Echocardiographic assessment of ventricular size and function in heart transplant patients

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Echocardiographic assessment of ventricular size and function in heart transplant patients

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LUND
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Abstract

The overall aims of this thesis were to use echocardiography to non-invasively, delineate early structural and functional changes following orthotopic heart transplantation (OHT), and to define reference values in the context of gender and bridging with mechanical circulatory support.

Several factors might affect myocardial function in OHT patients rendering the use of normal values for transthoracic echocardiography derived from healthy subjects unsatisfactory. Recent echocardiographic reference values have been specified by gender but the disparity in relation to gender and gender mismatch between donor and recipient has not been studied in the OHT cohort. Early ventricular adaptation following OHT is sparsely studied, and specific reference values adapted to this unique cohort are abscent. Moreover, the impact of pre-conditioning with left ventricular assist device (LVAD) used in a growing number of end-stage heart failure patients awaiting OHT needs further evaluation. Speckle tracking derived strain has gained increasing interest due to its ability to detect discrete changes in myocardial contractility. The possible additive value of this echocardiographic parameter to assess left- and right- (LV and RV) ventricular function in the OHT cohort warrants further investigation.

The results of this thesis delivers the findings that atrial enlargement is present and ventricular size and function is altered in OHT patients. In terms of measures of LV function, ejection fraction (EF) and LV global longitudinal strain (LVGLS) along with all measures of RV function were reduced compared to reference values for the normal population. With regard to gender we found that male recipients had larger LV mass, thicker septal wall and larger LV volume. A slightly higher EF was detected in female recipients vs. male recipients whereas no differences were observed for conventional RV function parameters between the genders. Both LV- and RV- ventricular strain was higher in females than in males. The male recipients receiving a female donor heart had comparable EF and strain parameters to the female recipients receiving a gender-matched heart. Analysis of early adaptation following OHT revealed that LV function parameters remained stable between one and twelve months after OHT while a continuous improvement in RV function parameters, including strain, was seen. In patients bridged with LVAD we found that RV adaptation post OHT was accelerated and the values of echocardiographic function parameters obtained at one month remained unaltered during twelve months follow-up. Thus, at twelve months differences between the groups were no longer detectable.

To clonclude, the distribution of several routinely used echocardiographic measures differ in stable OHT patients as compared to healthy subjects suggesting that specific reference values should be applied when assessing normality in this cohort. The fact that rejection is more common early following transplantation supports the importance of defining values of early normal adaptation in order to tailor the examination to detect adverse events. Moreover, the knowledge regarding how recipient gender and preconditioning with LVAD affect ventricular function following OHT is clinically relevant to adequately examine OHT patients with echocardiography.

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To: Those that holds a very special place in my heart!

A winner is a dreamer who never gives up
- N. Mandela

Live as if you were to die tomorrow,
Learn as if you were to live forever
- M. Ghandi

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List of papers

The present thesis is based on the following papers, referred to in the text by their respective Roman numerals.

I. **Ingvarsson A**, Werther Evaldsson A, Waktare J, Smith GJ, Roijer A, Rådegran G, Meurling C. Normal reference ranges for transthoracic echocardiography following heart transplantation. J Am Soc Echocardiogr. 2018 Mar; 31(3): 349-360.

II. **Ingvarsson A,** Werther Evaldsson A, Smith GJ, Waktare J, Nilsson J, Stagmo M, Roijer A, Rådegran G, Meurling C. Impact of gender on echocardiographic characteristics in heart transplant recipients. Clin Physiol Funct Imaging 2019; 39(4): 246-254.

III. **Ingvarsson A**, Werther Evaldsson A, Waktare J, Smith GJ, Roijer A, Rådegran G, Meurling C. Echocardiographic assessment of changes in chamber size and ventricular function during the first year following heart transplantation. Clin Physiol Funct Imaging 2021; 41(4): 355-365.

IV. **Ingvarsson A**, Gjesdal G, Borgenvik S, Werther Evaldsson A, Waktare J, Braun O, Smith GJ, Roijer A, Rådegran G, Meurling C. Impact of bridging with left ventricular assist device on right ventricular function following heart transplantation. Submitted to ESC Heart failure 210618.

Scientific contribution that are not included in this dissertation are as follows:

1. Ahlm A, **Ingvarsson A**, Wang X. Significance of lung hyperinflation in chronic obstructive pulmonary disease. Journal of organ dysfunction. 07/2009; 3(1): 44-54.
2. Hyllén S, Nozohoor S, **Ingvarsson A**, Meurling C, Wierup P, Sjögren J. Right ventricular performance after valve repair for chronic degenerative mitral regurgitation. J. Ann Thorac Surg. 2014; 98(6):2023-30.
3. Ostenfeld E, Werther Evaldsson A, Engblom H, **Ingvarsson A,** Roijer A, Meurling C, Holm J, Rådegran G, Carlsson M. Discriminatory ability of right atrial volumes with two- and three-dimensional echocardiography to detect elevated right atrial pressure in pulmonary hypertension. Clin Physiol Funct Imaging 2018; 38(2): 192-199.
4. Werther Evaldsson A, **Ingvarsson A**, Waktare J, Smith GJ, Thilén U, Stagmo M, Roijer A, Rådegran G, Meurling C. Right ventricular speckle tracking assessment for differentiation of pressure versus volume overload. Clin Physiol Funct Imaging 2018; 38(5): 763-771.
5. Werther Evaldsson A, **Ingvarsson A**, Smith GJ, Rådegran G, Roijer A, Waktare J, Ostenfeld E, Meurling C. Echocardiographic right ventricular strain from multiple apical views is superior for assessment of right ventricular function in patients with pulmonary hypertension. Clin Physiol Funct Imaging 2018; 39(2): 168-176.
6. Werther Evaldsson A, Lindholm A, Jumatate R, **Ingvarsson A**, Smith GJ, Waktare J, Rådegran G, Roijer A, Meurling C, Ostenfeld E. Right ventricular function parameters in pulmonary hypertension: Echocardiography vs. cardiac magnetic resonance. BMC Cardiovasc Disorders 2020 Jun 1; 20(1): 259.
7. Jumatate R, **Ingvarsson A**, Smith GJ, Roijer A, Ostenfeld E, Waktare J, Rådegran G, Meurling C, Werther Evaldsson A. Right ventricular stroke work index in adult patients with pulmonary arterial hypertension: - a comparison between echocardiography and right heart catheterization. BMC Cardiovasc Disorders 2021 Apr 30; 21(1): 219.
8. Borgenvik S, Jumatate R, Gjesdal G, Werther Evaldsson A, O Braun, Smith JG, Rådegran G, Meurling C, **Ingvarsson A**. Impact of post- transplant diabetes on left ventricular function following heart transplantation. Submitted

Summary

The overall aims of this thesis were to non-invasively, through echocardiography, delineate early structural and functional changes following orthotopic heart transplantation (OHT) and define reference values in the context of gender and bridging with mechanical circulatory support

Several factors might affect myocardial function in OHT patients that would render the use of normal values for transthoracic echocardiography (TTE) derived from healthy subjects unsatisfactory. Recently published echocardiographic reference values have been specified by gender, but the disparity in relation to gender and gender mismatch between donor and recipient has not been studied in the OHT cohort. Early ventricular adaptation following OHT is sparsely studied, and specific reference values adapted to this unique cohort are absent. Moreover, the impact of pre-conditioning with left ventricular assist device (LVAD) used in a growing number of end-stage heart failure patients awaiting OHT needs further evaluation. Speckle tracking derived (STE) strain have gained increasing interest due to its ability to detect discrete and early changes in myocardial contractility. The possible additive value of this echocardiographic parameter to assess left- and right- (LV- and RV-) ventricular function in the OHT cohort warrants further investigation.

