetic field around the impeller instead of mechanical bearings (94). This, however, adds complexity to the system (95). One potential risk is that these pumps are not fail-safe, because there are no valves in the system and mechanical failures result in the equivalent of severe aortic insufficiency (95).

The Jarvik 2000 Heart™ is one of these new implantable axial flow pumps. It can provide up to 6 L/minute of continuous blood flow, while maintaining some arterial-pressure pulsatility. The blood pump weighs around 90 g and is 2.5 cm in diameter. The hermetically sealed pump shell is constructed of titanium, and contains an electromagnetic direct-current motor. The electromagnetic motor spins the impeller at 8000 to 12,000 rpm, (93). Because the pump is so small, it can be placed within the left ventricle, eliminating the need for an inflow conduit (Fig 7, left and lower panel). The implantation in humans is performed via a left thoracotomy with partial CPB or without CPB. The outflow graft is sutured to the descending aorta. A modified method for externalizing the percutaneous power cable is under development, and this method may add additional protection against device related infection in patients undergoing long-term support (96), see Fig 7, right panel.
**Figure 7.** Left panel The Jarvik 2000 Heart™ comprising the pump in the left ventricle, a vascular graft anastomosed to the descending aorta, and a percutaneous electrical system. Right panel, The electrical cable is transmitted through the skin by way of a carbon pedestal screwed to the outer table of the skull to prevent movement. Redrawn from Westaby S, et al. J Thorac Cardiovasc Surg 1997;114:467-74.

IV. Right ventricular function during left ventricular assistance

A relatively new insight is that the right ventricle (RV) is more important in the context of perioperative cardiac failure than once thought (97-99). The RV is thin walled and irregular in shape. It has a high compliance and is distensible and can increase in size without any major change in its intracavity filling pressures. On the other hand, the muscle mass is less as compared to the LV, making it twice as sensitive as the LV to increases in outflow impedance. The RV systolic function has the same determinants as the LV function, namely preload, afterload, and contractility. The RV is perfused throughout the cardiac cycle, which makes it sensitive to systemic hypotension, which might cause ischemia, especially if the RV filling pressures are increased (RV perfusion pressure = diastolic aortic pressure - RVEDP).

The pericardium is important in mediating the direct interaction between the two ventricles. It eventually sets the limits for the dilatation of the heart and an increase in the RV volume increases the intrapericardial pressure and decreases the LV distensibility. A RV dilatation also causes a leftward shift of the intraventricular septum with a subsequent impairment of the LV distensibility.

The response of the RV during LVAD support includes a decrease in RV contractility due to a leftward septal shift. An impairment of the septal function occurs, due to a decreased contribution of the LV ventricular interdependence. The RV myocardial efficiency and power output is, however, maintained through a decrease in the RV outflow impedance and an increase in the right ventricular preload (100, 101). The RV free wall moves more and contributes more to the contraction of the right ventricle. The movement of the septum away from the right ventricular cavity and towards the LV is speculated to be one reason for RV failure with LVAD support. Other possible mechanisms for RV dysfunction during LVAD support might be increase in RV outflow impedance and decreased contractility due to RV ischemia. If pharmacological therapy is insufficient, a RVAD can be instituted. The prognosis for patients with RV dysfunction requiring RVAD is however poor (86, 102, 103).
V. Coronary artery bypass grafting on the beating heart with the use of an axial flow pump

Rationales for the procedure

There is a growing interest in performing coronary artery bypass grafting (CABG) on the beating heart, both as an open chest procedure for multiple grafting and as a minimally invasive operation (104-106). The rationales for performing CABG on the beating heart are several: to minimize the negative effects related to CPB, to avoid aortic manipulation, to perform a less-invasive procedure, to achieve quicker mobilization of the patients and thereby reduce the length of stay, and to decrease health care costs (107-109). Various stabilizers have been designed to facilitate the surgical procedure. The introduction of new surgical techniques has made it possible to perform multivessel CABG off pump, even on the posterior part of the heart (110). The technical development has even allowed video assisted bypass grafting on the beating heart (111).

Anesthetic considerations

The development of CABG on the beating heart has been extremely rapid. New techniques are frequently reported and the anesthetic management has also changed markedly. Due to the perioperative risks of systemic hypotension and of the induced regional myocardial ischemia with the possibility of cardiac dysfunction, an intense collaboration between the members in the team is mandatory.

Manipulations of the heart are required in order to obtain optimal exposure of target vessels. Therefore, the anesthesiologist has to face rapid changes in central hemodynamics (112). A continuous measurement of SvO\textsubscript{2} has been advocated by many as being a rapid and sensitive marker of critical impairment in the systemic circulation (113). During bypass surgery, the electrocardiographic vector is changed, thereby making ST-segment analysis less useful. Trendelburg position of the patient and liberal administration of fluids are used in an attempt to avoid systemic hypotension. The pharmacodynamics and pharmacokinetics of drugs administered are different compared to when CPB is used (114). Theoretically, this could allow for early extubation and mobilization. The sternotomy approach has been reported to cause less postoperative pain compared with thoracotomy (115).

The use of an axial flow pump in combination with a β-blocker can be looked upon as part of an evolutionary process in this field. In some patients with enlarged hearts, it can still be
difficult to perform bypass surgery on the posterior part of the heart. Other patients do not tolerate manipulation of the heart well enough to perform complete revascularization. In this situation, an axial flow pump used as a LVAD can be advantageous. It decompresses the LV and allows easier manipulation of the heart. The introduction of mechanical myocardial immobilizers has reduced the need for pharmacological adjuvants. β-blockers might still be useful in order to minimize myocardial ischemia (116), the risk of plaque rupture (117) and reperfusion injury (118).
AIMS OF THE STUDY

• Assess a treatment program for patients in the ICU with a temporary minimally invasive axial flow pump for postcardiotomy heart failure.

• Outline the anesthetic principles, including pharmacological therapy, and hemodynamic monitoring of patients undergoing CABG with the use of an axial flow pump.

• Assess the utility of a LVAD program as a bridge to heart transplantation in a non-transplanting center, and outline the perioperative surveillance and treatment.

• Describe the intermediate- and long-term follow-up in patients treated with an implantable LVAD.

• Evaluate the hemodynamic effects of a novel implantable axial flow pump in an acute heart failure model.
MATERIAL AND METHODS

Patients

The studies I to IV were approved by the Human Ethics Committee of the University Hospital, Linköping.

In study I, the treatment of 24 patients with an axial flow pump, Hemopump (DLP/Medtronic, Inc., Grand Rapids, MI), due to post cardiotomy heart failure is described. In addition to the pump therapy, the patients received pharmacological and metabolic treatment. The same patients have previously been reported by Lönn et al. (119), where the surgical considerations during axial flow pump therapy are described.

In study II, the clinical protocol for 17 patients with stable angina pectoris who had CABG performed on the beating heart with the use the Hemopump™, and a short-acting $\beta$-blocker, as alternative to CPB is reported. Five patients were presented by Lönn et al (120) in a pilot study examining the safety of the use of this technique. Nine of the 17 patients were included in a prospective randomized study comparing this technique with CPB (121).

In study III, 10 patients with end stage heart disease, due to either dilated cardiomyopathy or ischemic heart disease, underwent implantation of a left ventricular assist device, HeartMate TCI (Thermo Cardiosystems Inc., Woburn, MA), as a bridge to heart transplantation. This study is mainly focused on perioperative treatment, but also reports complications until transplantation. One patient was treated with the Hemopump™ due to post cardiotomy heart failure prior to the HeartMate™ therapy, and this is described in paper I.

