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Treatment of Right Ventricular Failure through Partial Volume Exclusion

An Experimental Study

PER VIKHOLM

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Abstract
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Implantation of a left ventricular assist device (LVAD) is a potential treatment in terminal heart failure. Right ventricular (RV) failure is a severe complication in these patients and sometimes requires additional placement of a right ventricular assist device (RVAD). RVAD implantation, however, is an invasive treatment associated with both increased mortality and morbidity. The aim of this thesis was to study whether partial volume exclusion of the RV through a modified Glenn shunt or cavoaortic shunt could treat severe RV failure. The ultimate goal would be to use it as an alternative to a RVAD in RV failure during LVAD therapy.

Swine were used as the model animal in all studies. In Study I, experimental RV failure was induced by ischemia, and verified by hemodynamic measurements and genetic expression. Treatment with a modified Glenn shunt reduced venous stasis and improved hemodynamics in general. In Study II, experimental RV failure was induced by the same method as in Study I. Treatment with a cavoaortic shunt in addition to LVAD therapy proved to reduce venous stasis and improved hemodynamics in general, which was feasible with preserved oxygen delivery despite cyanotic shunting. In Study III, experimental RV failure was induced by pulmonary banding, and verified by hemodynamic measurements and genetic expression. Treatment with a modified Glenn shunt reduced venous stasis but did not improve hemodynamics in general compared with a control group. In Study IV, the effects of LVAD therapy and subsequent treatment with a modified Glenn shunt on the normal RV function were studied. It demonstrated that LVAD therapy can put strain on the RV by increasing stroke work and end-diastolic volume, and that these effects can be reversed by treatment with a modified Glenn shunt during LVAD therapy.

In conclusion, partial volume exclusion through a modified Glenn shunt or cavoaortic shunt is a feasible treatment of experimental RV failure. Thus, it could potentially be used as an alternative treatment to a RVAD in severe RV failure during LVAD therapy.

Keywords: Right Heart Failure, Left Ventricular Assist Device, Glenn shunt

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To my family for all your love and support along the way

List of Papers

This thesis is based on the following papers, which are referred to in the text by their Roman numerals.

I Vikholm P, Schiller P, Johansson J, Hellgren L. A modified Glenn shunt improves haemodynamics in acute right ventricular failure in an experimental model. *Eur J Cardiothorac Surg.* 2013 Mar;43(3):612-8

II Vikholm P, Schiller P, Johansson J, Hellgren L. Cavoaortic shunt improves hemodynamics with preserved oxygen delivery in experimental right ventricular failure during left ventricular assist device therapy. *J Thorac Cardiovasc Surg.* 2014 Feb;147(2):625-31.

III Vikholm P, Schiller P, Hellgren L. A modified Glenn shunt reduces venous congestion during acute right ventricular failure due to pulmonary banding: a randomized experimental study. *Interact Cardiovasc Thorac Surg.* 2014 Apr;18(4):418-25.

IV Schiller P, Vikholm P, Hellgren L. A modified Glenn shunt reduces right ventricular stroke work during left ventricular assist device therapy. *Accepted for publication in Eur J Cardiothorac Surg.*

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Abbreviations

BiVAD	Biventricular assist device
BTC	Bridge-to-candidacy
BTR	Bridge-to-recovery
BTT	Bridge-to-transplantation
CO	Cardiac output
CVP	Central venous pressure
DNA	Deoxyribonucleic acid
DO_2	Oxygen delivery
DRVP	Diastolic right ventricular pressure
DT	Destination therapy
INTERMACS	Interagency Registry for Mechanically Assisted Circulatory Support
LV	Left ventricle
LVAD	Left ventricular assist device
MAP	Mean arterial pressure
PVR	Pulmonary vascular resistance
RA	Right atrium
RAP	Right atrial pressure
RNA	Ribonucleic acid
RV	Right ventricle
RVAD	Right ventricular assist device
RVCO	Right ventricular cardiac output
RVEDV	Right ventricular end-diastolic volume
RVSV	Right ventricular stroke volume
RVSW	Right ventricular stroke work
SaO_2	Arterial oxygenation
SRVP	Systolic right ventricular pressure
SVC	Superior vena cava
SvO_2	Mixed venous oxygenation
VO_2	Oxygen uptake

Introduction

The work of mechanical circulatory support was pioneered by Denton Cooley with the first implantation of a total artificial heart (TAH) in a human in 1969. Through the work of William DeVries, Willem Kolff and Robert Jarvik it was made a possible long-term treatment in 1981.

From initially a handful of implantations, the numbers increased rapidly with the introduction of left ventricular assist devices (LVADs) in the 1980s. Since then, right ventricular (RV) failure has been a persistent problem in these patients. The addition of a right ventricular assist device (RVAD) has been the standard treatment in refractory RV failure, but is unfortunately problematic.

As the number of LVAD implantations increase, the problem with RV failure is also growing. Thus, there is a need for an alternative treatment of refractory RV failure in LVAD patients. The aim of this thesis was to investigate whether partial volume exclusion could be a possible treatment of RV failure during LVAD therapy.

Background

Heart failure has a poor prognosis, both in terms of morbidity and mortality. The median survival after the first hospitalisation is about 2.5 years (1). Thus, the survival is worse than most types of cancer (2). In the last few decades, the number of patients with heart failure has grown, partly as a result of better survival rates after acute coronary syndromes (1). Nowadays, the average prevalence of heart failure is estimated to 2.5% in the U.S. (1). However, the diagnosis is clearly age related with a prevalence of 0.5% in those <50 years of age, and a prevalence of 10% in those >65 years of age (1).

In the majority of cases the treatment of heart failure is pharmacologic. However, in selected cases where pharmacologic treatment is insufficient, advanced treatment such as cardiac resynchronisation therapy (CRT), LVAD and heart transplantation are available (3). While the number of heart transplantations have stagnated worldwide the last couple of years due to the lack of donor hearts, the number of LVAD implantations increase rapidly (4). In the U.S., the number of heart transplantations is relatively stable at about 7/1,000,000/year. In contrast the number of LVAD implantations has increased from 4/1,000,000/year in 2004 to 22/1,000,000/year in 2011 (4, 5). It is estimated that about 0.2-0.4% of the total heart failure population are potential LVAD candidates, therefore, despite the increase in implantations the treatment is still underutilised (1, 4).

LVAD therapy

LVAD implantation is an established therapy that can be considered in cases of terminal heart failure despite otherwise optimal treatment (6). Essentially, the LVAD is a pump were an inflow cannula is implanted in the left ventricle (LV) of the heart, and an outflow graft is implanted in the ascending aorta (Figure 1). Thereby, the blood reaching the LV is mainly pumped through the LVAD to the aorta, which both unloads the LV from volume and increases the patient's blood flow.

The original purpose of LVAD therapy was to enable transplantation candidates to survive until a fitting donor heart was available. This is partly due to avoidance and sometimes even reversal of secondary organ dysfunction before transplantation, for example renal and liver failure (7). This type of

indication is known as bridge-to-transplantation (BTT) (6). In later years, LVAD therapy has also been increasingly used in patients with contraindications for heart transplantation, and account for almost 40% of LVAD implantations in the U.S. today (8). This indication is known as bridge-to-destination or destination therapy (DT), as the patient lives with the LVAD for the rest of their life (6). However, it is not uncommon that a patient initially has contraindications for transplantation, which might reverse after LVAD therapy. In such cases the patient can receive a LVAD with the aim of possibly becoming a transplantation candidate, which is known as bridge-to-candidacy (BTC) (9). In cases where the patient does not become a transplantation candidate, the aim of the treatment is converted to DT.