The results of this thesis give the finding that atrial enlargement is present and ventricular size and function is altered in OHT patients. Measures of LV function; ejection fraction (EF) and LV global longitudinal strain (LVGLS) along with all measures of RV function were reduced compared to reference values for the normal population. We also detected a tendency of further decreased EF and LVGLS in patients with previous treatment requiring rejection episodes. Regarding gender we found that male recipients had larger LV mass, thicker septal wall, and larger LV volume. A slightly higher EF was detected in female recipients vs. male recipients whereas no differences were observed for conventional RV function parameters between the genders. Both LV- and RV- longitudinal strain was higher in females than in males. Moreover, the male recipients receiving a female donor heart had EF and strain parameters in line with the female recipients receiving a gender-matched allograft. Analysis of early adaptation following OHT revealed that LV function parameters remained stable between one and twelve months after OHT while a continuous improvement in RV function parameters, including strain, was seen. In patients bridged with LVAD we found that RV adaptation post OHT was accelerated and the values of echocardiographic RV function-parameters obtained at one month remained unaltered during twelve months follow-up. Thus, at twelve months no difference between the groups were longer detectable.

To conclude, the distribution of several routinely used echocardiographic measures differ in stable OHT patients as compared to healthy subjects suggesting that specific reference values should be applied when assessing normality in this cohort. The fact that rejection is more common early following transplantation supports the importance of defining values of early normal adaptation in order to tailor the examination to detect adverse events. Moreover, the knowledge regarding how recipient gender and preconditioning with LVAD affect ventricular function following OHT is clinically relevant to adequately examine OHT patients with echocardiography.

Populärvetenskaplig sammanfattning

Hjärtsvikt definieras vanligtvis som att hjärtat inte förmår pumpa ut tillräckligt med blod för att tillgodose kroppens behov. Den vanligaste orsaken till hjärtsvikt i Sverige är kranskärlssjukdom och högt blodtryck. Mindre vanliga orsaker är olika former av hjärtmuskelsjukdomar, klaffel samt komplexa medfödda hjärtfel. Prevalensen av hjärtsvikt ökar kontinuerligt och för närvarande anser man att cirka 2 % av totalbefolkningen i Sverige lider av hjärtsvikt. Bland personer över 80 år har förekomsten ökat till cirka 10 %. Vid avancerad hjärtsvikt utgör, för selekterade patienter, hjärttransplantation (HTx) det sista behandlingsalternativet när all annan kirurgisk eller medicinsk behandling är prövad och befunnen otillräcklig. I väntan på hjärttransplantation kan en del patienter erbjudas understödjande behandling med en mekanisk pump (LVAD). Denna pump opereras in och ansluts till vänster kammare samt till kroppspulsådern och avlastar den sviktande vänsterkammaren för att upprätthålla tillräcklig hjärt-minutvolym och därmed minska hjärtsvikt-symptomen.

Vid Skånes Universitetssjukhus i Lund (SUS-Lund) har man utfört HTx sedan 1988 och från och med 2011 har Lund tillsammans med Göteborg tilldelats rikssjukvårdsuppdraget med nationellt ansvar för HTx. Uppföljning sker enligt ett väldefinierat omfattande program med täta kliniska kontroller, framför allt under det första året. Förutsatt att patienten är stabil glesnas kontrollerna sedan ut till årskontroller.

Det finns flera metoder för att med hjälp av bilddiagnostik bedöma hjärtats storlek och funktion. Vid de rutinmässiga kontrollerna efter HTx undersöks det transplanterade hjärtat vanligtvis med hjärtultraljud (ekokardiografi). Det är en förhållandevis enkel, smärtfri och ofarlig metod. Med hjälp av ekokardiografi kan man mäta hjärtrummens storlek, vänster kammares väggtjocklek samt på olika sätt värdera såväl vänster som höger kammares pumpförmåga. Ekokardiografi är liksom annan bilddiagnostik under ständig utveckling och nya mätmetoder utvecklas kontinuerligt, vilket skapar förbättrade förutsättningar för mer detaljerade bedömningar. För att värdera vänsterkammarens funktion används vanligen ejektionsfraktion (EF), vilket är en procentuell uträkning av skillnaden mellan vänster kammares volym i diastole och systole (hjärtats vilofas respektive kontraktionsfas). Med den nya metoden ”strain” kan man även mäta hur mycket hjärtmuskeln drar ihop sig relativt sin ursprungliga längd, vilket ger en ytterligare uppfattning om kammarens funktion. För höger kammare finns det flertalet surrogatmått som tillsammans beskriver kammarfunktion, men även här är ”strain” ett lovande tillskott.

De senaste åren har det kommit nya riktlinjer för normalvärden inom hjärtultraljud. Detta tillsammans med kunskapen om att HTx torde inverka på kammarfunktionen

har lett till ett behov av specifika normalvärden som är anpassade för denna patientpopulation.

Resultaten av detta avhandlingsarbete visar att HTx bortsett från förstorade förmak leder till lägre värden på de mått som används för att bedöma såväl vänster som höger kammares funktion. Hjärtfunktionen hos patienter som genomgått HTx skiljer sig således från publicerade normalvärden hos icke-transplanterade patienter. Vi fann även att det föreligger en skillnad mellan ekokardiografiska funktionsmått utifrån könet på mottagaren av det nya hjärtat. Våra studier har vidare påvisat att vänsterkammaren återhämtar sin funktion redan inom en månad efter HTx medan högerkammarens återhämtning är betydligt långsammare. Höger kammare förefaller gradvis öka sin funktion under det första året efter utförd HTx. Slutligen har vi visat att de patienter som behandlats med LVAD innan HTx tycks ha normaliserat sin högerkammarfunktion redan vid en månads uppföljning. Denna förblir därefter oförändrad under det första året. Först vid 1-års uppföljningen är högerkammarfunktionen hos de patienter som inte förbehandlats med LVAD på jämförbar nivå.