In study IV, the intermediate or long-term follow-up of seven of the patients with the longest treatment durations with the HeartMate™, is described, with special emphasis on the detection and quantification of inflow valve leakage.

Animals

In study V, five Swedish native calves, on average 2.5 months of age, were studied in an acute heart failure model to evaluate a novel implantable axial flow pump, the Jarvik 2000 Heart (Jarvik Heart Inc., New York, NY). The study was approved by the Animal Ethics Committee, University Hospital, Linköping.

Invasive measurements of central hemodynamics

In the studies performed in the perioperative or intensive care setting (papers I-III), all patients received a radial arterial catheter for continuous monitoring of arterial blood
pressure. During pump therapy, it was preferable to perform this monitoring from the femoral artery (paper I). All patients also had a triple lumen central venous catheter inserted via the internal jugular vein. A balloon-tipped pulmonary artery (PA) catheter with fast response thermistor and continuous measurements of mixed venous oxygen saturation (Baxter Healthcare, Irvine CA), was placed in 11 patients in paper I, in 9 patients in paper II, and in all patients in paper III. A conventional balloon-tipped PA catheter (Arrow Int., Inc., Reading, PA) was used in 13 patients in paper I. Furthermore, a surgically placed PA catheter was placed in eight patients in Paper II.

The patients described in paper IV, who were studied during long-term follow-up in order to evaluate their inflow valve leakage, had a conventional PA catheter and a radial artery catheter.

In the animal experiments in paper V, blood pressure was monitored from the common carotid artery. All animals had a conventional central venous catheter via the external jugular vein.

The following variables were measured or calculated; heart rate (HR), stroke volume (SV), systolic (SAP), diastolic (DAP) and mean (MAP) arterial blood pressures, mean pulmonary arterial blood pressure (PAPm), pulmonary capillary wedge pressure (PCWP), central venous pressure (CVP), systemic vascular resistance index (SVRI) and pulmonary vascular resistance index (PVRI). Cardiac output (CO) and cardiac index (CI) were measured during the whole respiratory cycle (means of triplicate measurements were used).

**Noninvasive measurement of cardiac function**

Transthoracic (2.5 MHz probe) and transesophageal echocardiography with monoplane, biplane or multiplane 5 MHz probes was performed using a VingMed 750 or 850 (Ving Med A/S, Horten, Norway) echocardiograph.

In paper I, echocardiography was used postoperatively to verify the decompression of the left ventricle (LV), for the assessment of the function of the right ventricle (RV), and also for identification of pericardial effusion. During weaning from the axial flow pump, echocardiography was used to assess the left and right heart function.
In paper III, echocardiography was performed after induction of anesthesia to assess shunts at the atrial level, LV dimensions and motion. The RV dimensions and function, aortic valve and atrio-ventricular (A-V) valve regurgitation, ascending aortic dimensions and signs of calcification and LV mural thrombus were investigated according to recommendations by Savage et al. (122). Serial evaluation, from preoperative to the first days postoperatively of RV end-diastolic and end-systolic dimensions was performed by echocardiography, at baseline from the transthoracic apical 4-chamber view, and on the other occasions from the transesophageal 4-chamber view. The fractional shortening of these linear measurements was calculated. The largest LV inner dimensions (preoperatively end diastolic) were measured in the same way.

Analyses of Doppler flow velocities and velocity-time integrals were performed for the determinations of pressures in the pulmonary circulation and estimation of the intracardiac flows (papers III and IV).

For the experimental animal study, the Ving Med™ system 5, with a 2.5 MHz epicardial probe was used for evaluation of the unloading effect of the LVAD.

**Invasive measurements of right heart function (papers I-III)**

Invasive measurements of the RV function were obtained with a fast-response thermistor catheter (Baxter, Healthcare, Irvine, CA). This catheter has a mounted thermistor with a response time of 50 to 100 msec, which makes it possible to measure beat-to-beat temperature variations and thus calculate the RV ejection fraction (RVEF) using the indicator dilution technique. Indirect calculations of RV end-diastolic volume (RVEDV) and RV end-systolic volume (RVESV) can also be obtained. The fast response thermistor gives a thermodilution curve with characteristic plateaus, representing beat-to-beat changes in temperature, which are synchronized with the R-waves obtained from ECG electrodes placed in the catheter, identifying the actual ventricular contractions. The RVEF is defined as the percentage of blood in the ventricle at end-diastole that is ejected at end-systole. This is calculated by measuring the incoming blood temperature ($T_b$) and two ejected blood temperatures ($T_1$ and $T_2$), using the equation $\text{RVEF} = 1 - (T_b - T_2) / (T_b - T_1)$. From the thermodilution measurements further volumes can be calculated: Stroke volume (SV) = CO / HR. Since $\text{RVEF} = \text{SV} / \text{RVEDV}$ it follows that $\text{RVEDV} = \text{SV} / \text{RVEF}$ and $\text{RVESV} = \text{RVEDV} - \text{SV}$. 
Measurements of peripheral circulation (paper V)

Femoral artery blood flow measurement was performed using a transit time Doppler flow probe (CM 2000, CardioMed, Norway). The output data were displayed as a pulsatile flow profile, with the calculated average blood flow expressed in mL/min. The flow pattern was recorded during on-off testing with the pump.

Laser Doppler perfusion imaging (LDPI) (PIM 1.0, Lisca AB, Linköping, Sweden) was used for mapping microvascular perfusion in the skeletal muscle. A low-power (1mW) helium-neon (He-Ne) laser beam was scanned over the tissue and a color-coded image was generated to show the spatial distribution of the perfusion. An area measuring approximately 3 x 3 cm of the vastus medialis muscle was mapped.

Physical exercise tests (paper IV)

Exercise tests were performed using bicycle ergometer tests or treadmill tests. Gas exchange measurements were made with an argon dilution technique using a mass spectrometer (AMIS 2000, Innovision A/S, Odense, Denmark) or with a Medgraphics’ CPX system (Medical Graphics, Co., St Paul; MN). Oxygen uptake (VO2), carbon dioxide elimination (VCO2) and pulmonary ventilation (VE) were measured continuously, respiratory exchange ratio (RER), and the quotients VE/VO2 and VE/VCO2 were calculated.

Blood gas- and blood chemistry analyses (papers I to V)

Blood gases were analyzed using an ABL 4 (Radiometer, Copenhagen, Denmark) or BGE (ILS Laboritories, Milano, Italy). Measurements of hemoglobin (Hb) levels and oxygen saturation were performed using an OSM 3 (Radiometer). In paper IV, the arterio-venous (A-V) oxygen difference was calculated using the following formula: A-V O2 difference = 1.38 x Hb-concentration x (A-V O2 saturation).

The enzymes alanine amino tranferase (ALT), aspartate amino transferase (AST) and troponin-T (TRP-T) were measured the day before surgery, and at 12 and 24 hours after surgery. Serum creatinine values were measured at the same times (paper II).
**Pharmacological and metabolic interventions**

The aim of the pharmacological interventions in papers I, III and V was to support the RV function and to achieve low pulmonary vascular resistance. Inotropic agents epinephrine and dobutamine were used in combination with the PDE-III inhibitors amrinone and milrinone. As low doses as possible were used in order to minimize adverse reactions to the individual drugs, and also in order to achieve a decrease in the RV outflow impedance. Nitroglycerine and sodium nitroprusside were used for vasodilatation. Nitroglycerin was also used for coronary vasodilatation. To counteract the low arterial blood pressures, when terminating the CPB (papers I and III), vasoconstrictors (norepinephrine and angiotensin II) were administered through a left atrial line. Four patients in paper III had administration of prostaglandin E1 (PGE1) in order to relieve RV failure due to increased pulmonary vascular resistance. Conventional treatment with vasodilators and PDE-III inhibitors were not sufficient in these patients. The pharmacological therapy was continued for 2 to 5 days postoperatively.