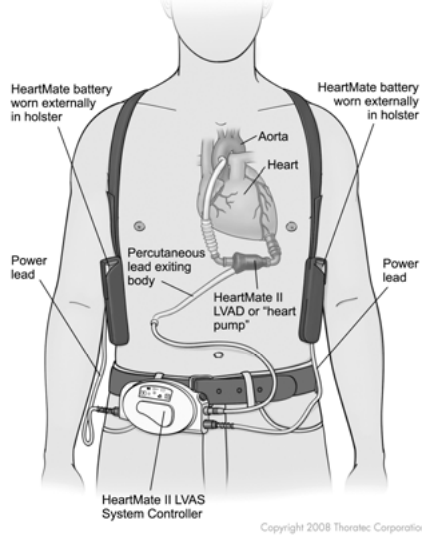

Figure 1. The picture demonstrates a LVAD of the type HeartMate II, which pumps blood from the LV to the aorta with a continuous flow. The pump is powered through a driveline that passes through the abdominal wall to a control unit connected to a pair of batteries. Reprinted with permission from Thoractec Corporation.

In some cases, the function of the heart may recover after LVAD implantation and the pump can be explanted. This is known as bridge-to-recovery (BTR) (6). Thus, there are four main indications for LVAD implantation:

1. Bridge-to-transplantation
1. Bridge-to-candidacy
2. Bridge-to-destination / Destination therapy
3. Bridge-to-recovery

There are many different types of LVADs, but they can mainly be grouped into two categories: those with a pulsatile flow and those with a continuous flow (10). It is widely debated whether pulsatile flow or continuous flow is best for the patients (10). Unlike continuous flow, pulsatile flow is physiologically normal. Moreover, continuous flow has been associated with an increased prevalence of gastrointestinal bleedings (10, 11). Despite this apparent advantage of pulsatile flow, the majority of LVADs implanted today use a continuous flow, since both survival and durability of continuous flow LVADs has been proven to be far better (10, 11).

The survival after LVAD implantation has improved immensely in the last few decades, partly due to the evolution from pulsatile to continuous flow devices (8). In patients who receive a LVAD as BTT the one-year survival is similar to patients going straight to heart transplantation, in other words about 85% (9, 12). In patients who receive a LVAD as DT the outcome is not as good, but these patients are generally older and have poorer health per definition as they are not considered for heart transplantation (9, 13). Still, the one-year survival in this population is about 70% with modern continuous flow LVADs, compared with about 30% in patients who receive optimal pharmacological treatment (13). Kirklin et al. also recently reported that in low risk subsets, the two-year survival in DT is similar to survival in heart transplantation (8).

Another important aspect is that both quality of life and functional class improves in LVAD patients. Among the surviving patients, over 80% improve to the New York Heart Association class I-II six months after LVAD implantation (13).

RV failure after LVAD implantation

Patients that are considered for LVAD implantation often have biventricular failure of varying degree, that is impaired function of both the left and right ventricle (14). However, in fact, the LVAD implantation per se can both induce and exacerbate RV failure, and this is an important cause of morbidity and mortality in LVAD patients (15, 16). The incidence of RV failure after LVAD implantation depends on how the condition is defined, but it is reported to be between 10-45% (15).

The cause of RV failure after LVAD implantation is not fully understood, but is most probably multifactorial. Firstly, the left and right ventricle affects each other *indirectly* through their preload and afterload (15, 17). Secondly, the left and right ventricle affects each other *directly* through their geometrical shape, as they share the same interventricular septum, a phenomena known as "ventricular interdependence" (15, 18). Experimental research has demonstrated that about 20-40% of the RV contractility and stroke volume is generated from the left ventricular contractions of the interventricular sep-

tum (18). The same study also demonstrates that RV dilatation dislocates the interventricular septum to the left, and can thereby impair LV function in terms of stroke volume and contractility (18).

Experimental research has also demonstrated that RV contraction during LVAD therapy is impaired secondary to a leftward dislocation of the interventricular septum due to suction from the LVAD (19). In fact, a negative correlation between LVAD flow and RV contractility was found, in other words higher LVAD flow further impaired the RV contractility (19). However, the same study also demonstrated that the RV maintained its efficacy as the LVAD therapy reduced afterload and increased preload of the RV (19). Thus, LVAD therapy seems to be a double-edged sword for the RV, as it has positive effects by increasing preload and decreasing afterload and at the same time negative effects because of a flow dependent decrease in contractility.

It has also been suggested that perioperative and postoperative factors such as ischemia, air embolism, blood transfusions, reperfusion injury, and inflammatory reactions secondary to extracorporeal circulation (ECC) contribute to the risk of developing RV failure after LVAD implantation (15).

Several studies have tried to identify risk factors associated with development RV failure after LVAD implantation, with the aim of predicting the condition preoperatively (15, 20-24). In these studies, hemodynamic parameters, biochemical markers and echocardiographic measurements were evaluated. Despite these efforts, a model with acceptable predictive value is still to be found (15, 25-27). Important limitations in these studies are that they are retrospective, involve small numbers of patients and have different definitions of RV failure (15). However, common features of patients that develop RV failure in these studies are that they are more “frail” due to liver dysfunction, renal impairment, preoperative ventilator treatment, and preoperative intra-aortic balloon pump (IABP) treatment, for example (15).

Standard treatment of RV failure after LVAD implantation is initially to optimise RV preload, for instance by fluid treatment, dialysis and adjusting LVAD flow (15, 26, 28). Furthermore, the patients are treated with drugs that decrease pulmonary vascular resistance (PVR) in order to decrease RV afterload (e.g., nitric oxide and phosphodiestrease inhibitors), and inotropic agents that increase RV contractility (15, 16, 26, 28, 29). In cases of refractory RV failure despite these efforts, the last option is to add a RVAD or veno-arterial extra corporeal membrane oxygenation (VA-ECMO) to support the failing RV (15, 16, 26, 28, 30). Biventricular support by both a LVAD and RVAD — known as biventricular assist device (BiVAD) therapy — is, however, associated with both increased morbidity (i.e., infection, bleeding, neurological dysfunction) and mortality (31, 32). The reason for this is partly due to the fact that patients with severe RV failure are in worse clinical condition, but also because it involves another major surgical procedure on an already critically ill patient (32, 33). Furthermore, BiVAD therapy is associ-

ated with an increased risk of device malfunction and is also more complicated, as flows must be balanced between the right and left side of the heart as the normal Frank-Starling mechanisms are eliminated (32, 34, 35). As there is no established RVAD therapy that enables discharge, the patients are bound to the hospital during this support (25, 34). In cases where the RVAD cannot be weaned, the only available option today is heart transplantation. Thus, refractory RV failure requiring RVAD therapy is a major problem in patients that receive a LVAD as DT, as there are no long-term treatment options.

With the increasing use of continuous flow devices, the incidence of severe RV failure has decreased (14). Still, severe RV failure requiring RVAD after implantation of modern continuous flow LVADs is reported to be 4-6% (13). In these patients the outcome is poor with a one-year mortality of about 45% compared to about 20% in patients not requiring a RVAD (31).