Sammanfattningsvis stödjer våra resultat att specifika referensvärden som föreslagits i **arbete I** bör användas för denna patientpopulation. Förståelse för den tidiga återhämtningen det första året (**arbete III)**, tillsammans med kunskap om hur mottagens kön (**arbete II**) samt förbehandling med LVAD (**arbete IV**) kan inverka på hjärtfunktionen utgör viktig klinisk information för att bedöma dessa patienters hjärtultraljud på ett korrekt sätt.

Abbreviations

2D	two-dimensional
3D	three-dimensional
BP	blood pressure
BSA	body surface area
CAV	cardiac allograft vasculopathy
CI	cardiac index
CMR	cardiac magnetic resonance
CO	cardiac output
CVP	central venous pressure
CW	continuous wave
DAP	diastolic arterial pressure
DM	diabetes mellitus
dPAP	diastolic pulmonary arterial pressure
e´	tissue doppler of early diastolic velocity
E/A	ratio between MVE and MVA
E/e´	ratio between MVE and e´
Ea	effective arterial elastance
EDV	end diastolic volume
ESV	end systolic volume
EF	ejection fraction
FAC	fractional area change
FS	fractional shortening
GCS	global circumferential strain
GLS	global longitudinal strain
HF	heart failure
HFpEF	heart failure with preserved ejection fraction
HR	heart rate
HTx	hjärttransplantation
ISHLT	International Society of Heart and Lung Transplant
IVA	isovolumetric acceleration time
IVC	inferior vena cava
IVSd	interventricular septum diameter
LA	left atrium
LV	left ventricle
LVAD	left ventricular assist device

LVEDV	left ventricular end diastolic volume
LVEF	left ventricular ejection fraction
LVESV	left ventricular end systolic volume
LVGCS	left ventricular global circumferential strain
LVGLS	left ventricular global longitudinal strain
LVOT	left ventricular outflow tract
LVPWD	left ventricular posterior wall diameter
MAP	mean arterial pressure
M-mode	motion mode
mPAP	mean pulmonary arterial pressure
mRAP	mean right atrial pressure
MVA	PW of LVOT representing atrial filling
MVE	PW of LVOT representing early filling
NYHA	New York Heart Association
OHT	orthotopic heart transplantation
PAP	pulmonary arterial pressure
PAWP	pulmonary arterial wedge pressure
PH	pulmonary hypertension
PLAX	parasternal long axis view
PVR	pulmonary vascular resistance
PW	pulsed wave
RA	right atrium
RHC	right heart catheterization
RIMP	right ventricular index of myocardial performance
ROI	region of interest
RV	right ventricle
RV basal	right ventricular basal diameter
RVEDA	right ventricular end diastolic area
RVESA	right ventricular end systolic area
RVET	right ventricular ejection time
RVfree	right ventricular strain of the lateral free wall
RVGLS	right ventricular global longitudinal strain
RV outflow	right ventricular outflow tract
RV long	right ventricular length
RV mid	right ventricular mid diameter
RVSWI	right ventricular stroke work index
S′	systolic tissue doppler velocity

SA node	sinoatrial node
SAP	systolic arterial pressure
SAX	short axis view
SD	standard deviation
sPAP	systolic pulmonary arterial pressure
STE	speckle tracking echocardiography
SV	stroke volume
SVI	stroke volume index
TAH	total artificial heart
TAPSE	tricuspid annular plane systolic excursion
TTE	transthoracic echocardiography
TVET	tricuspid valve ejection time
VAD	ventricular assist device
VTI	velocity time integral

Introduction

Historical perspective

Echocardiography

Ultrasound is used by mammals, such as bats and dolphins, who thereby have the natural ability to visualize their environments sonically (**Figure 1**). Since this gift is not given to humans the development of machines enabling us to visualize ultrasonically has been revolutionary.

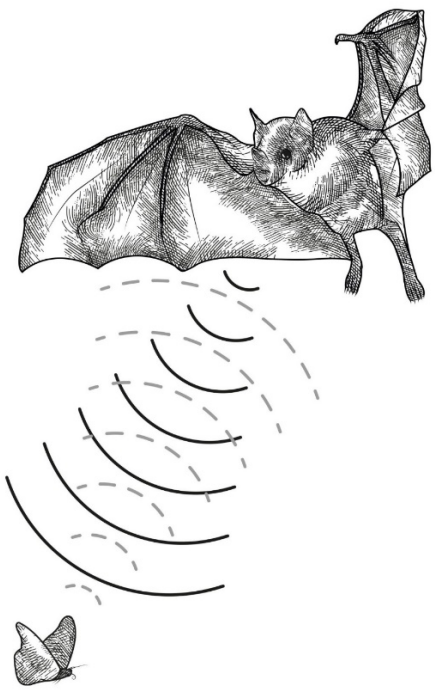


Figure 1. Echolocating animals emits signals to the environment and listen to the echoes of those signals returning from objects close by. These echoes are used to locate and identify objects and potential prey.
Illustration by Sandra Persson

The evolution of echocardiography has been dramatic, and the methodology is in constant evolvement. The technology date back to Curie and Curie who first discovered piezoelectricity in the 1880´s, thereby allowing the creation of ultrasonic waves. The first patent for ultrasonic, non-destructive flaw detection was issued in 1937 and during World War II the application was later used for naval sonar [1].

The first documentation of "ultrasound cardiography" that begins to resemble what we know as transthoracic echocardiography (TTE) was performed in Lund by Inge Edler and Hellmuth Hertz (**Figure 2**).

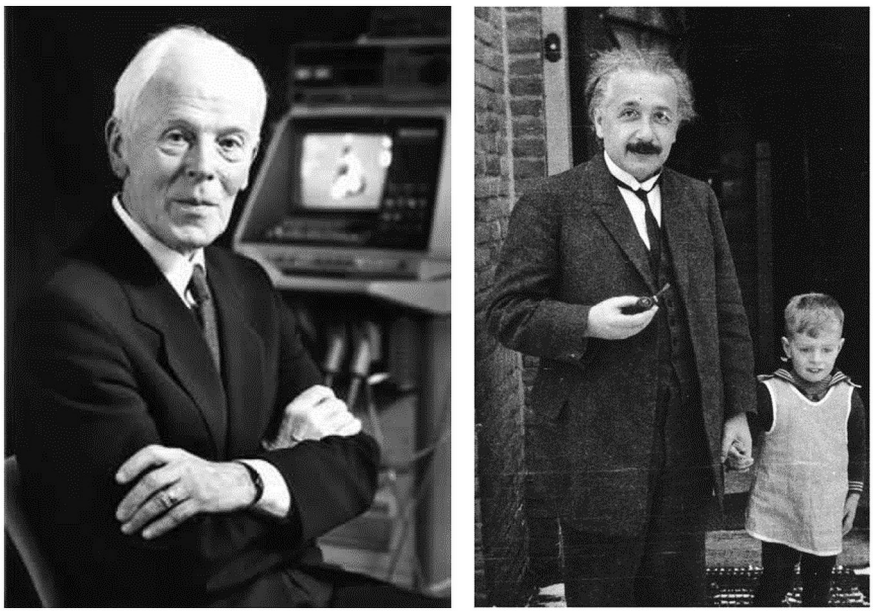


Figure 2. On the left Professor Inge Edler and on the right young Professor Helmut Hertz togheter with the renowned family friend Albert Einstein.
Photo by Medicinhistoriska sällskapet sällskapet Syd by permission from Kjell Lindström