The adjuvant treatment with esmolol hydrochloride was started with a bolus dose of 1 mg/kg, followed by a continuous infusion of 300 to 400 µg/kg/min (paper II). The infusion rate was increased stepwise after further bolus doses of 0.5 mg/kg until the surgeon was satisfied with the reduced motion of the heart. During surgery, phenylephrine was administered if mean blood pressure decreased below 45 mm Hg with a concomitant decrease in mixed venous oxygen saturation below 50%.

In the animal study, paper V, lidocaine was given to decrease the risk for malignant arrhythmia’s during coring of the left ventricular apex. The drug was administered topically to the apex of the heart, supplemented with an i.v. bolus dose and continuous infusion. A bolus dose of amiodarone was also given. A continuous infusion of isoprenaline was used for pulmonary vasodilatation. A median of 575 µg/kg/min (range, 0 to 1000 µg/kg/min) of esmolol was administered in addition to coronary ligation for the heart failure model.

All patients except one (paper I), received metabolic support with glucose-insulin-potassium. Eight patients received a combination of glucose-insulin-potassium and glutamate. Two patients received a combination of glucose-insulin-potassium, glutamate, and aspartate, and one patient had glutamate only.
STUDY PROTOCOLS

Paper I

The patients had severe LV failure, isolated or in combination with ischemia, RV failure, or both. They all had shown an insufficient or adverse response to pharmacological therapy. When a patient could not be weaned from CPB at the first attempt, an additional reperfusion period was employed. A complete investigation of grafts and anastomoses was performed. The axial flow pump, Hemopump™ (HP), was inserted when weaning could not be accomplished on the second attempt, or if the heart failed after termination of CPB despite pharmacological and metabolic therapy. The time points of the hemodynamic measurements (bottom line), intervention with the HP, pharmacological and metabolic support are depicted in Figure 8. If recovery of the myocardial function was observed, after 24 to 48 hours, a gradual weaning from the pump was conducted.

Figure 8. Illustration of the perioperative care of patients treated with an axial flow pump due to postcardiotomy heart failure.

Paper II

A schematic illustration of the study design is presented in Figure 9. With the axial flow pump properly located in the LV and on full speed, the esmolol infusion was started. The bypass surgery was performed when the LV was decompressed and the motion of the heart was decreased. The esmolol infusion was stopped when the last anastomosis was almost completed. The HP was continued for 15 to 20 min after termination of the β-blockade. Hemodynamic monitoring was continued until the morning after surgery (bottom line).
Figure 9. Clinical protocol for CABG performed on the beating heart with an axial flow pump and a short-acting β-blocker.

Paper III
All patients were treated in the ICU before LVAD implantation. An illustration of the perioperative care is shown in Figure 10. Vasoactive drugs were administered in the ICU before the implantation, and continued until hemodynamic stabilization after LVAD implantation. Hemodynamic measurements (bottom line) were performed before and up to 2 to 5 days after LVAD implantation. Mobilization and enteral nutrition were started as soon as possible according to the clinical status of the patients.

Figure 10. Study design for the perioperative care of HeartMate™ treated patients.
Paper IV
Seven patients had submaximal and maximal exercise tests 3 to 4 months following the LVAD implantation. Three patients did not have any more exercise tests before transplantation as depicted in Figure 11. Four patients were followed 9 to 18 months postimplant. Submaximal and maximal exercise tests and echocardiography were performed to determine changes in exercise capacity and native heart function for patients with and without device complications.

**Figure 11. Illustration of the intermediate- and long-term follow-up of LVAD treated patients.**

Paper V
Figure 12 illustrates the experimental procedure with the Jarvik 2000 Heart™. After instrumentation and LVAD implantation, heart failure was induced. The pump was turned on at the minimal speed setting of 8000 rpm, and the hemodynamic changes were observed at various pump speeds as depicted in Figure 12. During the test period, all medications and fluid infusion rates remained constant.
Statistics and methodological considerations

The studies presented in the thesis (papers I-IV) were done during the process of treating critically ill patients. We attempted to follow an intended monitoring protocol and plan for data collection. It was, however, not always possible to collect all relevant data during these conditions, especially not during emergency situations where all efforts were focused on keeping the patients alive (papers I and III). All clinical studies (papers I-IV) were open, and without controls. These circumstances with its inherent methodological shortcomings could limit the scientific value of our studies. Potential sources of the variability concern measuring and collecting the data (papers I and III), using different devices (papers III and IV), preferences and approaches of the surgical teams providing the treatment (papers I-V).

Besides studies in humans, one publication describes a study done in the calf (paper V). This animal was chosen due to our and other’s previous experience with this model in the setting of MCS evaluation (123). Should other animals have been used, results may have been different. An animal model that properly reflects the pathophysiology of the human heart does not exist.

The patient and animal materials are limited and therefore the results and conclusions based on them have to be carefully interpreted. However, results from the studies could be used as a basis for a critical clinical judgement and planing of future work.
Descriptive statistics were performed to summarize the results of the different treatments. In methodological terms, these tasks were performed using \( t \)-tests and by calculating distributions of all the variables.

Significance testing was the main approach used when analyzing the data. The motivation is following: if we have a basic knowledge of the underlying distribution of a variable, then we can make predictions about how this particular statistic will behave in repeated samples of equal size. One important assumption made is that the variables are normally distributed. That means that in repeated samples of equal size, the standardized means will be distributed following the \( t \) distribution (with a particular mean and variance).

The \( t \)-test is the most commonly used method to evaluate the differences in means between patient variables and groups. The \( t \)-test is often used for large data sets, but can also be used if the sample sizes are small, as long as the variables are normally distributed within each group, and the variation of scores in the two groups is not reliably different (124).

The patients material was normally distributed and, therefore, parametric tests of significance were found applicable (papers I, II, III). In the study with 7 patients only (paper IV) we have carried out a descriptive study based on the median and range values. It should be noted that when sample sizes are small, nonparametric methods could be more appropriate. However, the tests of significance of many of the nonparametric statistics are also based on asymptotic (large sample) theory.

In this thesis the analyses were carried out with consideration to the sample size and to the scopes of the research as described in the following subchapters corresponding to the articles. The statistical package used was SPSS (124).
RESULTS

Review of the papers

1 Postoperative management of patients treated with Hemopump support after coronary artery bypass grafting

Fourteen patients (58%) survived and 10 died. Eight of the nonsurvivors had severe biventricular failure, and the right ventricle (RV) was not able to deliver sufficient blood to the left ventricle (LV) and thereby to the axial flow pump. Two patients died of LV failure despite adequate pump support and pharmacological therapy. Seven of the nonsurvivors died in the OR, and 3 in the ICU. All patients weaned from the pump support were discharged from the hospital.

During the first 12 to 24 hours after Hemopump™ (HP) insertion, with optimal pharmacological therapy, an entirely nonpulsatile arterial blood pressure curve was observed (Fig 13). The unloading of the LV was effective which could be illustrated with echocardiography, showing that the aortic cusps were closed around the HP cannula. The relatively low LV filling pressures during HP treatment also suggested a correct unloading of the LV. These findings are similar to those reported by Meyns et al (85).