Treatment of RV failure through partial volume exclusion

An increase in cardiac output (CO) from the left side of the heart as a result of LVAD implantation forces the RV to produce the same increase in CO, as they are both coupled in series. If the function of the RV is impaired it will be difficult to meet this increased demand, especially since the contractility is further impaired by the LVAD therapy. This will result in blood stasis with increase central venous pressures (CVP). Recent studies demonstrated that increased CVP is one of the main causes of impaired renal function during heart failure (17, 36). Impaired renal function in turn is one of the main predictors of poor outcome in chronic heart failure, including in LVAD recipients (17, 36-39). Thus, the RV needs to be unloaded from excessive volume in cases of venous stasis after LVAD implantation.

One potential method of partially unloading the RV from excessive volume after LVAD implantation could be to create a Glenn shunt, that is a conduit between superior vena cava (SVC) and pulmonary artery. The Glenn shunt concept was originally created for palliation of congenital heart defects as a part of a Fontan procedure or a total cavopulmonary connection (TCPC) (40, 41). The modern Glenn shunt is created by an end-to-side anastomosis between the SVC and right pulmonary artery, which is known as a “bidirectional Glenn shunt” (Figure 2) (40, 41). This enables the blood to flow passively from the SVC to both the right and left pulmonary artery without passing the RV. This means that the venous return from the upper body, which is about one third of the total venous return, is diverted directly to the pulmonary circulation (40, 42). Since the flow through the Glenn shunt is passive, it is dependent on the existence of a pressure gradient between the

SVC and pulmonary artery (42). Thus, the PVR must be near normal. In general, the mean pulmonary arterial pressure must be <18 mmHg and the PVR <2 Woods units/m^2 (<160 dyn·s·cm^{-5}/m^2) in order for the Glenn shunt to function properly (42).

As previously mentioned, a Glenn shunt could be a potential treatment of RV failure after LVAD implantation, and could likely eliminate the need of a RVAD in some instances. Thereby, it would be possible to avoid another major surgical procedure and eliminate the problems associated with BiVAD therapy.

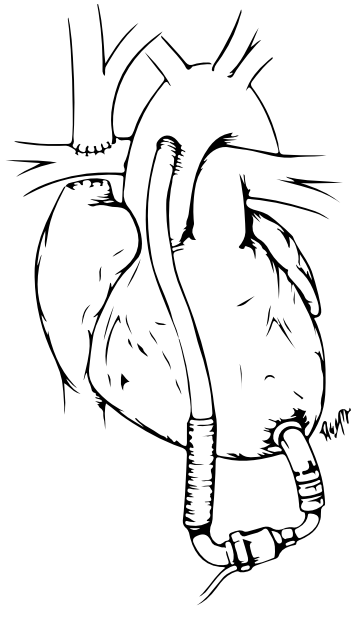

Figure 2. A Glenn shunt has been created by anastomosing the SVC to the right pulmonary artery in a heart supported with a HeartMate II LVAD. Reprinted with permission from Elsevier Incorporation.

As existing risk models of RV failure after LVAD implantation do not have reasonable predictive value, RV failure often unmasks itself in the perioperative setting after LVAD therapy is initiated (15, 26, 27). In fact, of all RVAD implantations about 65% are implanted during the primary LVAD surgery (8, 43). Furthermore, Takeda et al. reports that in 11% of patients where isolated LVAD implantation was planned, the addition of a RVAD was necessary due to refractory RV failure (43). Only 50% of these RVADs could be successfully weaned, meaning that in the remaining cases, BiVAD support was necessary until transplantation in eligible patients (43).

Unlike a RVAD, a Glenn shunt is a potential long-term treatment in patients who received the LVAD as DT and would give these patients a treatment option. This is important, as more LVAD implantations are performed with DT as the intended indication, and these patients also have an increased risk of developing RV failure (8, 20).

One major drawback of the Glenn shunt, however, is that it is not an option in pulmonary hypertension, which is estimated to affect about 40% of LVAD recipients (42, 44). However, many cases of pulmonary hypertension in chronic heart failure are secondary to LV failure (45). Thus, the pulmonary hypertension will in many cases gradually reverse over time if LV failure is treated by a LVAD (46-48).

Aims

General aims

- To create a reproducible experimental model of RV failure, and try to strengthen the validity of the model through genetic expression.
- To study the hemodynamic effects of partial volume exclusion during LVAD therapy.
- Study whether partial volume exclusion of the RV could be a potential treatment of RV failure.

Specific hypothesis

Specific hypothesis in respective study were:

Study I

Partial volume exclusion of the RV through a modified Glenn shunt will reduce venous stasis and improve hemodynamics in general (i.e. mean arterial pressure (MAP), mixed venous oxygenation (SvO_2), CO) in experimental ischemic RV failure.

Study II

Partial volume exclusion of the RV through the incorporation of a cavoaortic shunt in the LVAD circuit will reduce venous stasis and improve hemodynamics in general (i.e., MAP, CO) in experimental ischemic RV failure. This will be possible with acceptable oxygenation, despite cyanotic shunting. Since the cavoaortic shunt bypasses the pulmonary circulation, it will be a possible treatment in pulmonary hypertension, unlike the modified Glenn shunt.

Study III

Partial volume exclusion of the RV through a modified Glenn shunt will reduce venous stasis and improve hemodynamics in general (i.e., MAP, SvO_2, CO) in experimental RV failure induced through pulmonary banding.

Study IV

Partial volume exclusion of the RV through a modified Glenn shunt during LVAD therapy will reduce right ventricular stroke work (RVSW).

Methods

Experimental method

In all studies, Swedish country breed pigs weighing between 33-43 kg were used. The pigs were anesthetised and intubated, and the ventilator was set to a fraction of inspired oxygen (FiO_2) of 40% in Studies I, III and IV, and 21% in Study II. Positive end-expiratory pressure (PEEP) was set to 5 cmH_2O and volume controlled ventilation was used to reach an arterial partial carbon dioxide pressure (PCO_2) between 5.0-5.5 kPa.

A Swan-Ganz catheter was inserted through the external jugular vein, and was advanced to the pulmonary artery for measurements of pressures, CO and SvO_2. Another catheter was inserted into the external jugular vein for measurement of CVP. The femoral artery was catheterised to measure arterial blood pressure and for blood gas sampling. After these preparations, a median sternotomy was performed, and catheters were placed in the right atrium (RA) and RV for pressure measurements.

Modified Glenn shunt

In Studies I, III and IV, a modified Glenn shunt was created by anastomosing a 12 mm vascular graft end-to-side between the SVC and pulmonary artery. This enabled diversion of the flow through the modified Glenn shunt by simply placing a vascular clamp between the shunt and RA. Shunting could also easily be discontinued by removing the vascular clamp and placing it on the shunt instead. After the modified Glenn shunt was created, the azygos and hemiazygos veins were ligated to avoid collateral flow from the upper body reaching the RA when the modified Glenn shunt was in use.

Microarray

Microarray is a technique where large amounts of biological material is analysed simultaneously on a small surface, often in the form of a chip (49). Thus, there are many types of microarray platforms where, for instance, deoxyribonucleic acid (DNA), ribonucleic acid (RNA), proteins or antibodies can be analysed.

In the present studies, the microarray technique was used to analyse changes in genetic expression, which was achieved by extracting RNA from RV myocardial biopsies. The RNA was then converted to fluorescent marked complementary DNA (cDNA) and allowed to bind to the microarray chip, where there was a well with corresponding complementary sequences for each gene. Therefore, the amount of RNA in the tissue sample correlates to the amount of binding into the chip, and thereby the light intensity in the specific well (49). By comparing the light intensity in each well between two chips, it is possible to estimate the relative difference in gene expression between these microarray platforms (49). However, with this technique it is not possible to measure the absolute amount of RNA.