Edler being a cardiologist and Hertz a physicist, developed the method for medical use to focus on mitral stenosis [2, 3]. Starting off using a commercial reflectoscope (**Figure 3a**) used for non-destructive testing, Hertz examined himself and detected a signal that moved with cardiac motion. From this instrument the field of echocardiography, using the time-motion or motion-mode (M-mode) approach, commenced, and the first structure to be detected by M-mode was the mitral valve (**Figure 3b**). Edler and Hertz found that the optimal frequency for heart ultrasound were 2.5 MHz in adults and 5 MHz in children and in 1967 the first echocardiographic two-dimensional (2D) image was acquired. Echocardiography was firstly used in clinical practice to detect pericardial effusion and to evaluate

mitral stenosis, and in 1954 the first scientific article “The Use of Ultrasonic Reflectoscope for Continuous Movements of the Heart Wall” was published [1, 4] (**Figure 3c**).

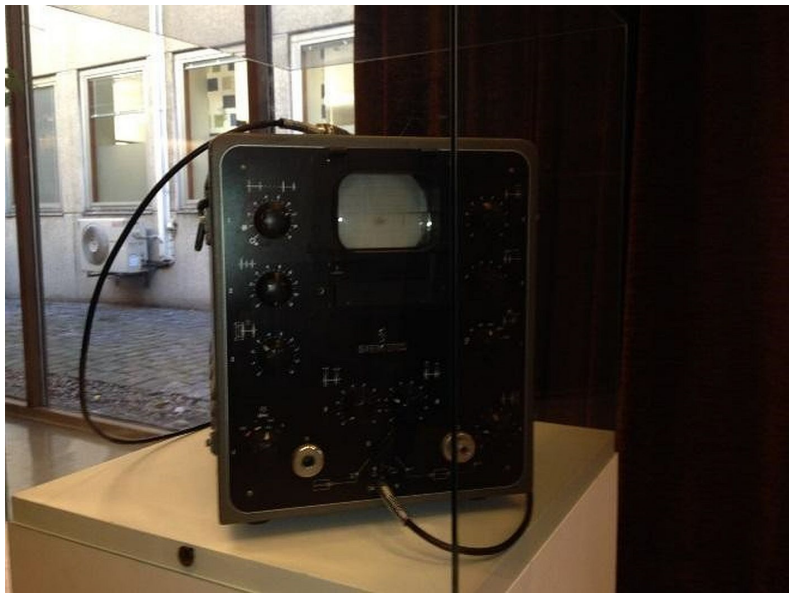


Figure 3a. The original reflectoscope used by Edler and Hertz.
Photo by Carl Cronstedt Meurling

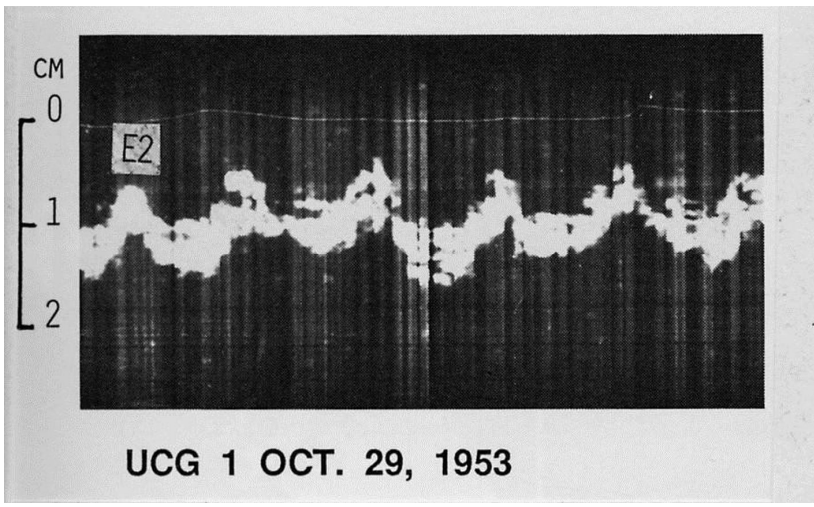
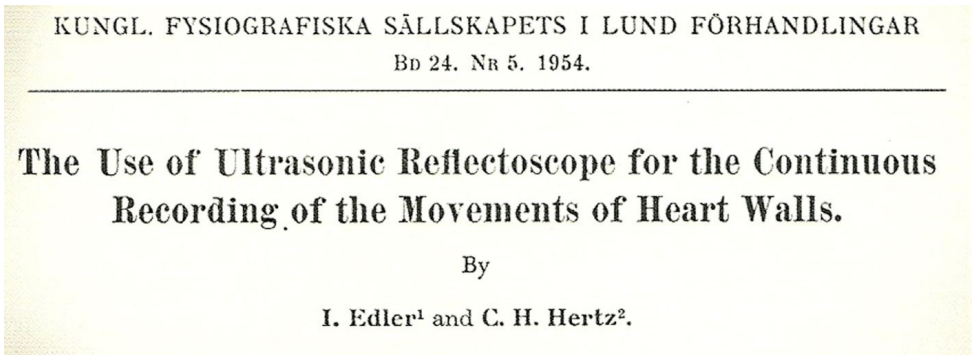


Figure 3b. The first m-mode registration of the mitral valve.
Photo by Inge Edler and Kjell Lindström by permission from Kjell Lindström



KUNGL. FYSIOGRAFISKA SÄLLSKAPETS I LUND FÖRHANDLINGAR

Bd 24. Nr 5. 1954.

The Use of Ultrasonic Reflectoscope for the Continuous Recording of the Movements of Heart Walls.

By

I. Edler[1] and C. H. Hertz[2].

Figure 3c. The original publication of Edler and Hertz from 1954.
Photo by Carl Cronstedt Meurling

In 1955 Shigeo Satumora developed the doppler technique that was latterly further enhanced in clinical use by Liv Hatle. Ever since these achievements, there has been continuous enhancements in the field of echocardiography, reaching from A-mode and M-mode to 2D and eventually to three- (3D-) dimensional echocardiography. Although more novel imaging techniques are evolving, TTE remains easily available, cost effective and brings no discomfort or side effects for the patients [2, 5]. It is fair to say that the invention of echocardiography was ground-breaking, and the method is now routinely used as the primary modality for structural cardiac evaluation.