Figure 13. Illustration of the almost non-pulsatile arterial blood pressure recording during Hemopump™ support in one patient. A pulsatile flow is observed from the right heart. The following are shown, from top to bottom: ECG, ABP, as the mean arterial blood pressure; CVP, central venous pressure; PAP pulmonary artery blood pressures; SpO₂, arterial oxygen saturation by pulsoximetry.
It was possible to give catecholamines in rather low doses and mean arterial blood pressure was maintained by infusion of angiotensin II. A combination of other vasodilators and vasoconstrictors was also used to balance the circulation. In this way, we could avoid heavy administration of cathecolamines. The pump was afterload sensitive and performed better when the peripheral resistance was low as reported earlier (74, 84). Thus, we deliberately kept the systemic vascular resistance index (SVRI) in the lower range. On line mixed venous oxygen saturation (SVO$_2$) measurement, mean arterial blood pressure (MAP) and diuresis were the most effective variables to guide drug and fluid therapy.

We gave metabolic support to all patients, since it has been discussed as a beneficial therapy (49).

The majority of survivors started to show signs of recovery of the LV function within 24 to 48 hours. Recovery was indicated by an increase in pulsatile activity on the arterial pressure recording. A gradual weaning from the pump over 6 to 8 hours was then performed.

The HP was inserted in most patients when they were still on CPB. Therefore the cardiac index (CI) prior to pump insertion was relatively high. During pump treatment, there was an increase in CI, with further improvement after removal of the pump. The average SvO$_2$ value was low before pump insertion, but showed an increase during pump therapy (Fig 14).

**Figure 14.** Values for cardiac index (CI) and mixed venous oxygen saturation (SvO$_2$) before, during and after Hemopump™ (HP) support. Data are shown as mean ± SD; * = p < 0.05 Abbreviations: ICU: intensive care unit; pre– and post wean, before- and after weaning from the pump support.
Both MAP and SVRI values were low before pump insertion (Fig 15). During pump treatment, the MAP increased over time. Low SVRI levels were noticed before, during, and after the pump support.

The right ventricular ejection fraction (RVEF) had a tendency to rise throughout the treatment.

![Image](image_url)

**Figure 15.** Values for mean arterial blood pressure (MAP) and systemic vascular resistance index (SVRI) before, during and after Hemopump support. Data are shown as mean ± SD. For abbreviations see Fig 14.

II Anesthetic management of patients undergoing coronary artery bypass grafting with the use of an axial flow pump and a short-acting β-blocker

When this study was carried out, we had no stabilizers for local myocardial immobilization. To allow precise surgery, the unloading of the LV by the Hemopump™ (HP) had to be combined with esmolol to decrease the contractility and motion of the heart.

Times of surgery, anesthesia and of HP support averaged 164, 231, and 61 minutes, respectively. No device-related complications were observed. The patients received a mean of 1.6 grafts (range, 1 to 3). All patients except one received left mammary artery grafts, and three patients received right mammary artery grafts.

The average esmolol dose was 729 µg/kg/min. During surgery, the average dose of nitroglycerin was 0.9 µg/kg/min. The average heparin dose was 9,352 U. After pump removal, the heparin effect was reversed with protamin and in the ICU all patients had regained their preoperative activated coagulation time (ACT) levels.
Intra- and postoperative blood losses were moderate, in average 365 mL (range, 100 to 700 mL) and 734 mL (range, 300 to 1270 mL), respectively. The majority of the blood loss was autotransfused. One patient received two units of blood due to low hematocrit values before and during surgery. No other patients required homologous transfusion.
All patients were separated from HP support without the need for inotropic support. One patient received metabolic intervention with glucose and insulin.

**Hemodynamic response**

Fig 16 shows a significant fall in MAP during maximal HP support and esmolol infusion, but with normalization after surgery. Heart rate (HR) remained unchanged until arrival in the ICU, when it increased significantly.
No significant change in CI was observed during the procedure. The SvO$_2$ fell significantly during maximal HP support and esmolol infusion. Except for three, all patients had values above 60% at this measurement. After surgery all patients had normal SvO$_2$ values. The pulmonary capillary wedge pressure (PCWP) remained unchanged compared with the baseline measurement.
No significant changes in systemic or pulmonary vascular resistance index (SVRI, PVRI) were observed compared with baseline measurements. A significant decrease in RVEF during bypass surgery was observed, with an increase after removal of the HP. A non-significant increase in central venous pressure was observed during HP support and maximal esmolol infusion.
The body temperature was decreased during bypass surgery. One patient showed ischemia on the ST analysis during surgery.

**Postoperative period**
The average time on the ventilator was 6.3 hours (range, 3 to 16 hours) and average stay in the ICU and total hospital stay were on average 1.2 days (range, 1 to 3 days) and 9.9 days (range, 6 to 23 days), respectively.
One patient had to be readmitted to the ICU three days after the bypass operation due to a septic episode originating from the urinary tract. The patient needed ventilator treatment for another 108 hours, and this second ICU stay including sepsis therapy was 7 days long. Taking in account this additional ICU stay, the average time on ventilator and ICU stay for the 17 patients will change to 12.6 hours, and 1.7 days, respectively. The range for ventilator treatment and ICU stay will change to 3 to 114 hours, and 1 to 7 days, respectively. Regarding
this patient as an outlier, and calculating median values, times on ventilator and ICU stays for the 17 patients are similar even if this second ICU period is included. The total hospital stay remains unchanged.

The levels of the enzymes aspartate aminotransferase (AST), alanine aminotransferase (ALT), and troponin-T were low postoperatively, but with a significant increase in AST. One patient had a non-Q wave myocardial infarction, while all other patients had normal ECGs. All patients survived and were discharged from the hospital.

Figure 16. Hemodynamic response before, during and after bypass surgery with the combined use of an axial flow pump and a β-blocker. Measurement points: Baseline = before surgery; HP = during maximal Hemopump (HP) support and with maximal esmolol dose; 30 min = 30 min after removal of the HP; ICU = 6 hours after arrival in intensive care unit (ICU); First postop day = the morning after surgery. Filled squares represent heart rate (HR), and open circles represent mean arterial blood pressure (MAP).
III  Management of patients with end-stage heart disease treated with an implantable left ventricular assist device in a non-transplanting center

Nine patients completed the HeartMate™ (HM) therapy and were transplanted. One patient died after 78 days of ICU treatment, as a result of an endovascular infection with intractable sepsis.

The total surgical and anesthesia times for the primary HM operation were on average 402 ± 172 min and 420 ± 137 min. The aortic cross clamp and CPB times averaged 39 ± 12 min and 126 ± 23 min, respectively. Median time on the ventilator was 6 days (range, 1 to 78 days), and the median time in the ICU was 14 days (range, 6 to 78 days). The pharmacological support averaged 5 days (range, 2.5 to 13 days).

The main hemodynamic findings are illustrated in Fig 17. CI increased during the preoperative ICU stay, with a further improvement after implantation of the left ventricular assist device (LVAD). The SvO₂ showed the same pattern. The PCWP and mean pulmonary artery pressure (PAPm) both decreased after pump implantation (Fig 16).

![Fig 17. Changes in cardiac index (CI), mixed venous oxygen saturation (SvO₂), mean arterial pulmonary blood pressure (PAPm) and pulmonary capillary wedge pressure (PCWP). Values are presented as mean ± SD. * = p < 0.05. Measurement points: 1 = in the intensive care unit (ICU) the day before pump implantation; 2 = in the operating room before surgery; 3 = after pump implantation and hemodynamic stabilization in the operating room; 4 = 24 hours after pump implantation in the ICU; 5 = 2 to 5 days after surgery, before removal of the pulmonary artery catheter.](image-url)
The left ventricular end diastolic dimension (LVDD) measured using echocardiography was highly elevated before pump implantation. Immediately postoperatively, when the LV was unloaded by the LVAD, the LV dimensions decreased. The RV diameter was moderately increased preoperatively, and the RV dilatation increased postoperatively, see Fig 18.