Conductance catheter

A conductance catheters is a device that can be placed inside a ventricle of the heart and allow real-time measurements of pressure and volume with very high resolution. The values can be plotted in a so-called "pressure-volume loop" from which several crucial hemodynamic measurement can be derived. One particularly important measurement is the work generated by the ventricle, which can be measured through the area of the pressure-volume loop.

The technique is described in detail by Baan et al. elsewhere (50-52). Briefly, the conductance catheter works by passing a high-frequency low-amplitude current from the tip to the base of the catheter, which generates an electrical field that passes through blood, myocardium and surrounding tissues. An additional pair of electrodes ordered in a segmental fashion on the catheter measures the conductance continuously, which varies with the amount of blood in the ventricle (i.e., more blood in diastole means higher conductance, and less blood in systole means lower conductance). The following equation allows calculation of the volume by the conductance measurements:

$$\text{Volume} = (1/\alpha) \cdot \rho \cdot L^2 \cdot (G - G_p)$$

In this formula: α is a volume calibration factors derived by a golden standard measurement of cardiac output, ρ is the measured resistivity of the blood, L is the segment length of the catheter, G is the sum of the instantaneously measured segmental conductance, and G_p is the so-called parallel conductance of the surrounding tissues.

Study I

A modified Glenn shunt was created in swine (n=11) (Figure 3). After the shunt was created it was closed with a vascular clamp until further use. RV failure was then induced by ligating 4-6 coronary arteries supplying the RV free wall, and was defined as right atrial pressure (RAP) >20 mmHg. After RV failure was present, the RV was partially volume unloaded for 15 minutes by diverting the blood through the modified Glenn shunt.

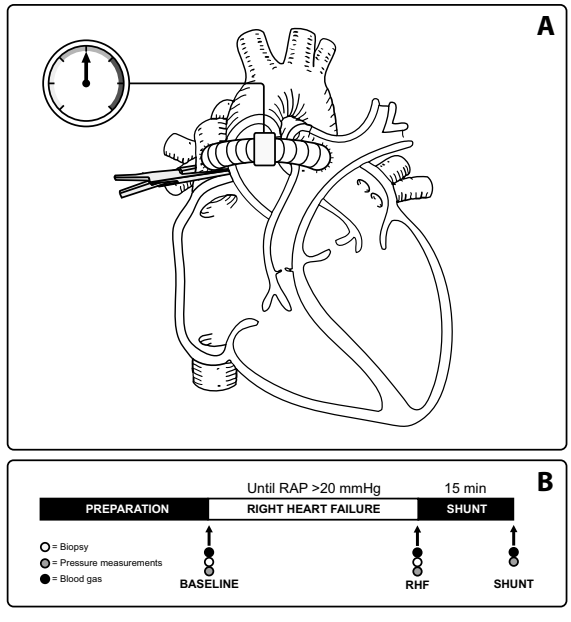

Figure 3. Demonstrates the experimental method in Study I. The modified Glenn shunt is shown in the top left with a vascular clamp on the SVC, diverting the blood through the shunt.

Measurements

During the experiment, hemodynamic measurement, blood gas analysis and RV biopsies were sampled at three time points:

1. Baseline
1. RV failure
2. Partial volume exclusion through the modified Glenn shunt

The biopsies were used for microarray analysis to study global gene expression at RV failure. CO was measured through thermodilution at baseline and RV failure. As it was impossible to use this technique when the modified

Glenn shunt was open, CO was calculated using Fick's principle. The flow in the modified Glenn shunt was measured using an ultrasonic flow probe.

Study II

RV failure was induced in swine (n=10) by ligating 4-6 coronary arteries supplying the RV free wall, and was defined as a RAP ≥20 mmHg. After RV failure was present, the LV was supported for 20 minutes by a LVAD with the flow set to the baseline CO. The LVAD circuit was created by cannulating the LV apex with a 28F venous cannula, which was connected to the inflow of a pre-primed centrifugal pump that delivered the blood to the ascending aorta trough a 16F arterial cannula (Figure 4).

After LVAD therapy, partial volume exclusion of RV was initiated by adding a cavoaortic shunt to the LVAD circuit. Treatment with LVAD and cavoaortic shunting was then continued for another 20 minutes. The cavoaortic shunt was created by cannulating the RA with a 24F venous cannula, which was then connected to LVAD circuit (Figure 4). The flow in the cavoaortic shunt was adjusted to 33% of the LVAD flow, thereby the total flow reaching the aorta was 133% of the previous LVAD flow.

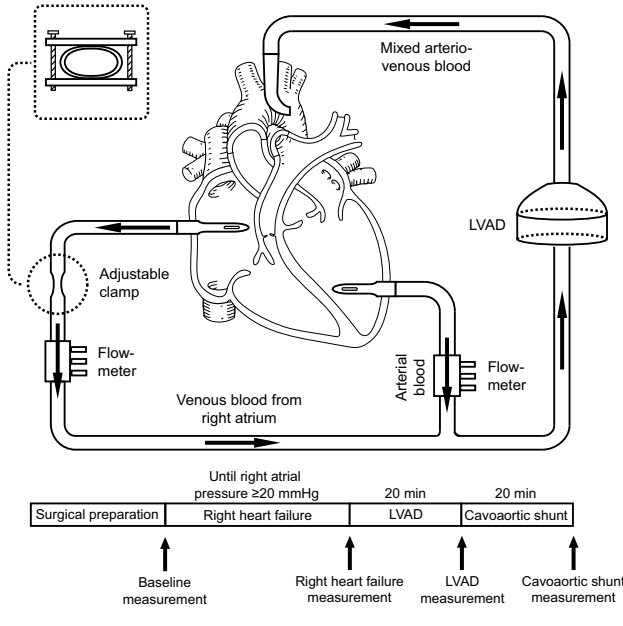

Figure 4. Demonstrates the experimental method in Study II. A LVAD was created and a cavoaortic shunt from the RA was later added to the LVAD circuit. The flow in the cavoaortic shunt was regulated by an adjustable clamp.

Measurements

During the experiment, hemodynamic measurement and blood gas analysis were sampled at four time points:

1. Baseline
2. RV failure
3. LVAD therapy
4. LVAD therapy and partial volume exclusion by cavoaortic shunting

CO was measured through thermodilution at baseline and RV failure. During LVAD therapy and cavoaortic shunting the measured LVAD flow was used as a substitute for CO. From blood gas analysis oxygen delivery (DO_2) and oxygen consumption (VO_2) were calculated at each time period.

Study III

A modified Glenn shunt was created in swine (n=11) (Figure 5). After the shunt was created it was closed with a vascular clamp until further use. RV failure was then induced by constricting the pulmonary artery, and was defined as a systolic right ventricular pressure (SRVP) twice that of the baseline value for 120 minutes. After RV failure was present, the swine were randomised to either continued pulmonary banding for 60 minutes or continued pulmonary banding with partial volume exclusion through the modified Glenn shunt for 60 minutes.