Right heart catheterization

With the use of brass pipes inserted into the venous and arterial systems of a horse already in 1711, physiologist Stephen Hales is reported to have made the first measurement of blood pressure and cardiac output (CO). Additional studies by Auguste Chauveau and Étienne-Jules Marey who graphically recorded the auricular and ventricular pressures in a horse led to the first cardiac catheterization by Claude Bernard in 1844 [6]. Although, Dr. W Forssmann in 1922 demonstrated the usefulness and safety of the first human cardiac catheterization, it was not until early 1940´s that diagnostic right heart catheterization (RHC) was introduced. The development of cardiac catheterization enabling measuring of hemodynamic pressures invasively has since played a fundamental role in the progress of understanding of cardiac physiology and was revolutionary as a diagnostic tool [7, 8]. In the 1970´s the Swan-Ganz catheter, that is still used today, was introduced, aiming at measuring right heart chamber and pulmonary artery pressures along with measurements of CO by the thermodilution technique in critically ill patients [6, 9].

Mechanical circulatory support

In a way, the history of mechanical circulatory support began in 1953, when the introduction of the first heart lung machine allowed complex open-heart surgery. At this time-point, simple pumps for temporary circulatory support in patients with post-operative low CO following cardiopulmonary bypass were developed [10]. In 1966, Dr. M DeBakey and colleagues implanted the first pneumatically driven ventricular assist device followed by the implantation of the first total artificial heart (TAH) in 1969, intended as a bridge to heart transplantation. In the early1980´s the first TAH was implanted as permanent treatment, but the patient died after barely four months from severe sepsis [11, 12].

Cardiac support through single chamber pumps started the area of ventricular assist devices (VAD). These VADs were designed to generate additional blood flow in parallel with the relevant ventricle. The first generation of VADs were either pneumatically or electrically driven membrane pumps that generated pulsatile flow with artificial heart valves as inlet and outlet. Connected to the heart via cannulas, these pumps can be used either as isolated left-, right- or bi- ventricular assist devices. The most commonly used VADs are designed to support the left ventricle (i.e. LVAD) and can be placed intracorporeally [11]. In 1984 the first successful transplantation after LVAD-implantation was performed and by the 1990's development of continuous flow centrifugal pump devices were improving patient outcome by reducing size and susceptibility to infections (**Figure 4**).

Figure 4. The patient with the first left ventricular assist device implanted at Skane University Hospital, Lund, in 1993 out walking with a large control unit.
Photo by Björn Kornhall

The modern devices are much smaller and consists of a propeller surrounded by a metal case, referred to as impeller (**Figure 5**). Initially VADs were only approved as a bridge to transplant, but since 2010 they have received approval as end stage therapy in some countries.

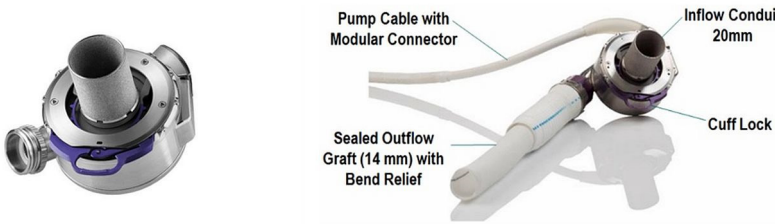


Figure 5. to the left LVAD impeller and to the right impeller connected to outflow graft and stearing unit cable. Image courtesy of Abbott

Heart transplantation

Successful solid organ transplantation is one of the greatest achievements in the past century of modern medicine. Several challenges regarding ethics and legality where faced in the beginning of this era. However, orthotopic heart transplantation (OHT) has evolved from being an experimental procedure to a mainstay treatment for many chronic cardiac conditions despite improvements in competing device technology.

The first human heart transplantation was performed in 1964. This was a xenotransplant, since the donor heart originated from a chimpanzee and unfortunately the recipient died within an hour since the allograft was unable to maintain adequate circulatory load [13]. In December 1967 Dr. Christiaan Barnard performed the first heart transplantation at the Groote Schuur Hospital, in Cape Town, South Africa (**Figure 6**) [13, 14]. The recipient, a 54-year-old man in end-stage ischemic cardiomyopathy, received the heart of a young girl. Initially the procedure went well, but unfortunately the patient died on the 18th postoperative day due to pneumonia. The achievement was no surprise to the medical community and the work was pioneering by experimental work carried out by Alexis Carrel, Frank Mann, Norman Shumway, and Richard Lower. Three days later the second transplantation was performed elsewhere in a paediatric recipient and during the year that followed 102 transplants were made in 17 countries at 52 different centers [15, 16].

The first OHT in Sweden were performed at Sahlgrenska University Hospital in Gothenburg in 1984, however using a donor heart from West Germany. One month later, the concept of brain death was formally ratified by Swedish law, and in February 1988 the first OHT was performed in Lund. Since then, the number of

OHT has gradually increased. From 2011, OHT surgery in Sweden is centralized to Lund and Gothenburg, and at present approximately 30 OHTs are being performed yearly in Lund.

Due to refinement in technology, improvements in both surgical technique and organ preservation along with advances in the field of immunosuppression, OHT is now established as a standard treatment option for end-stage heart failure in selected patients [17, 18].