The right ventricle transverse diameter fractional shortening (RV FS) remained virtually constant during the observation period (Fig 18).

*Figure18. Echocardiographic changes in the left ventricular diastolic dimensions (LVDD), represented by open squares. Filled circles, upper part, represent the right ventricular diastolic dimensions (RVDD). The right ventricular transverse diameter fractional shortening (RV FS) remained principally unchanged over the period (lower part). Values are presented as mean ± SD. * = p < 0.05. For measurement points, see Fig 17.*

A short period of RV failure occurred in two patients after weaning from CPB. Transesophageal echocardiography revealed a decrease in the motion of the free wall of the RV, and that the septum was bulging into the LV. CPB was restarted with 20 minutes of reperfusion, while the pulmonary vasodilator therapy was optimized.
The dominating complications were infections, neurologic disturbances and LVAD dysfunction (Table 1). Device related infections varied from local drive line infections, requiring local treatment, to episodes of fever and abscesses in the pump pocket with positive blood cultures, requiring long-term antibiotic therapy. Two patients had transient neurologic disturbances in the postoperative period, but without sequelae. Two patients had embolic injuries to the brain, and one of these patients had minor neurologic disturbances after the transplantation. Two patients had a total of three episodes of inflow valve insufficiency. One of these patients had a pump replacement and another patient had pump replacement due to intraabdominal fracture of the driveline.

**Complications During Left Ventricular Assist Device Therapy**

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<tr>
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<th>Days after LVAD</th>
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<tr>
<td>Early complications*</td>
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<tr>
<td>Intraoperative right-sided heart failure</td>
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<tr>
<td>Reoperation for bleeding</td>
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<tr>
<td>Bacterial pneumonia</td>
<td>2</td>
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<tr>
<td>Transitory neurologic complication</td>
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<td>2 and 7</td>
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<td>Late complications*</td>
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<tr>
<td>Drive-line infection</td>
<td>2</td>
<td>96 and 245</td>
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<tr>
<td>LVAD pocket abscess</td>
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<td>Noted at Htx</td>
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<tr>
<td>Inflow conduit bleeding requiring exploration</td>
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<td>97</td>
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<tr>
<td>Cerebellar embolism requiring neurosurgery</td>
<td>1</td>
<td>96</td>
</tr>
<tr>
<td>Drive-line fracture requiring LVAD exchange</td>
<td>1</td>
<td>310</td>
</tr>
<tr>
<td>LVAD inflow valve incompetence requiring LVAD exchange</td>
<td>1</td>
<td>232</td>
</tr>
<tr>
<td>LVAD inflow valve incompetence not requiring LVAD exchange</td>
<td>2</td>
<td>181 and 226</td>
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<td>Endovascular pump infection with septicemia, multiple organ failure and death</td>
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<td>78</td>
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<tr>
<td>Multiple emboli</td>
<td>1</td>
<td>564</td>
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<tr>
<td>Incisional diaphragmatic hernia</td>
<td>1</td>
<td>After Htx</td>
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*Complications occurring intraoperatively or in the intensive care unit.

*Complications occurring 3 months or more after implantation.

The median time on HM support was 241 days (range, 56 to 873 days), with outpatient treatment of 4 patients for a median time of 414 days (range, 165 to 584 days). Patients with the pneumatic system had shorter treatment times as compared to patients with the electrical device, due to longer waiting times in the latter part of the study period (Fig 19).
RESULTS

Figure 19. Time on the left ventricular assist device. Patient 5 had a pneumatic pump changed to an electrical pump after 310 days, and patient 6 had an electrical pump exchange after 232 days.

IV Long term follow-up of patients treated with an implantable left ventricular assist device as an extended bridge to heart transplantation

The median time on HeartMate™ (HM) therapy for seven patients studied was 462 days (range, 93 to 873 days). All patients had submaximal and maximal exercise tests at 3 to 4 months after LVAD implantation. The peak oxygen consumption showed a wide range at this measurement point, median 17.5 mL/kg/min (range, 12 to 37 mL/kg/min). All patients exercised to their cardiovascularly limited performance capacity, as reflected by high respiratory exchange ratios, median 1.13 (range, 1.04 to 1.16). The ventilatory equivalent for oxygen (VE/VO2) was moderately or highly elevated in all except one patient, with a median value of 29 (range, 23 to 40) at submaximal steady state exercise. A wide variation in maximal native heart rates was observed from 96 to 185 beats/min. The HM flow increased by about 1 L/min during maximal exercise, compared with the submaximal work loads.

Three inflow valve leaks occurred in two patients 181, 214 and 226 days, respectively, after LVAD implantation. One of these pumps had to be replaced due to severe cardiac deterioration.

These two patients and two others were followed with exercise tests and echocardiography 9 to 18 months post implant. In patients with normal HM function, the peak oxygen consump-
tion and maximal workload increased between the 3 to 4 months and the latest follow-up. The left ventricular inner diastolic dimensions decreased. The two patients with inflow valve incompetence showed a decline in peak oxygen consumption and maximal workload, and the left ventricular inner diastolic dimension increased (Fig 20).

![VO$_2$ max](image)

![LVID ed](image)

**Figure 20.** Changes in peak oxygen consumption (VO$_2$ max) at maximal exercise tests in two patients without (open symbols) and two patients with inflow valve incompetence (filled symbols) (upper panel). Changes in left ventricular inner end diastolic dimension (LVID ed) over the same time period for the same patients (lower panel).

When suspicion of inflow valve leak occurred, the diagnosis was confirmed by echocardiography. Invasive measurements were used in order to quantify the degree of the backflow. The pump was set at various speeds in fixed mode or turned off. One patient had had a regurgitant volume of 33 to 38 mL/stroke and because of signs of severe cardiac decompensation, the pump was exchanged. When this patient later suffered a second valve leak, there was less hemodynamic deterioration and this pump could be retained until
transplantation. Invasive and noninvasive data indicated an insufficient systemic circulation, which tended to be more pronounced at lower HM rates, probably as a result of a positive net effect of the pump, despite a significant regurgitation, 23 to 29 mL/stroke. At the lowest pump rate, 20 strokes/min, there were obvious signs of insufficient native cardiac output with low pulmonary velocity time integral (VTI) and sub aortic VTI with increases in tricuspid insufficiency velocities.

In the second patient, the regurgitant stroke volume was 31 mL. The native heart function was evaluated with the pump turned off. Increases in heart rate, and pulmonary capillary wedge pressure with concomitant increases in A-V O$_2$ differences and low SV indicated insufficient native heart function. At rest, the echocardiographic left ventricular end diastolic dimension increased and the subvalvular VTI increased over time. However, this patient exercised at 80 Watts and not changing the pump but await heart transplantation was believed to be justified.