Measurements

During the experiment, hemodynamic measurement, blood gas analysis and RV biopsies were sampled at three time points:

1. Baseline
1. RV failure (i.e., pulmonary banding for 120 minutes)
2. Glenn shunt (i.e., continued pulmonary banding for 60 minutes combined with partial volume exclusion through the modified Glenn shunt) / Control (i.e., continued pulmonary banding for 60 minutes)

The biopsies were used for microarray analysis to study global gene expression at RV failure and the effect of partial volume exclusion. CO was measured through thermodilution at baseline and RV failure. As it was impossible to use this technique when the modified Glenn shunt was open, CO was cal-

culated using Fick's principle. The flow in the modified Glenn shunt was measured using an ultrasonic flow probe.

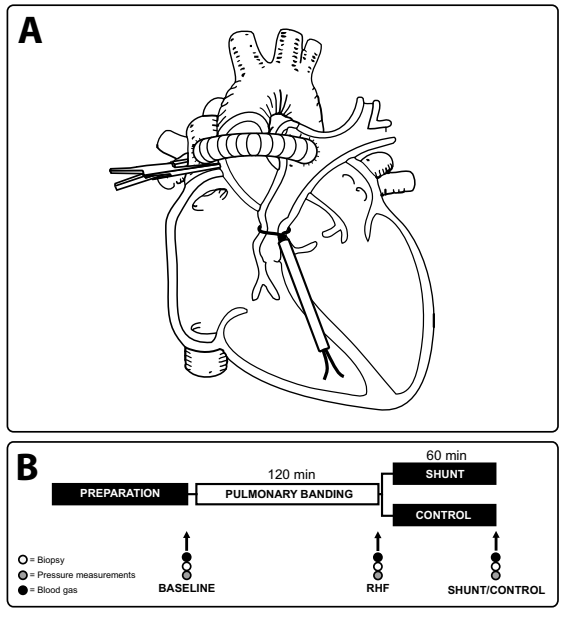

Figure 5. Demonstrates the experimental method in Study III. The pulmonary trunk was constricted with an adjustable snare. The modified Glenn shunt is shown in the top left with a vascular clamp on the SVC, diverting the blood through the shunt.

Study IV

A modified Glenn shunt was created in swine (n=8) (Figure 6). The modified Glenn shunt was then open for 20 minutes and the effect on the normal heart was studied. Afterwards the shunt was closed with a vascular clamp until further use. A LVAD was created by cannulating the LV apex with a 28F venous cannula, which was connected to a pre-primed centrifugal pump that delivered the blood to the ascending aorta trough a 16F arterial cannula (Figure 6). The LVAD was started with a flow matching the measured CO in baseline, and after 20 minutes the effects of LVAD therapy were studied. After LVAD therapy, the modified Glenn shunt was opened once again and LVAD therapy was continued for another 20 minutes, after which the effect of partial volume exclusion was studied.

Measurements

During the experiment, hemodynamic measurement, RV pressure-volume loops with the conductance catheter, and blood gas analysis were sampled at four time points:

1. Baseline
1. Partial volume exclusion through the modified Glenn shunt
2. LVAD therapy
3. LVAD therapy with partial volume exclusion through the modified Glenn shunt

Right ventricular cardiac output (RVCO) was measured through the conductance catheter, and the flow in the modified Glenn shunt was measured using an ultrasonic flow probe. The total CO was calculated as the sum of the RVCO and the flow in the modified Glenn shunt.

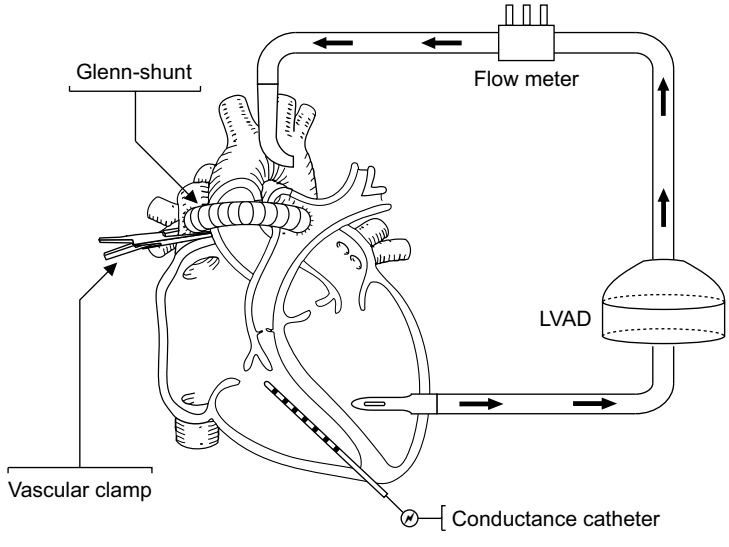

Figure 6. Demonstrates the experimental method in Study IV. A LVAD circuit was created. The modified Glenn shunt is shown in the top left with a vascular clamp on the SVC, diverting the blood through the shunt. The conductance catheter was inserted into the RV through the apex of the heart.

Statistics

During the experiments, the hemodynamic values used at each time point were based on the mean of five measurements, while blood gas analysis was

based on one measurement. For pressure volume-loops, the value at each time point was based on the mean value of 25 loops.

Data analysis was performed in the statistical programs SPSS Statistics and R. As the experiments contained relatively few subjects, normal distribution could not be assumed. Hence, non-parametric statistics were used. In the case of in-subject comparison the Wilcoxon signed-rank test was used, and in case of between-subject comparison the Mann-Whitney U test was used. Values are presented as median with 95% confidence interval in brackets in Studies I-III, and as median with interquartile range in brackets in Study IV. P-values ≤ 0.05 were considered statistically significant.

Statistical analysis of genetic expression was performed in Partek Genomic Suite through variance analysis in Study I. Statistical analysis of genetic expression in Study III was performed in the statistical program R. Relative differences in gene expression were compared with a moderated t-test, and are presented as fold change using the binary logarithm. To address the problem with multiple hypotheses testing, the p-values were adjusted according to the method of Benjamini and Hochberg to a q-value in Study III. Q-values ≤ 0.1 were considered statistically significant. Genes with a q-value ≤ 0.01 and fold change ≥ 2.0 were converted to homologous human genes and grouped in gene ontology categories for analysis of genetic pathways.

Results

Study I

Baseline versus RV failure

RAP increased from 6.6 mmHg (6.1-7.8) to 20 mmHg (20-21) at RV failure (Figure 7). CO decreased from 3.7 L/min (3.5-4.2) to 2.3 L/min (2.0-2.6), and MAP decreased from 73 mmHg (67-94) to 56 mmHg (48-56). Furthermore, SvO_2 decreased from 72% (57-81) to 32% (19-44) (Figure 8).

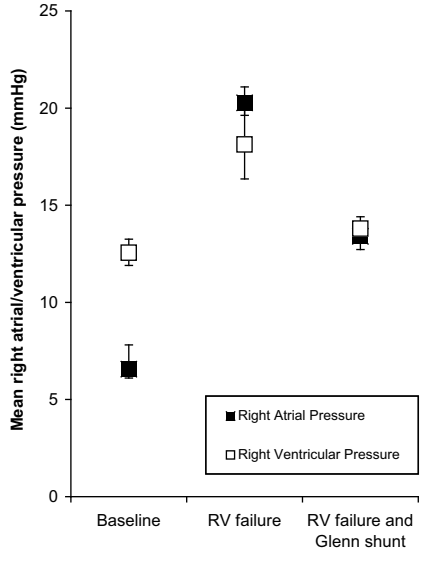

Figure 7. Demonstrates median values of RAP and mean RV pressure with 95% confidence interval.