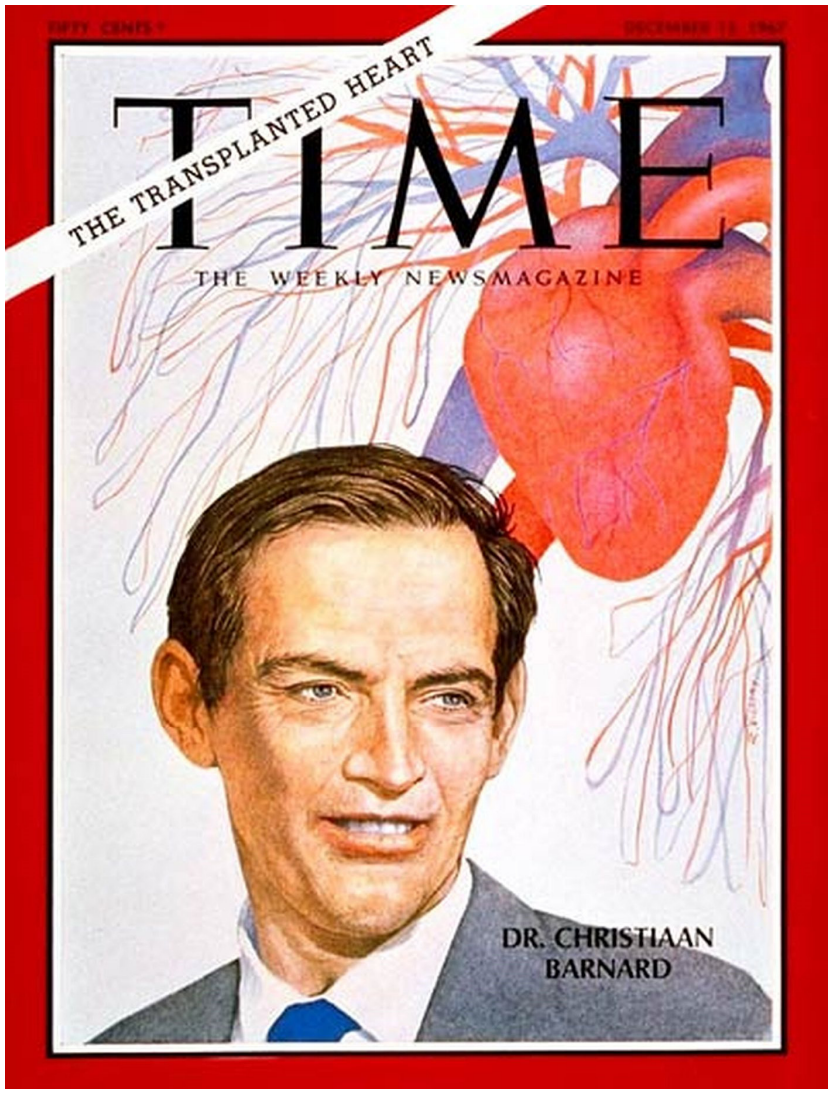


Figure 6. Cover of Time magazine following the first human orthotopic heart transplantation.

Cardiac structure and function

The heart is a four-chambered double pump forming the centre of the circulatory system (**Figure 7**).

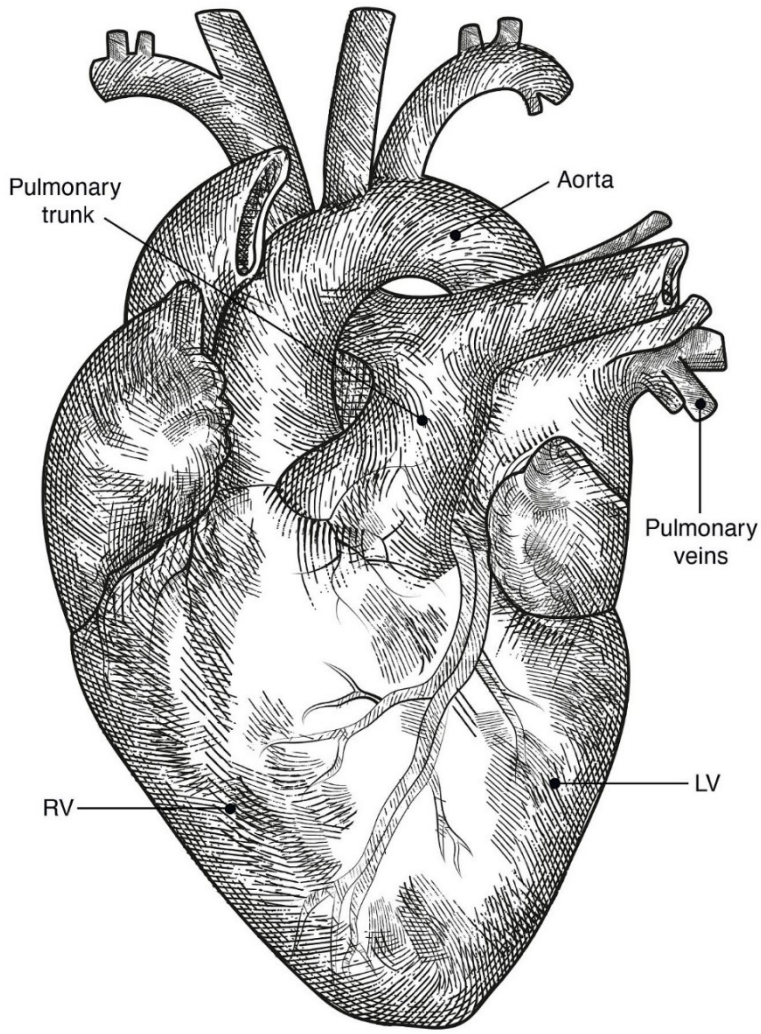


Figure 7. Sketch of the heart showing the left ventricle (LV), the right ventricle (RV), aorta, pulmonary trunk and the pumonary veins connected to the left atrium.
RV= right ventricle, LV= left ventricle
Illustration by Sandra Persson

The muscular wall of the heart consists of several layers. Surrounding the heart is the thin pericardium consisting of two layers separated by pericardial fluid. Cardiac muscle tissue (myocytes), containing a single nucleus and large amount of mitochondria for high energy output, is specifically found in the heart. Cardiac muscle tissue is striated, and has an extensive capillary network enabling a high capacity of blood supply. The heart, as a single organ, receives around 5% of the total CO [19]. Cardiomyocytes are individual muscle cells that are organized into sarcomeres which are connected via intercalated discs, allowing synchronized contraction of the myocardium. Physiological or pathological changes of cardiac demand and/or impairment of blood supply induce adaptive changes in the left ventricle (LV). These changes include myocyte hypertrophy and increased vascularization or in selective cases fibroblast proliferation that leads to fibrosis, and eventually cell apoptosis.

Anatomy and physiology of the left heart

Left atrium

The left atrium (LA) receives oxygenated blood from the lungs via four pulmonary veins entering the posterior aspect of the LA. The LA is separated from the right atrium (RA) by the interatrial septum, and in addition each atrium is separated from the ventricle of the same side by the atrioventricular valves (i.e. mitral and tricuspid valve). The LA is positioned slightly above and behind the RA. As result of the fact that the LA is exposed to higher pressures, the myocardial wall is slightly thicker when compared to the RA. The LA has an auricular appendage which is distally curved and is partially overlapping the trunk of the pulmonary artery.

The LA size as an imaging marker has been shown to be a powerful predictor of outcomes in different cardiovascular disorders. Enlargement of the LA can be seen in different pathological conditions such as severe mitral regurgitation and/or stenosis, or in the setting of decreased LV diastolic compliance causing increased filling pressures. Atrial function has been conventionally divided into three integrated phases: a) *reservoir*; the expansion phase during LV systole where the LA stores pulmonary venous return during LV contraction and isovolumic relaxation, b) *conduit*; the phase where blood is passively transferred to the LV during early ventricular diastole, and c) *booster*; the contractile component where the LA actively contracts during the final phase of diastole and contributes between 15-30% of LV stroke volume (SV) under normal physiological conditions [20, 21]. In patients with diastolic dysfunction, augmented left atrial booster function serves as a compensatory mechanism for decreased early filling.