V  Hemodynamic evaluation of the Jarvik 2000 Heart$^{TM}$ during heart failure in a calf model

Fig 21 shows the main central hemodynamic findings in the acute heart failure model with the pump running at different speed. The cardiac index increased from baseline heart failure measurement, with stepwise increases of the pump speed. A decrease towards the baseline value was observed when the pump was turned off. The diastolic and mean arterial blood pressure values increased from baseline to the maximal pump speed, 12 000 rpm. The systolic blood pressure remained fairly constant during the study period. With the pump turned off, the diastolic and mean blood pressures decreased, but with a slight increase in the systolic pressure. The femoral artery flow followed the increases in pump speed. The left atrial pressure decreased with increased pump support. However, when the pump was turned off, it returned to baseline level.
**Figure 21.** The hemodynamic changes from baseline of acute heart failure, with variable pump support, and finally with the pump turned off. From above are illustrated changes in cardiac index (CI), arterial blood pressures measured as systolic, diastolic and mean blood pressure, and femoral artery flow. At the bottom, the left atrial pressure is shown. * Significant compared to baseline measurement.
Echocardiography showed a significant reduction in the left ventricular dimensions in conjunction with on-off testing of the pump. The flows in the femoral artery with pump support showed that some pulsatility was maintained but with a small pulse pressure. When the pump was turned off, the pulse amplitude increased but the mean blood flow decreased (Fig 22).

Peripheral muscle perfusion measured by laser-Doppler imaging was rather low and constant throughout the experiment. Any variations changed in parallel with the femoral blood flow.

**Figure 22.** The flows in the femoral artery during on-off tests with the pump. With the pump running, the femoral artery flow showed only small pulsations. When the pump was turned off the pulse amplitude increased and the mean blood flow decreased.
DISCUSSION

Post cardiotomy heart failure

This study started in 1991 with the use of a temporary axial blood flow pump as an alternative to the traditional treatment with the intra-aortic balloon pump (IABP). We were attracted by the idea of supporting the heart without the need for heavy inotropic support and thereby high metabolic demand. Intraventricular unloading reduces wall tension and decreases myocardial oxygen demand (125). Experimental studies with the axial flow pump, the Hemopump™ (HP), had shown an increase of the myocardial perfusion to the left ventricle, with a decrease in myocardial oxygen consumption and positive effects on the myocardial metabolism (126, 127). A reduction in the area of myocardial damage during acute myocardial infarction in animals models had also been demonstrated (127, 128).

We found it possible to treat patients with postcardiotomy heart failure. Thirteen of 17 patients treated in the ICU had various degrees of recovery of left ventricular function. They survived without signs of vital-organ failure and were discharged from hospital. One patient without signs of myocardial recovery after 3 days received a HeartMate™ left ventricular assist device and then underwent successful transplantation after 3 months.

Inotropic drugs were required in only low to moderate doses and the principles of pharmacological therapy were to optimize pulmonary and systemic vascular resistances. The axial flow pump performs better when the systemic vascular resistance is kept low (74, 84). The mixed venous oxygen saturation (SvO₂), mean arterial blood pressure (MAP), and diuresis were the most important clinical guidelines used to evaluate the adequacy of the therapy. Before and during pump support, vasoconstrictor agents had to be administered in order to maintain MAP, SvO₂ and diuresis within acceptable levels. Angiotensin II was frequently used, and no clinical negative effects from the splancnic circulation were observed. In comparison with the IABP, improvement in renal and hepatic flows has been shown experimentally with the HP (129).

The nonpulsatility of the produced flow did not seem to affect the organ perfusion or function. Our results are in accordance with those previously reported by Meyns et al (85) and Wiebalck et al (74). Hemolysis was not a clinical problem, but earlier studies have shown some decrease in platelet count and increase in plasma free hemoglobin (74, 84).
Patients with biventricular failure had a poor prognosis despite attempts to improve the right heart function with pharmacological treatment. Eight out of these 10 patients died. The majority of these patients had undergone several attempts to reperfuse using CPB. IABP had also been inserted in some of these patients prior to the axial flow pump. The global myocardial function was considered to be too low, which is why the decision was taken not to use a RVAD. Resuscitation in the ICU with an emergency operation was the indication for HP treatment in five patients. Two of these patients survived and three died. In our 24 patients, Higgins’ score varied between 0-13. Our patient material is too small to allow further analysis of risk factors for postcardiotomy heart failure. Many attempts have been made with different risk stratification systems, both prior to and after heart surgery (130-133). Unfortunately, most of these systems are poor predictors of the outcome for the individual patient (134).

Our retrospective study without controls can not answer the question of whether this treatment is superior to IABP treatment. Randomized studies comparing treatment with the HP and IABP were planned some years ago, but were not possible to carry out due to the complexity to randomizing critically ill patients after often long and complicated surgery.

**Coronary artery bypass grafting on the beating heart**

The unloading effect of the HP was used in another study to facilitate beating heart coronary artery bypass surgery (CABG). This was during the time before beating heart surgery was really accepted in our country and before the modern era with different technical innovations to support and stabilize the heart. The heart-lung machine was routinely used and all intraoperative routines were based on that.

The rationale behind HP-supported CABG was the possibility to decompress the heart and support the circulation while avoiding the potential adverse effects of cardiopulmonary bypass (CPB), aortic crossclamping and cardioplegic arrest (135). Despite major advances in the technology, CPB is an inherent pathologic condition in which blood is continuously exposed to nonendothelial surfaces of the pump oxygenator circuit (136). This exposure activates a generalized inflammatory response, resulting in alterations in the complement, coagulation, and fibrinolytic systems (136, 137). The response varies from individual to individual, and may result in organ dysfunction such as myocardial, and pulmonary dysfunction, neurologic disturbances, renal impairment and coagulation disorders.
The left ventricle was partially unloaded by the HP, reducing the wall tension and the oxygen demand (125), while the heart was still perfused with its own blood. The lungs were ventilated and oxygenated the body. The short-acting β-blocker esmolol was used to decrease contractility and motion of the heart and may also have had a cardioprotective effect (116, 118, 138, 139).

Precise surgery was dependent upon these indirect means of reducing heart motion and manual manipulation of the heart. Therefore, active interaction between the surgeon and anesthesiologist became important in order to maintain adequate systemic circulation. The arterial blood pressures recorded with the HP on full speed, showed a decrease in systolic, and increase in diastolic pressure. When the maximum esmolol dose had been reached, the arterial blood pressure recording showed only small pulsations, indicating that the HP delivered most of the blood from the left ventricle to the systemic circulation. The marked decrease in MAP during bypass surgery was probably an effect of the negative inotropic effect of esmolol, a slight decrease in systemic vascular resistance and manipulation of the heart. A low MAP of approximately 45 mm Hg was accepted as long as other variables, such as SvO₂ and blood gas values, were within normal limits. When a concomitant reduction in both MAP and SvO₂ (45 mm Hg and 50%, respectively) was observed, a bolus dose of phenylephrine was administered to increase venous return to the heart. The low MAP values during bypass surgery might have induced hypoperfusion of vital organs. Our study did not monitor this in detail, but no neurological sequelae were observed. Urinary output was often reduced during surgery, and most patients received loop diuretics at the end of the procedure in order to increase urinary production. Diuresis normalized in the ICU, and the serum creatinine level was unchanged as compared to preoperative values.

During bypass surgery, a decrease in right ventricular ejection fraction (RVEF) was observed, with a concomitant decrease in pulmonary vascular resistance index. The negative inotropic effect of esmolol, together with manipulation of the heart might explain this decrease in the RV systolic function. With a low MAP and a slight increase in central venous pressure, it can be argued that the coronary perfusion to the RV may be critically impaired. However, no severe RV dysfunction was observed. Esmolol was an important adjunct to the HP to optimize the conditions for surgery. The drug has, however, a dose dependent negative inotropic effect, with a great interindividual variation as shown by others and ourselves (140, 141). The finding that heart rate remained unchanged remains unexplained.
We believe that a real time measurement of $\text{SvO}_2$ is the method of choice when monitoring immediate changes in central circulation. At the end of the series, transesophageal echocardiography (TEE) was found valuable in this setting, in order to monitor regional wall motion abnormalities before and after CABG. It was also a valuable guide for the surgeon when passing the HP into the left ventricle and for evaluating the degree of decompression of the left ventricle. During coronary surgery on the beating heart, accurate TEE interpretation of myocardial function and ischemia is difficult when the heart is elevated perpendicular to the thoracic cavity (112). In many institutions, however, TEE has become the first line monitoring of patients undergoing bypass surgery on the beating heart (109).

