Summary

Congestive Heart Failure (CHF) is a major health problem with a high mortality rate. Its ultimate therapy, heart transplantation, is limited by the shortage of donor hearts. Since decades researchers have been working to solve this problem by developing Mechanical Circulatory Support Systems (MCSS) that can replace or assist the failing heart.

The Pulsatile Catheter (PUCA) pump is a trans-arterial left ventricular assist device (LVAD) that can be used as a short-term (up to 3 days) support. The device consists of an extracorporeally placed pneumatically driven single-port membrane pump connected to a reinforced valved indwelling catheter. The PUCA pump is ECG triggered, aspirates blood from the left ventricle (LV), and ejects it into the ascending aorta during the diastolic phase.

Chapter 1 describes the background of the PUCA pump project and the aim of this thesis.
The basic concept of the device was published by Hans Zwart in 1966, when he described in his thesis a closed-chest LV bypass in dogs. Discussing the principle of Dr. Zwart's assist device with Prof. Dr. W.J. Kolff at the Laboratory for Artificial Organs Research (Salt Lake City, Utah, USA) in 1990, Dr. G. Rakhorst sketched at the back of an envelope the concept of the PUCA-pump, a new trans-arterial assist device. The PUCA pump project became a part of EUREKA project EU 68211 (formally 68210) "Trans-Arterial Blood Pumps", accepted in April 1992 by the High Level Group at the Helsinki Meeting. The project was financially supported by the Netherlands and Swiss governments, and by the Dutch Heart Foundation (Nederlandse Hart Stichting). Although the German government had decided not to contribute to this project, some German universities and companies participated in this European research project.
The first dual valved PUCA pump prototypes were built in 1990-1992 by Prof. Dr. W.J. Kolff (University of Utah, Salt Lake City, USA) and by Prof. Hennig (Free University of Berlin, Germany). The American prototype was made from a standard reinforced venous cannula for extracorporeal circulation (ECC) with build-in valves and was driven by a single-port membrane pump connected to a pneumatic driver. The German prototype was made from a standard non-reinforced venous cannula for ECC and was pneumatically driven as well.

The first thin walled valved polyurethane PUCA pump catheters were produced from 1995 until 1997 by J. Hoks at the faculty workshop. All prototypes were made from stainless steel reinforced Estane 74 A (B.F. Goodrich, Cleveland, OH, USA) using a vertical dipping method (patent pending).
Since 1998 the latest version of the PUCA catheters have been produced with a machine designed at the Division of Artificial Organs, Department of BioMedical Engineering of the Faculty of Medical Sciences. The catheters that are made from Ni-Ti reinforced Tecothane® (Thermedics, Inc., Woburn, Mass., USA), are 40 cm long and have 7.4 mm inner diameter. Until 1998 separate inflow and outflow valves were positioned in the PUCA pump prototypes (PUCA-I) to guide the blood from the left ventricle towards the membrane pump and from the membrane pump towards the aorta. The single valve version of the PUCA pump (PUCA-II), produced since 1998 at the Division of Artificial Organs, has a miniaturized combined inflow/outflow valve (patent pending) positioned twelve centimetres from the tip.
The work described in this thesis started in 1994 as a part of the developments described above. At the onset of this thesis, the aim was defined as:

- To develop a good functioning PUCA pump prototype.
- To develop an easy, fast, and safe surgical introduction technique for the PUCA pump.
- To test the PUCA pump prototypes in vitro and in vivo (healthy animals).
- To develop a large animal model of acute ischemic left ventricular heart failure that can be used to assess the influence of the PUCA pump on the heart and circulatory system under realistic conditions.