Left ventricular anatomy

The LV contains an inlet portion encompassing the mitral valve apparatus, an outflow tract (LVOT) connecting to the aortic valve, and an apical portion. The LV has a semi-elliptic form. The septal component of the ventricular wall is curved so that when the heart is viewed from the anterior aspect, most of the LV is concealed by the right ventricle (RV). At the apex, the myocardium is relatively thin (making it suitable for placement of LVAD cannula). The base of the LV extends from the papillary muscles to the atrioventricular plane. The free wall of the LV is an area of the ventricular wall which is not in contact with the interventricular septum nor with the apex. The endocardial portion of the wall is characterized by a criss-crossing meshwork of thin muscle bundles (i.e. trabeculations) located particularly at the apical third of the ventricle. In contrast, the outlet portion of the septum is relatively smooth while thicker muscle bundles line the anterior, inferior and posterior walls. As an integral component of the LV wall the papillary muscles supporting the mitral apparatus can be seen (**Figure 8**) [22].

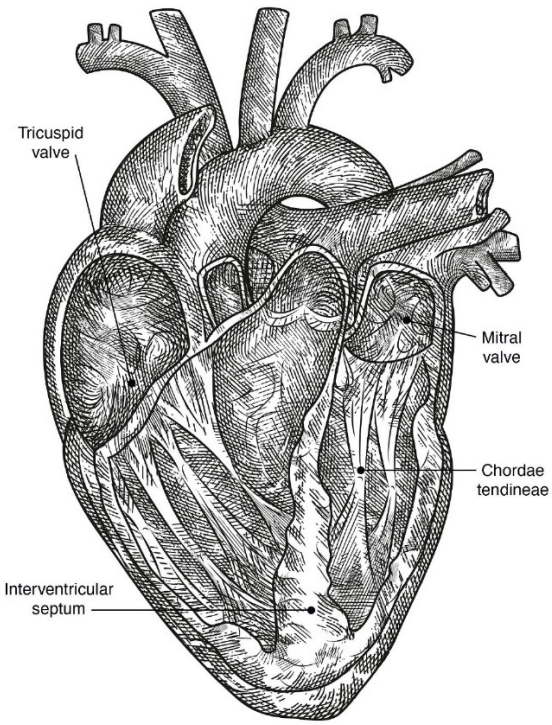


Figure 8. Intersection sketch of the heart illustrating the interventricular septal wall. The sketch also shows the atrioventricular valves and their connection to the myocardium through chordae tendineae.
Illustration by Sandra Persson

The LV wall comprises three different layers according to a longitudinal alignment of the myocardial strands: a superficial (epicardial), middle (myocardial), and deep (endocardial) layer (**Figure 9**) [22].

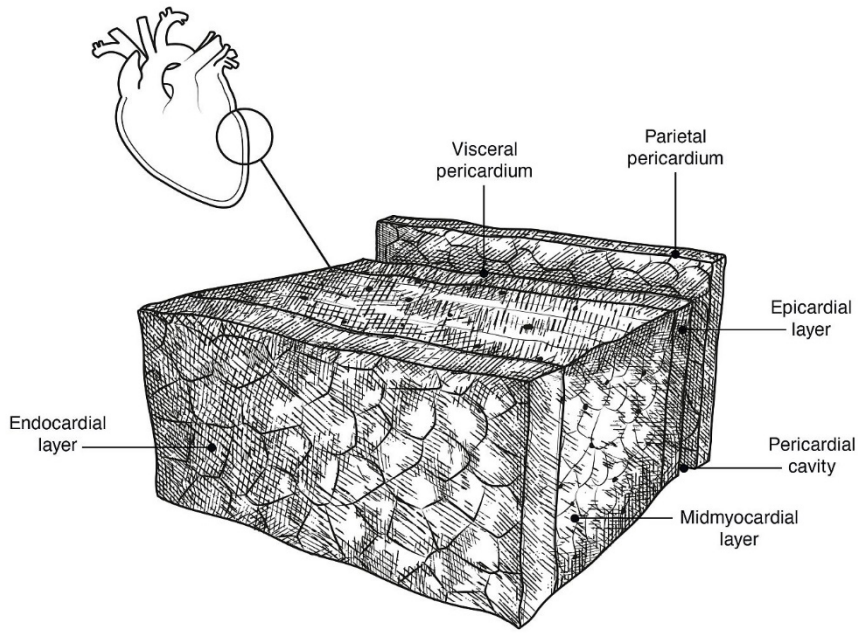


Figure 9. Drawing illustrating the different layers of the left ventricular wall; Thin inner layer of endocardium, thick midlayer of myocardium and the outer layer of epicardium.
Illustration by Sandra Persson

The different layers represent changes in orientation of the myocardial strands transmurally, and each layer continuously intersect with strands of the next layer. When traced from the base to the apex, the superficial layer arises from the insertion of the atrioventricular valves and spreads from one ventricle to the other. The epicardium accounts for approximately 25% of the wall thickness. At the vortex of the LV, the myocardial strands form a spiral pattern to give rise to the subendocardial layer. There is a similar continuity between superficial and deep layers at the base of the ventricle.

The myocardial strands of the middle layer are more circumferentially arranged, parallel to the plane of the mitral orifice [23]. This layer occupies approximately 55% of the ventricular wall thickness and its fibres do not insert into the mitral or aortic valves, nor to the ventricular apex. Starting at the apex the deep layer of myocardial strands radiates in longitudinal orientation in the endocardium, to insert into the aortic and mitral valves and the membranous septum. This is the thinnest muscular layer accounting for <20% of the wall thickness [22]. Together the

different layers account for the different motions of the LV; longitudinal, circumferential as well as rotation and torsion since the base and the apex twist in different directions (**Figure 10**) [24].

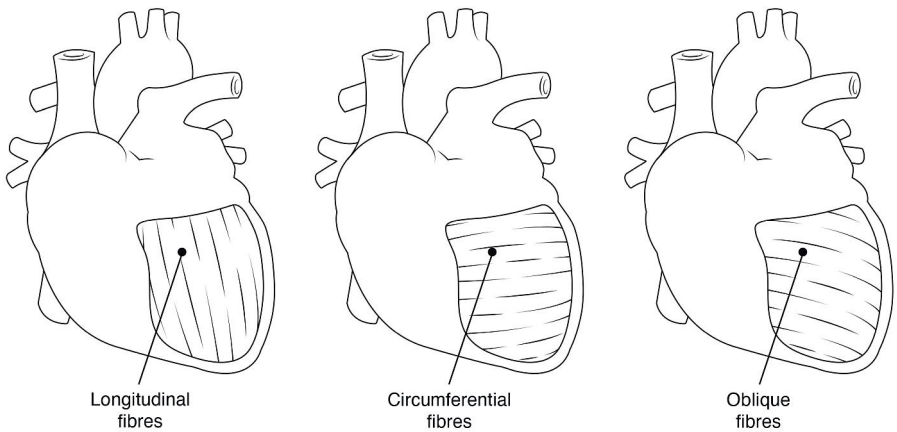


Figure 10. Sketch illustrating the complex arrangement of the left ventricular heart muscle; longitudinal, circumferential and oblique muscle fibres, enabelling it to produce contraction in different directions.
Illustration by Sandra Persson

Left ventricular function

The main function of the LV is to provide sufficient CO to maintain adequate blood flow to other organ systems. In daily clinical routine though, LV function is commonly estimated by LV ejection fraction (LVEF) [25].