Small doses of heparin were used, aiming at an ACT of approximately 200 seconds to avoid embolic events. We used a synthetic colloid for volume expansion but also to depress the effect of the platelets. None of the patients showed postoperative signs of graft occlusion. The authors tried to minimize heat losses during the procedure because low body temperature at the end of surgery diminishes drug metabolism, prolongs the need for postoperative ventilation, deteriorates coagulation and increases the risk of postoperative myocardial ischemia (142). This aim was not, however, completely fulfilled and remains a problem with beating heart surgery today.

The anesthesia and postoperative care did not change in our routines by the time of the study. Pharmacokinetics are changed with this technique as compared to the use of CPB (114). The technique offers the potential of early extubation and mobilization. As low doses of heparin are used, epidural analgesia throughout the perioperative period could be favorable. It may also be beneficial for myocardial perfusion and central hemodynamics (143, 144).

Technical developments in the setting of beating heart surgery have been very rapid. There is now a vast amount of technical equipment facilitating beating heart surgery. Therefore, multivessel CABG can often be performed nowadays without circulatory support (145, 146). Even today, however, there are sometimes serious hemodynamic effects of manipulating the heart in order to perform surgery on the posterior part of the heart. There are a few current partial support systems available that aim to address this problem (147, 148).

An implantable left ventricular assist device as a bridge to heart transplantation

In 1993, having gained good experience with the minimally invasive axial flow pump for short term assistance, we started a program using an implantable device, HeartMate™ (HM), in order to support transplant candidates who were deteriorating while waiting for a donor.
heart. This program was developed in cooperation with the University hospital of Lund, the transplant center for our region (149, 150). Prior collaboration in the transplant program made it possible to introduce this therapy program. Our hospitals were among the first centers in Europe to introduce the HM therapy as bridge to heart transplantation.

We started with a pneumatic system requiring a pump console but later on switched to implantation of the electrical device. With this system, including belt worn batteries, the patient can benefit in terms of quality of life and outpatient treatment (76, 90, 151). Our study, which included 12 pump implants in 10 patients, confirmed that the HM system is a powerful tool for unloading the left ventricle and supporting the systemic circulation.

Transesophageal echocardiography (TEE) was one of the essential monitoring methods in the operating room and in the early postoperative period for additional guidance of therapy. TEE and transthoracic echocardiography (TTE) have become key monitoring and diagnostic modalities in patients having LVAD placement (122, 152, 153). In the ICU, both TEE and TTE are valuable for the follow-up, with regard to the right heart function, decompression of the LV and LA, and the flows from the LVAD. During long term follow-up of LVAD patients, repeated echocardiographic examinations are important for evaluation of native heart-and LVAD function at rest and during exercise (154). Device related complications can be diagnosed with echocardiography (155). Our early postoperative hemodynamic findings, with a marked increase in CI, SvO$_2$, RVEF with concomitant decrease in LV filling pressure and mean pulmonary pressure are in agreement with others (86, 156). The echocardiographic findings with a decrease in LV dimensions before and after LVAD implantation have also been reported earlier (157). The concomitant increase in RV dimensions found by us, is at variance with previous report from the Cleveland group (156). This group found a decrease in RV diastolic volumes early after implantation with further decrease before transplantation with the automatic boundary technique via acoustic quantification. In part, the different measurement techniques might explain the observed difference. In our patients, the RV seemed to function adequately after LVAD implantation, with conventional therapy including low to medium doses of catecholamines and PDE-III inhibitors. Two patients had a short period of RV failure after weaning from CPB, but were managed with prostaglandin E1. Nitric oxide was not available at our center at the time of the study, and there was no need for RVAD. We found no relationship between the pre- and postoperative RV function. Drug treatment was discontinued when the circulation was stable, according to clinical observations and hemodynamic measurements, and echocardiography indicated a good interaction between the right ventricle and the LVAD.
Enteral nutrition was started as soon as possible in an attempt to avoid intestinal edema and infectious complications from the visceral organs (158). The caloric intake was measured carefully, and nutrition was optimized in an attempt to avoid a longstanding catabolic state. Early exercise led by specially trained physiotherapists was one way of facilitating the overall recovery of the patient (91, 159-161). Daily training in the gym or treadmill exercise was undertaken.

Bleeding diathesis during surgery was an unpredictable event. Low doses of heparin were used until the patients were fully mobilized, then therapy was switched to aspirin (89). Four patients had neurologic symptoms, two of them mild and transient. One patient became unconscious after a cerebellar embolus. After neurosurgical intervention with partial resection of the cerebellum, the patient recovered and was eventually transplanted. This patient had mild neurological sequelae after the transplantation. One patient needed rescue transplantation after multiple embolization with temporary neurological symptoms. Based on our own experience, we currently use warfarin in the case of pump dysfunction, atrial fibrillation, or transient neurologic events. Infectious complications were the most common problem during long pump treatment times. Device-related infections caused morbidity but were suppressed with antibiotics until transplantation. The extended period with LVAD therapy, might in part explain some of the complications (76, 77). All but one patient was eventually transplanted. This patient died after 2.5 months of ICU treatment because of an intractable sepsis.

The start of a LVAD program is a matter of organization, education, and multidisciplinary involvement. No special facilities are required, in contrast to introducing a transplant program. A dedicated team, involving different specialties, which covers all the known problems with this therapy and with the same treatment philosophy is mandatory for the care of these patients. Regular meetings between the members in the team before and during LVAD treatment are important. Repeated education of all staff members is of great importance for the care of these patients. Hospitals responsible for LVAD patients should have the possibility of dealing with various device related complications and the knowledge of pitfalls when giving anesthesia and surgery to such patients undergoing noncardiac surgery (162). Good communication with the transplant center is mandatory.

The benefits of a LVAD program can be obtained at a reasonable cost. Outpatient management depends on the proper training of members from the referring hospitals and of the family of the patient (90, 150, 151).
Parallel to this program we 1995 also initiated a protocol aiming at evaluating the HeartMate™ as permanent treatment in elderly patients not accepted for transplantation. Two patients 67 and 69 years of age were included. Both patients died in the ICU due to multiorgan failure. Due to this fact and gaining more experience about the shortcomings of the present system for long-term use, we did not continue this protocol.

**Intermediate- and long-term follow up of patients treated with a left ventricular assist device**

Of the 9 survivors, seven were followed from 93 to 873 days with a median treatment time of 462 days. The long treatment times were due to difficulties in finding a suitable donor heart and gave us the experience of extended treatment. Device complications occurred in 3 patients. In one patient the pneumatic driveline was fractured within the abdomen and an emergency pump replacement had to be carried out. Leakage of the inflow valve occurred in 2 patients and has been reported earlier (150). In one very tall patient the leakage started after 214 days, and after 232 days the pump had to be replaced. One hundred and eighty days after this operation, the new valve conduit started to leak. The patient slowly got worse and was eventually transplanted in rather stable condition. In the second patient, the inflow valve leak started after 226 days. A method combining noninvasive and invasive measurements was developed for quantification of the leakage and its effect on systemic circulation. Repeated standardized exercise tests and echocardiography showed to be important tools for evaluation of patients undergoing long-term LVAD treatment.