RV failure versus modified Glenn shunt

The median flow in the modified Glenn shunt was 681 mL/min (483-777). After shunting, RAP decreased from 20 mmHg (20-21) to 13 mmHg (13-14) ($p<0.01$) (Figure 7). CO increased from 2.3 L/min (2.0-2.6) to 2.9 L/min (2.5-3.3) ($p<0.01$), and MAP increased from 56 mmHg (53-60) to 68 mmHg (66-76) ($p<0.01$). Moreover, SvO_2 increased from 32% (27-38) to 49% (45-56) ($p<0.01$) (Figure 8).

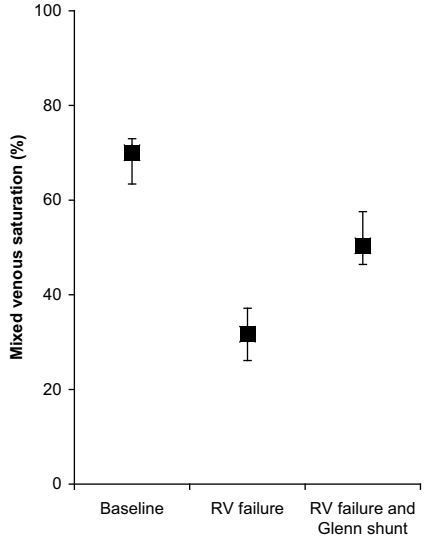

Figure 8. Demonstrates median SvO_2 with 95% confidence interval.

Microarray

Several genes previously associated with heart failure were up-regulated at RV failure. The three most up-regulated genes were: Heat shock protein 27 kDa protein 2 (HSPB2) ($p=0.05$), Natriuretic peptide A (NPPA) ($p=0.02$), and Forkhead box J3 (FOXJ3) ($p<0.01$).

Study II

Baseline versus RV failure

CO decreased from 3.4 L/min (2.6-4.2) to 2.0 L/min (1.5-2.5) (p=0.01), and RAP increased from 11 mmHg (9.0-11) to 20 mmHg (20-22) (p<0.01) (Figure 9). Furthermore, DO_2 decreased from 379 mL/min (296-502) to 176 mL/min (131-200) (p<0.01), and VO_2 decreased from 185 mL/min (130-202) to 81 mL/min (70-103) (p<0.01) (Figure 10).

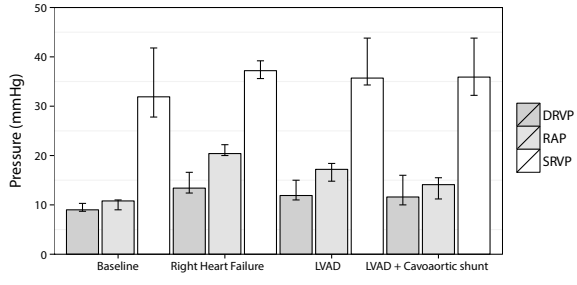

Figure 9. Demonstrates median values of RAP, diastolic RV pressure (DRVP) and SRVP with 95% confidence interval.

RV failure versus LVAD

The median LVAD flow was 3.4 L/min (2.6-4.2). During LVAD therapy RAP decreased from 20 mmHg (20-22) to 17 mmHg (15-18) (p<0.01) (Figure 9). Moreover, DO_2 increased from 176 mL/min (131-200) to 271 mL/min (197-308) (p<0.01), and VO_2 increased from 81 mL/min (70-103) to 148 mL/min (107-152) (p<0.01) (Figure 10).

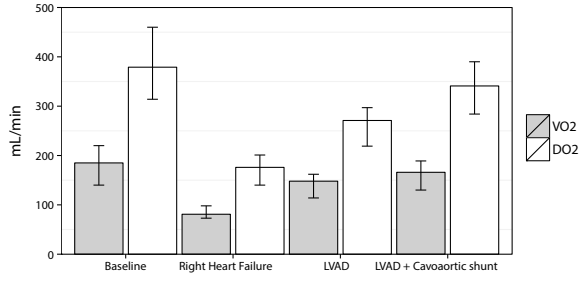

Figure 10. Demonstrates median values of VO_2 and DO_2 with 95% confidence interval.

LVAD versus LVAD with cavoaortic shunt

During cavoaortic shunting the LVAD flow increased from 3.4 L/min (2.6-4.2) to 4.9 L/min (3.5-5.6) ($p<0.01$), and RAP decreased from 17 mmHg (15-18) to 14 mmHg (11-16) ($p<0.01$) (Figure 9). MAP increased from 71 mmHg (68-80) to 82 mmHg (71-93) ($p<0.01$). SaO_2 decreased from 96% (95-98) to 87% (83-92) ($p<0.01$), while DO_2 increased from 271 mL/min (197-308) to 341 mL/min (271-386) ($p<0.01$) (Figure 10). Both SvO_2 ($p=0.24$) and VO_2 ($p=0.07$), on the other hand, remained unchanged during cavoaortic shunting compared with LVAD therapy alone (Figure 10).

Study III

Baseline versus RV failure

RAP increased from 10 mmHg (9.0-12) to 18 mmHg (16-22) ($p<0.01$), and SRVP increased from 31 mmHg (26-35) to 57 mmHg (49-61) ($p<0.01$) (Figures 11 and 12, respectively). Furthermore, the heart rate increased from 68 bpm (62-84) to 93 bpm (78-109) ($p<0.01$). However, both CO ($p=0.14$) and MAP ($p=0.06$) remained unchanged.

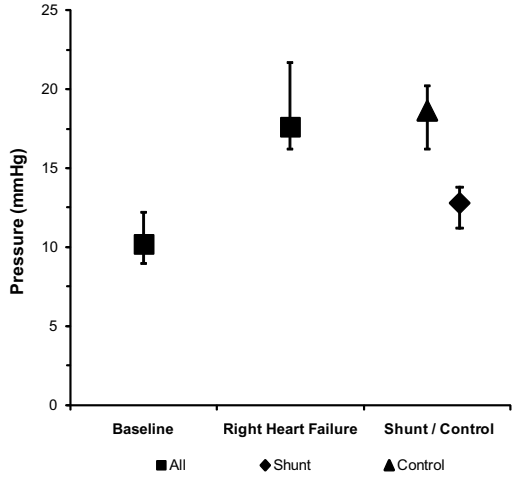

Figure 11. Demonstrates median RAP with 95% confidence interval.

RV failure versus Glenn shunt (In-group comparison)

The median shunt flow was 451 mL/min (214-626). RAP decreased from 18 mmHg (15-20) to 12 mmHg (11-14) (p=0.03) after the shunt was opened (Figure 11). However, SRVP remained unchanged (p=0.75) (Figure 12). MAP decreased from 63 mmHg (56-80) to 53 mmHg (44-58) (p=0.03), while CO remained unchanged (p=0.08).

Glenn shunt versus control (Between-group comparison)

RAP was lower in the Glenn shunt group, 12 mmHg (11-14), compared with the control group, 19 mmHg (16-20) (p<0.01) (Figure 11). The heart rate was also higher in the Glenn shunt group, 108 bpm (95-120), compared with 87 bpm (70-99) in the control group (p=0.02). Otherwise, there was no difference in general hemodynamics between the two groups.