Chapter 2 categorizes and reviews the development of Mechanical Circulatory Support Systems (MCSS), highlights the medical indications and contraindications of pump implantation, advantages and disadvantages of the various systems, and results of animal and clinical studies. It was found that substantial progress has been made in the development of Mechanical Circulatory Support Systems during the past decades. The development of MCSS has been directed towards two major research areas: development of Total Artificial Heart (TAH) and development of Ventricular Assist Devices (VAD's).
Major breakthroughs have been made in the development of TAH. The first significant step forward has been the introduction of the two-stage cardiac replacement concept by Cooley in 1969. The concept launched the idea that the TAH could be used not only as a permanent cardiac replacement device, but also as a bridge to transplantation in patients with severe heart failure. The second breakthrough has been made in materials and engineering science, the change

from pneumatic into electric TAH. The bulky drive consoles and the high incidence of infections, caused by the percutaneous drivelines, made the pneumatically driven TAHs unsuitable for long-term use. The new generation electric TAHs are expected to be compact, totally implantable, and will use wireless percutaneous energy transmission. The implanted rechargeable batteries are used only as a back-up power source. Also the use of titanium instead of stainless steel made the devices lighter. The highly smooth segmented polyurethane replaced the silicon rubber improving significantly the biocompatibility of the devices. Pericardial tissue valves and biolized blood-contacting surfaces may eliminate the need of systemic anticoagulation.
Major breakthroughs have been made in the development of VAD's as well. The development of a percutaneous insertion technique for the Intra-Aortic Balloon Pump (IABP) allowed fast device application without major surgery and made the IABP the most used device for temporary support of the failing left ventricle. The Hemopump was the first transarterial blood with a high pumping capacity. The minor hemolysis developed by the Hemopump stimulated researchers to develop new high-speed axial pumps for short-term and intermediate-term use. The most advanced axial pumps are magnetically suspended, ultracompact, and practically noise-free. Essential mechanical and material improvements have been made in the VADs as well. Like the new generation TAHs, the long-term VADs are nowadays totally implantable, compact, and electrically powered. The use of textured blood-contacting surfaces as well as porcine/bovine valves allowed antiplatelet agents to be used instead of systemic anticoagulation. The use of sophisticated electric motors resulted in a low incidence of device failure. Wearable drive/control units allow patients to perform their daily life activities

Chapter 3 describes the development of a numerical model of the PUCA pump. With this model the hemodynamic functioning of the PUCA pump can be predicted for each type of pump configuration. A validation study showed, that the numerical model is able to predict the behavior of the PUCA pump accurately. When the PUCA pump is introduced into the axillary artery, a catheter with an internal diameter of at least 5.5 mm must be used to realize a flow of 3 L/min without pump or blood damage. If the PUCA pump is introduced directly into the aorta, a catheter with an internal diameter of at least 7.0 mm must be used to realize a flow of 5 L/min without pump or blood damage. The amount of blood damage caused by mechanical forces can be reduced by limiting the driving pressure and shear stress. Several pressure or velocity profiles, depending on catheter configuration and heart frequency, are necessary to obtain an efficient driving system. The influence of patient hemodynamics on the necessary driving pressures is only minor, so mean values can be used. The study showed that the influence of the

flow resistance of the valves is more distinct. Decreasing the flow resistance is an effective way to improve PUCA pump performance.
It was concluded that the numerical simulation model is a very useful instrument to get an impression about the functioning of a left ventricular assist device. With a simulation model, building several prototypes and testing them on their flow behavior can be avoided, saving money, time, and animals.

Chapter 4 explains the development of a new introduction technique for the PUCA pump. The aim of the study was to develop an easy, fast, and safe surgical technique to introduce the PUCA pump catheter into the left ventricle. Four different ways of catheter introduction were tested in 20 acute open-chest experiments with calves: catheter introduction without any guidance at all, by X-ray guidance only, by using a guide-wire plus X-ray guidance, and by using a guiding pressure catheter. Introducing the PUCA pump catheter into the LV cavity by using a pigtail guiding pressure catheter proved to be easy to perform. The large-bore pump-catheter followed the guiding catheter and passed the aortic valve well. The position of the catheter tip in the aorta or in the LV was controlled easily by examining the characteristic pressure patterns derived from the guiding catheter. In this way the tip of the pump-catheter could be positioned accurately just within the LV outflow tract, thereby avoiding contact with arrythmiogenic cardiac tissues by penetrating too deep into the LV. The technique is inexpensive and uses widely available equipment. Furthermore the technique does not require X-ray guidance and in this way avoids radiation of the patient and the staff.