The ventilatory equivalents for oxygen at the submaximal exercise test 3 to 4 months after LVAD implantation were elevated, indicating that the circulatory and respiratory adaptations to exercise were not fully normalized. The peak oxygen consumption (VO₂) differed markedly between the patients, but the median value of 17.5 mL/kg/min is in accordance with other reports (163-165). Regular long-term follow-up from 9 to 18 months has so far not been reported. The long-term effects of inflow valve leak, compared with patients with normal LVAD function, were a decrease in exercise capacity and peak VO₂ with increases in LV-dimensions.

The interaction of the native heart and LVAD at rest and during exercise have been documented by Branch et al (166). The authors found that, at rest, the native heart and the LVAD function in series but during exercise they have a parallel function. Deng et al (167),
later described a method for quantification of the contribution of the native heart to the total cardiac output. The authors stated that this method could be used to assess the risks associated with LVAD dysfunction, as well as prediction of recovery of native heart function with potential of weaning from the LVAD. In our cases with inflow valve incompetence, the pump had to be turned off completely or maximally slowed down to eliminate the effects of regurgitation on the native heart. Invasive measurements and echocardiography gave information concerning the native heart function. Quantification of the regurgitation from the LVAD into the left ventricle was performed at various pump settings and rates. The regurgitant volume was quantified by comparing the LVAD output with the invasive cardiac output. As long as the native heart and the LVAD can maintain an acceptable hemodynamic situation, the LVAD can still be used as a bridge to transplantation.

Our patient material is small compared to the experience at big centers (76, 77, 168), but the total treatment time of 2992 days has convinced us that the current HeartMate™ system is adequate for maintaining life in most patients who are deteriorating while waiting for a heart transplantation. For a long-term therapy, however, we hope for a better solution (169).

**A novel axial flow pump**

Although the first generation axial flow pump, the Hemopump™, is now off the market, it has shown the potential for the technology. Several ongoing programs use this concept with slightly different technical solutions (93-95, 170). The Jarvik 2000™ axial flow pump has been previously evaluated in animals before and the first human implants have recently been made (171, 172). The pump is very small and implantation can be made via sternotomy or thoracotomy, with operation on the beating heart as a possibility. The pump graft is connected to the ascending or descending aorta. The drive cable must be secured and the optimal solution for this remains still to be found (173).

In our animal study with acute heart failure, the pump showed to be effective in unloading the left ventricle. In 3 animals, the left ventricular dimensions decreased during on off tests from 4.2 cm to 2.0 cm, as measured by echocardiography from the apical four-chamber view. The cardiac index increased from the baseline heart failure measurement, with stepwise increases of the pump speed. A decrease towards the baseline value was observed when the pump was turned off. A concomitant decrease in left atrial pressure was also observed. The femoral
blood flow and peripheral muscular perfusion were also assessed. Femoral flow followed changes in pump speed. Muscular perfusion remained unchanged during the investigation. These findings suggest a preserved distal perfusion during periods of mainly nonpulsatile flow. The pump delivers principally a nonpulsatile flow but some pulsatility is maintained due to interaction with native heart function.

The goal of circulatory support with the Jarvik 2000™ is to augment left ventricular function, not unload the ventricle completely (123). The long-term effects of a mainly nonpulsatile blood flow are still unknown. However, it has been shown in a calf model, that some pulsatility is maintained as a result of cardiac activity (123). In another animal study, no renal dysfunction or neurological disturbances were observed (174).

In April 2000, clinical trials started at the Texas Heart Institute and shortly thereafter in Oxford, UK to evaluate the Jarvik 2000™ for bridging patients to heart transplantation and for long-term support (171, 172). Another potential for this system is as a bridge to myocardial recovery, in which case the device may be removed after sufficient myocardial function returns (174).

This technology with small axial flow pumps holds great promise. With the introduction of the Hemopump™, researchers showed that high-speed, continuous-flow pump could support the circulation without causing significant hemolysis or thrombosis (172). Experimental data with the Jarvik 2000™ have shown that this pump can provide the same benefits.

**Future aspects**

The need for mechanical circulatory support (MCS) after heart surgery will probably decrease in conjunction with better medical treatment of acute ischemic heart disease. Myocardial infarction will continue to be treated more efficiently with reduction of myocardial damage. There will probably be fewer patients coming to surgery with severely impaired heart function. When needed, there will be several MCS options in treating postcardiotomy heart failure, i.e. small axial flow pumps similar to the Hemopump™, catheter-mounted rotor pumps that accelerate the blood in the aorta, pump systems using double-lumen cannulae to minimize the extracorporeal circuit.

Regarding severe congestive heart failure, several of the current MCS systems have become standard treatment as bridge to transplant. About 2500 HeartMate™ devices have now been implanted worldwide. The limited durability of the devices is still a critical factor for a more
extended use. Technical refinement is an on-going process. A totally implantable system with energy transmission through induction coils has been the technical endpoint for many programs but so far no commercial product has been presented. Therefore, it is still difficult to estimate the possibility for this technology to become a realistic alternative to heart transplantation. In the near future the cost-benefit and cost-effectiveness of MCS devices for long-term use will be questioned.

MCS as bridge to recovery now is, and will still be debatable in the future. Device removal has been possible in some patients but the long-term success has been unpredictable. In this setting, better MCS devices are necessary that are simpler, smaller, safer, more reliable, easier to insert, less expensive and with less complications. If this challenge is met, one could argue that these pumps should be inserted much earlier in the course of heart failure than they are now. It may be that by the time chronically ill patients reach the stage of profound circulatory perturbation, and, particularly, collapse, healing the heart is impossible.

Some of the new very small axial flow pumps hold great promise in this respect. They may be valuable in augmenting heart function in patients with irreversible heart failure and to allow myocardial recovery in select patients with depressed heart function of different etiologies. A partial unloading of the left ventricle with maintenance of a pulsatile flow could be the best way of promoting native heart function. In this way a reversal of structural remodeling of the heart linked with a similar change in molecular function could be achieved.

Future research in the pathophysiology of heart failure and in combining MCS and new drugs is necessary to clarify these suggestions. Management of the patients will even more than today require a multidisciplinary approach.
CONCLUSIONS

• The axial flow pump for short-term use was effective in decompressing the failing left ventricle until recovery of the heart was achieved. The principles of pharmacological therapy aimed at optimizing pulmonary and systemic vascular resistances. Mixed venous oxygen saturation, arterial mean blood pressure, and diuresis were the most important parameters to guide the therapy.

• Coronary artery bypass grafting on the beating heart was safely performed with the combination of the axial flow pump and a short-acting β-blocker. This technique could still be beneficial for beating heart bypass surgery, especially for securing an acceptable hemodynamic situation when operating on the posterior part of the heart.

• The introduction of a LVAD program in a non-transplanting center can be achieved with good results.

• An implantable LVAD was a powerful tool in unloading the chronic failing left ventricle and to support the systemic circulation. The device was adequate for maintaining life in patients deteriorating while waiting for a heart transplant. Device related complications were a big problem, especially during extended treatment times.

• Repeated standardized exercise tests and echocardiography are important tools for evaluation of long-term pump function. Quantification of inflow valve regurgitation and its effect on systemic circulation can be achieved with a combination of noninvasive and invasive methods.

• A novel implantable axial flow pump was effective to decompress the left ventricle, to improve central hemodynamics and to maintain the peripheral circulation in an acute heart failure model.
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