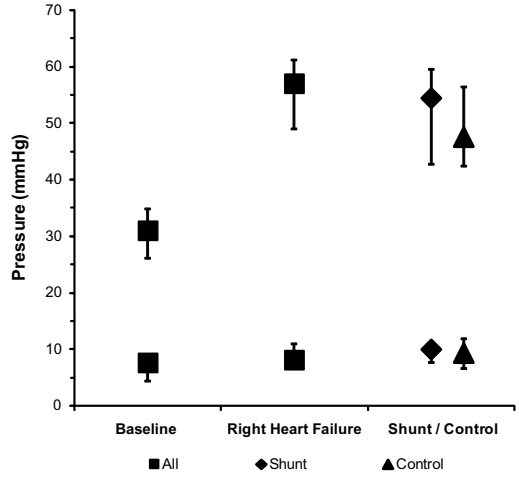

Figure 12. Demonstrates median values of DRVP and SRVP with 95% confidence interval.

Microarray

9363 genes were significantly altered between baseline and RV failure. Among the most up-regulated genes, important common genetic pathways identified were: “organ development”, ”negative regulation of cellular process”, ”negative regulation of programmed cell death”, “cell migration”, “cell motility” and “inflammatory response”. Furthermore, genes previously associated with both heart failure and myocardial fibrosis were up-regulated.

There were, however, no significant alterations in gene expression after treatment with the Glenn shunt.

Study IV

Baseline versus LVAD

After LVAD therapy was initiated, RAP increased from 9 mmHg (9-9) to 15 mmHg (12-15) (p=0.01), right ventricular stroke volume (RVSV) increased from 30 mL (29-40) to 49 mL (42-53) (p<0.01), and right ventricular end-diastolic volume (RVEDV) increased from 50 mL (49-67) to 85 mL (55-88) (p=0.05). RVCO also increased from 2.8 L/min (2.2-3.2) to 4.8 L/min (3.7-5.8) (p<0.01) (Figure 13). Moreover, RVSW increased from 535 mmHg*mL (424-717) to 708 mmHg*mL (654-1193) (p=0.04) (Figure 14). MAP increased from 86 mmHg (74-99) to 98 mmHg (88-103) (p=0.04), and SvO_2 increased from 58% (46-62) to 64% (58-70) (p=0.02).

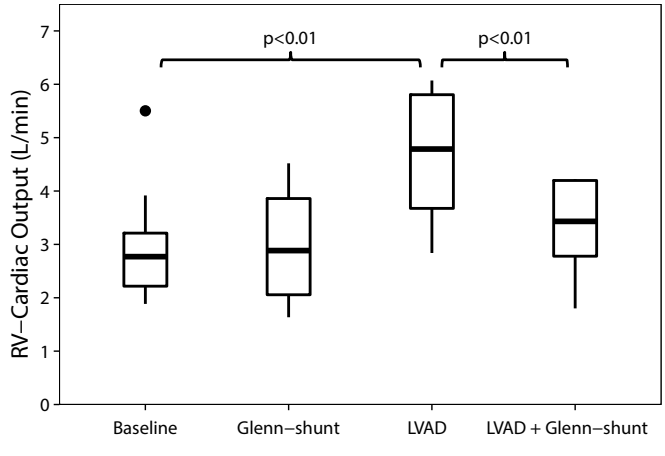

Figure 13. Demonstrates box plots of RVCO at the different time points of the experiments.

LVAD versus LVAD with modified Glenn shunt

The median flow in the modified Glenn shunt was 580 mL/min (430-700). After the modified Glenn shunt was opened, RAP decreased from 15 mmHg (12-15) to 10 mmHg (7-11) (p=0.01), RVSV decreased from 49 mL (42-53) to 34 mL (33-38) (p<0.01), and RVEDV decreased from 85 mL (55-88) to 60 mL (48-69) (p=0.05). RVCO also decreased from 4.8 L/min (3.7-5.8) to

3.4 L/min (2.8-4.2) ($p<0.01$) (Figure 13). Furthermore, RVSW decreased from 708 mmHg*mL (654-1193) to 465 mmHg*mL (366-711) ($p=0.02$) (Figure 14). MAP decreased from 98 mmHg (88-103) to 84 mmHg (74-89) ($p=0.02$), and SvO_2 decreased from 64% (58-70) to 46% (35-55) ($p<0.01$).

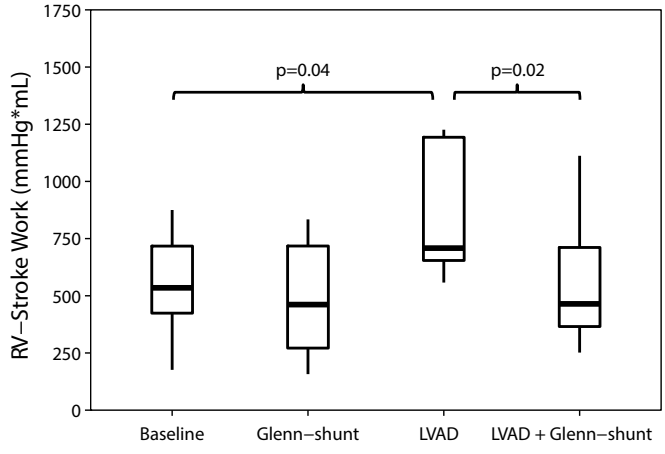

Figure 14. Demonstrates box plots of RVSW at the different time points of the experiments.

Discussion

Right heart failure is a complex clinical syndrome with many different etiologies (53). The clinical manifestations can roughly be divided into backward failure with fluid retention (i.e., peripheral edema, ascites) and forward failure (i.e., low CO) (53). However, right heart failure can also exist as RV dysfunction without clinical manifestations, evident only as abnormalities of filling properties and contractions (53). This illustrates the complexity of the syndrome, and why there is a lack of a clear and uniform definition of RV failure (16, 22).

Perioperative right heart failure after LVAD implantation is even more complex since several eliciting causes often exists (e.g., volume overload, ventricular interdependence, ischemia, reperfusion injury) (15). This makes the condition even harder to assess and treat properly, and efforts to optimise preload, afterload and contractility must be made simultaneously (15, 16, 26, 28, 29). Despite the more complex nature of perioperative right heart failure during LVAD therapy, the clinical manifestations in terms of forward and backward failure are the same as in right heart failure without LVAD therapy.

Since forward failure of the RV causes forward failure from the LV, their clinical effects are the same (i.e., hypoperfusion). Thus, backward failure with fluid retention and thereby venous congestion is the main clinical feature of RV failure. Venous congestion has recently been recognised as an important cause of morbidity in heart failure, mainly by causing secondary renal and liver failure (17, 36, 54). As renal failure is known to be one of the main determinants of poor outcome in heart failure, more efforts have recently been made to reduce fluid retention and venous pressures in these patients (17, 36, 54, 55).

Experimental models

The purpose of this thesis was to investigate whether partial volume exclusion could be used as a treatment of RV failure. The ultimate aim was to use the concept of partial volume exclusion to treat refractory RV failure after LVAD surgery. Given the lack of definition, RV failure first had to be defined in order to create an experimental model in which it could be studied.

As previously mentioned, venous congestion is the main clinical manifestation of RV failure. Furthermore, the importance of venous congestion as a marker of RV failure has also been recognised in clinical studies, and CVP is therefore used in several risk scores to predict the need for RVAD implantation after LVAD surgery (16, 24, 31). Increased CVP (>18 mmHg) is also a main criterion in INTERMACS' suggested definition of RV failure after LVAD surgery, in addition to symptoms such as peripheral edema and ascites (i.e., backward failure), and reduced CO (i.e., forward failure) (15).