Chapter 5 evaluates of the optimal driving mode for the PUCA pump during LV assist. Left ventricular myocardial oxygen consumption (LV MVO_2), pump flow, and coronary flow were studied during acute experiments in calves using asynchronous and ECG-synchronous assist modes.
LV MVO_2 decreased significantly during the asynchronous (from 7.77 to 6.46 ml/min/100 gr) as well as during the ECG-synchronous mode (from 8.88 to 7.84 ml/min/100 gr). The pump flow was highest during the ECG-synchronous assist mode 1:2 (2.94 L/min), followed by the asynchronous assist (2.79 L/min). The peak coronary flow depended strongly on pump ejection timing and showed the best flow patterns during the ECG-synchronous assist. The results obtained led to the conclusion that for PUCA pump support both asynchronous and ECG-synchronous assists significantly reduce LV MVO_2 and the pump flow generated is enough to maintain the systemic circulation. However, we find the ECG-synchronous mode preferable, because this mode optimises coronary flow patterns at the same time. The choice of the optimal ECG-synchronous assist mode (1:1 or 1:2) depends strongly on the heart rate: 1:1 assist mode is method of choice by heart rate below

60 beats/min, 1:2 or 1:3 assist modes should be used in case of higher heart rate. The asynchronous assist should be used in case of severe cardiac arrhythmia or when a good triggering signal cannot be achieved.

Chapter 6 describes the development of an animal model of selective coronary atherosclerosis by combining a local endothelial injury with an administration of cholesterol-enriched diet. The aim of this study was to develop an atherosclerotic plaque in an animal's coronary artery and in this way to develop myocardial ischemia in order to test the PUCA pump under realistic conditions. Twelve pigs were subjects of a guide-wire induced endothelial injury of LAD. Six animals (control group A) were fed a standard pig food; the remaining six animals (cholesterol group B) were fed a 6% cholesterol-enriched diet. Three animals from group A were terminated immediately after the endothelial injury (acute control group A_0). The other three animals from the control group (chronic control group A_4) and all animals from the cholesterol group were terminated four weeks after the injury. The endothelial surface and the media of the LCX were intact in all animals. Long eccentric areas of endothelial injury were found in the LAD in the acute control group. Numerous fibrous atherosclerotic plaques in LAD were found in the chronic control group as well as in the cholesterol group, but were highly pronounced present in the last group. Lipid accumulation was not found in the plaques of both groups. We concluded that administration of 6% cholesterol diet for a period of six weeks as such is not sufficient to develop coronary atherosclerosis in pigs. Selective coronary atherosclerosis can be induced within four weeks with the same diet when the blood vessel has been injured with a guide-wire. Although undoubtedly successful in the development of selective coronary atherosclerosis, the model was not able to develop within the period of 4 weeks a plaque that can lead to myocardial ischemia. Therefore we concluded that this model could be used to study atherogenesis as well as for investigations of mechanical properties of the coronary arteries, but the model is unsuitable for testing of the PUCA pump during acute heart failure conditions. Long-term experiments should be performed to study the progress of the developed plaques and their effects on the myocardial blood supply. In addition, the present study emphasized the need of a cholesterol-reducing treatment for patients with hypercholesterolemia before and after invasive diagnostic or therapeutic procedures in the arteries (PTCA, introduction of catheters, guide-wires, etc.). This will prevent the development of "iatrogenic atherosclerosis" in patients with hypercholesterolemia.