Given this importance of venous congestion, RAP was used to define RV failure experimentally, and also as the main treatment effect in this thesis. More specifically, RV failure was defined as a RAP $\geq$20 mmHg in the ischemic model used in Studies I-II. Moreover, RAP reduction was also the main outcome measurement in these studies. In Study III, a pressure-volume overload model was used instead, and RV failure was defined by SRVP. However, RAP reduction was also the main outcome measurement in this study.

In both experimental models, genetic expression analysis revealed upregulation of genes previously associated with heart failure. Thus, RV failure was defined both by hemodynamic parameters and genetic expression in this thesis. This strengthens the validity of the experimental models, compared with most previously published models which only used hemodynamic measurements to define RV failure.

Effects of partial volume exclusion

The main finding of this thesis is that partial volume exclusion of the RV is a feasible treatment of experimental RV failure. It demonstrates that both the modified Glenn shunt and cavoaortic shunt effectively reduced venous congestion and improved general hemodynamics in experimental ischemic RV failure. Moreover, it demonstrates that LVAD therapy puts a strain on even the normal RV through increased RVSW and increased RVEDV with secondary venous congestion as a consequence. These deleterious effects of LVAD therapy were effectively reduced by partial volume exclusion through a modified Glenn shunt. It is likely that the strain caused by the LVAD on the normal RV would have more negative effects if the case of preexisting RV dysfunction.

The concept of partial volume exclusion through a Glenn shunt has since long been used in congenital heart surgery (40, 42). However, the potential use in RV failure during LVAD therapy is limited to case reports and experimental studies (56-58). Danton et al. previously demonstrated that a modified Glenn shunt improves contractility and relaxation of the LV by limiting RV dilatation, and restoring LV geometry during experimental ischemic RV failure (57). Moreover, Succi et al. demonstrated that a Glenn shunt reduced

RV pressures and overload in addition to improving pump flow during concomitant LVAD therapy in severe biventricular heart failure (58).

However, the ability to use partial volume exclusion in the structurally normal heart to reduce venous congestion is previously not well described. This potential use of partial volume exclusion is an intriguing finding of this thesis, as venous congestion is recognised as a major determinant in the development of both secondary liver and renal failure in heart failure patients (17, 36, 54). Worsening renal function in particular has been demonstrated to be strongly associated with increased CVP (17, 36, 54). Mullens et al. has even suggested the term "congestive kidney failure" to describe this condition (54). This negative impact of increased CVP on renal function exists even in the absence of reduced CO (36, 54). However, increased CVP has even more negative impact on renal function if it exists in conjunction with a low CO state (36).

In LVAD patients, preoperative renal failure has repeatedly been demonstrated to be a main determinant of poor outcome both in the short and long term (37-39). Moreover, the HeartMate Risk Score, which has been demonstrated to predict poor outcome after LVAD implantation, consists mainly of marker of renal (i.e., creatinine) and liver dysfunction (i.e., albumin and international normalised ratio [INR]) (39, 59). Thus, reducing venous congestion and potentially improving both renal and liver function is likely to have positive effects on the outcome in LVAD recipients. Prevention of secondary end-organ failure (e.g., renal, liver) in LVAD recipients is also important since it may be a contraindication to future heart failure in BTT patients (60). Moreover, impaired renal function is also associated with a worse outcome after heart transplantation (61).

Clinical implications

As the number of LVAD implantations increase, so will likely the numbers of patients with RV failure (4). Since BiVAD therapy is problematic, as it is associated with a poor outcome, and RVAD therapy cannot be weaned in about half the patients, an alternative treatment is needed (32, 34, 35, 43). Given the feasibility of partial volume exclusion as a treatment in experimental RV failure, it is likely that it also could be used to treat RV failure during LVAD therapy in a clinical situation. In some instances, it might even eliminate the need of a RVAD.

A Glenn shunt would have several advantages over a RVAD in RV failure without pulmonary hypertension. It is less invasive than a RVAD implantation, permits hospital discharge and enables a long-term treatment in DT. The latter is important as implantations with this indication increases and these patients have an increased risk of developing RV failure (8, 20). A Glenn shunt would also eliminate the problem with pump flow mismatch

associated with BiVAD therapy, as the normal compensatory mechanisms in the RV is left intact (34, 35). Another possible indication for a Glenn shunt could be patients with less severe RV failure since it would permit higher pump flows without straining the RV, in addition to reducing venous congestion. Higher pump flow is not only beneficial because it increases CO and thereby prevents secondary end-organ failure, but also because it decreases the risk of pump thrombosis (62).

A cavoaortic shunt could be an alternative to a RVAD in RV failure with pulmonary hypertension, where the Glenn shunt would not be feasible. Like the Glenn shunt, the cavoaortic shunt is also less invasive and eliminates the problem with pump flow mismatch compared with a RVAD. Moreover, as it increases systemic blood flow without affecting pulmonary blood flow, the flow is not limited by the PVR. As the PVR can be increased by both long-standing left ventricular failure and perioperative factors it often improves after LVAD implantation (15, 46-48). Thus, a cavoaortic shunt could be used instead of a RVAD as a bridge until the PVR decreases and the shunt can be weaned. In the case of PVR normalising but RV failure persisting, the cavoaortic shunt could also be used as a bridge to a Glenn shunt.

Limitations

This thesis has several limitations. One obvious limitation is that all experiments are of acute nature; therefore, the results have not been verified in a longer perspective. Moreover, in all of the experiments an open chest model with open pericardium was used. This may have reduced the secondary consequences of RV dilatation on the LV (63). Furthermore, the technique of pressure-volume loops was initially developed for measurements of the LV. However, the method has more recently been used in the RV as well, and has been found to give accurate measurements (64).

The Glenn shunt technique is limited in that some patients develop arteriovenous malformations in the pulmonary circulation, resulting in right-to-left shunting with progressive cyanosis (65, 66). Also, development of collateral circulation where venous return from the SVC can reach the inferior vena cava occurs (65). However, arteriovenous malformation only develops in about 10-25% of patients and usually occurs in young children (65, 66). Moreover, both of these complications take years to develop, which are a long time span in the LVAD population (65, 66).

Conclusions

Two models of experimental RV failure were created: one ischemic and one due to pressure volume overload. Both models were validated through genetic expression.

Study I

A modified Glenn shunt reduces venous congestion and improves general hemodynamics during experimental ischemic RV failure. Thus, partial volume exclusion through a modified Glenn shunt is feasible as a treatment of acute ischemic RV failure.

Study II

A cavoaortic shunt reduces venous congestion and improves general hemodynamics during LVAD therapy. This is feasible with sustained oxygen delivery despite cyanotic shunting. Thus, partial volume exclusion trough a cavoaortic shunt is a possible treatment of acute ischemic RV failure with pulmonary hypertension during LVAD therapy.

Study III

A modified Glenn shunt reduces venous congestion, but does not improve general hemodynamics compared with a control group during experimental RV failure due to pulmonary banding. Thus, the use of a modified Glenn shunt in this setting is limited to reducing venous congestion. Furthermore, pressure-volume overload of the RV has a profound impact on genetic expression.

Study IV

LVAD therapy can put a strain on the RV trough dilatation, increased stroke work and venous congestion. These effects can be partly reversed by a modi-

fied Glenn shunt. Thus, a modified Glenn shunt is a feasible treatment of the deleterious effects of LVAD therapy on the RV.

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