Chapter 7 explains the development of a large animal model of acute ischemic left ventricular heart failure. We tested the hypothesis that mild stenosis of the coronary artery in combination with mild ventricular pacing induces acute heart

failure condition. Mean aortic pressure (AoP), left ventricular end-diastolic pressure (LVEDP), stroke volume (SV) and myocardial systolic shortening (MSS) were compared 30 minutes after a pacemaker-induced tachycardia in anaesthetized sheep (n=3) without and with ±50% stenosis of the proximal LCx. All parameters measured restored to the basic levels when the stenosis was absent. When the LCx was partially occluded, the mild PM-induced tachycardia resulted in decreased AoP (-29%, *P*=0.045) as well as in decreased SV (-25%, *P*=0.048); the LVEDP remained high (+98%, *P*=0.002). Also the recovery of the MSS was impaired when stenosis was present (*P*=0.002). These values indicate that acute heart failure conditions were present. The technique used proved to be safe and allows fine-tuning of the demand ischemia. The study emphasized that a mild ventricular pacing alone is not sufficient to develop an acute heart failure. The combination between mild coronary stenosis and mild PM-induced tachycardia developed acute heart failure in sheep due to demand-induced ischemia. This model is clinically realistic since many patients with coronary artery disease show ischemic symptoms during exercise. Because the PUCA pump is meant to be used during acute heart failure, the developed model will be used in further experiments to assess the influence of the device on the heart and circulatory system during these pathological conditions.

Chapter 8 describes the in vitro and in vivo experience with the second version of the PUCA pump (PUCA-II). The device was tested for valve leakage, flow resistance, and for thrombus formation. During the in vitro experiments a maximum valve leakage of 6% during ejection and 21% during aspiration was found. The maximum flow resistance coefficient (*K*) was 4. The animal experiments demonstrated that the PUCA-II could be positioned within a few minutes into the left ventricle without X-ray guidance and without using a vascular graft. Thrombi were not found in the combined valve after total pump time of 3 hours, which proved the good washout of the valve. Initial experiments to position the pump in the right ventricle through the pulmonary artery were successful and contributed to the development of a new application for the device.

In **Chapter 9** the place of the PUCA pump in the group of VAD's, the indications for ventricular support with the PUCA pump, as well as the potential market for the device are discussed.
The PUCA pump is the only trans-arterial LVAD that combines direct LV unloading with pulsatile flow on counterpulsation basis. The device in fact combines the direct LV unloading effect of the Hemopump (Medtronic, Inc., Minneapolis, MN, USA) with the counterpulsation effect of Intra-Aortic Balloon Pump (IABP), a combination that has proven to provide an excellent support for the ischemic, failing heart. Due

to the presence of unique single-valve, the PUCA pump can be temporary switched off and kept in place without backflow from aorta to LV.

The PUCA pump is indicated for a short-term (up to 3 days) LV support in patients with acute ventricular failure after heart operation, myocardial infarction, acute myocarditis, or as prophylactic in patients with mild heart failure during non-cardiac operations or high-risk Percutaneous Trans-luminal Coronary Angioplasty (PTCA). Reducing the distance between the catheter tip and the combined valve a right ventricular application for the PUCA pump was developed. The initial animal experiments demonstrated that the short-tip catheter could be introduced into the RV via the main pulmonary artery in the same way as the LVAD version. Further animal experiments are needed however to study the influence of the right ventricular as well as biventricular support with the PUCA pump on the pulmonary and systemic circulation.

The potential market for the PUCA pump can be calculated from the market of IABP. The indications for use of the PUCA pump as LVAD are comparable with the indications for use of IABP. As known, about 200,000 IABP disposable sets are sold per year worldwide. In about 10% of the cases the LV support with the IABP fails and a LV support with other LVAD is required. The combination between a relatively low price, easy introduction, direct ventricular unloading with pulsatile flow on counterpulsation basis, and the simple control makes the PUCA pump a first-choice LVAD. Therefore it can be estimated that the potential market of the PUCA pump is about 20,000 per year.

The PUCA pump is almost ready for the first clinical trials. However, some essential preceding steps are necessary: short-term and intermediate-term animal tests for hemolysis, thrombus formation, and mechanical failures, the production technique of the combined valve should be improved in order to reduce valve leakage during aspiration to below 10%, and the driver should be adapted according to the requirements of the PUCA pump.