LVEF is calculated using the following equation:

LVEF = Stroke volume (SV) / End diastolic volume (EDV)

However, LVEF is a surrogate measure of LV function since the method is limited with regards to estimations of ventricular volume and thereby may fail to correctly reflect SV and actual CO.

CO can be calculated using the following equations:

CO = Heart rate (HR) * SV

Although CO can be estimated with echocardiography the method has several limitations. More accurate assessment of CO can be obtained with RHC [26] or cardiac magnetic resonance imaging (CMR).

There are several mechanisms involved in maintaining adequate EF (and CO) related to the different compensatory contractile mechanisms (i.e. radial and circumferential contraction) of the LV. Contractility of the heart can be assessed with TTE through speckle tracking echocardiographically (STE) derived strain [25]. Strain, being a measure of myocardial shortening, could be argued to better reflect what the heart actually does, whereas LV EF merely is a measure of volume.

In comparison to that of the RV, the free wall of the LV is much thicker to manage the physiological conditions. Although the LV is constructed to work in a high-pressure circuit, it can be affected by alterations in loading conditions. Preload is defined as the load during diastole. Higher preload volumes, within physiological limits, increase contractility through the Frank-Starling mechanism (**Figure 11**). This mechanism occurs when the preload volume lengthens the myocyte sarcomeres. Afterload is the pressure that the LV ejects the blood against during systole. Conditions like hypertension, atherosclerosis, and aortic stenosis all require the LV to generate more force to overcome the elevated afterload pressure. If this occurs chronically, the LV will undergo remodelling with hypertrophic adaptations.

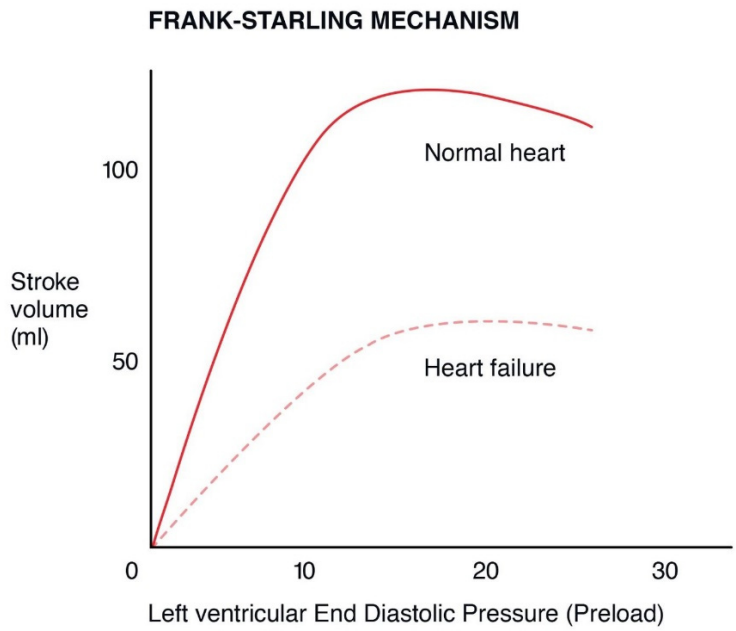


Figure 11. Diagram showing the preload-dependence of left ventricular stroke volume in a normal heart vs. in heart failure.
Drawing by Sandra Persson

Anatomy and physiology of the right heart

Right atrium

The RA is designed to assist in the filling of the RV and is sensitive to alterations in preload. Inferior- and superior vena cava delivers a high load of deoxygenated blood that is rapidly transferred through and by the RA to the RV [27]. The work of the RA can be divided into the same three phases during the cardiac cycle as the LA.

Right ventricle

The RV has a very complex geometry consisting of three different parts: the outflow tract, the inflow tract and the markedly trabeculated apical section. Viewed from the side, the RV has a triangular shape while in a cross section it forms the shape of a crescent. The intraventricular septum is concave against the LV due to pressure differences (**Figure 8 and 12**).

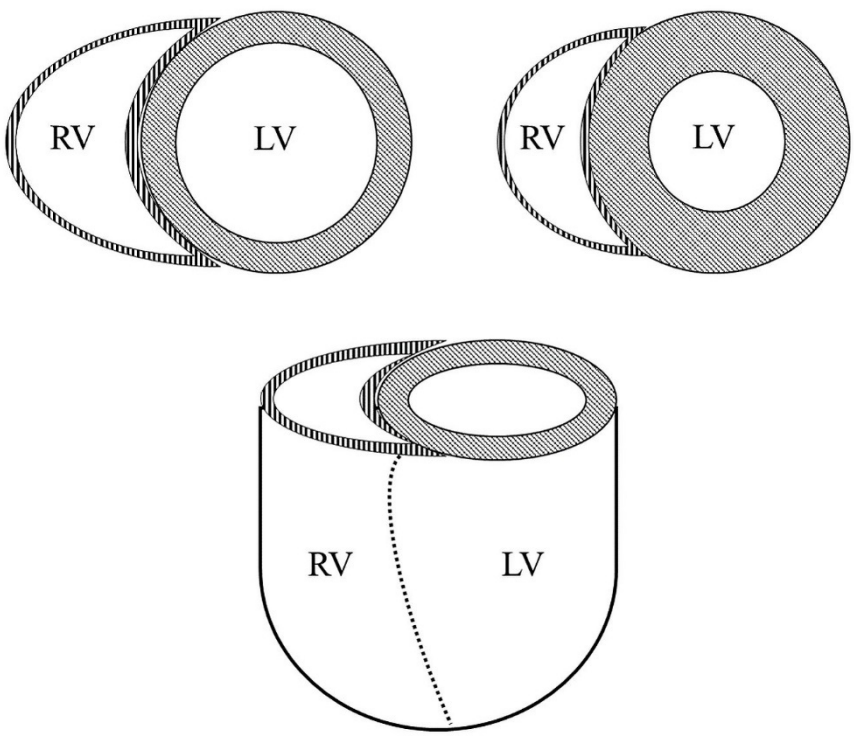


Figure 12. Schematic sketch. Upper two drawings illustrate the crescent shaped RV in relation to the LV in cross sectional view (left = diastole, right = systole). Lower drawing illustrate the concave curvature of the intraventricular septum against the right ventricle seen under normal physological circumstances.
RV = right ventricle, LV = left ventricle
Illustration by Annika Ingvarsson

The RV is a thin walled structure with a slightly larger volume than the LV. The RV is sensitive to increase in afterload while tolerating volume overload (i.e. preload) quite well [28]. Compared to the LV the endocardium of the RV is heavily trabeculated and the endocardial borders may be difficult to define (at least echocardiographically).

The RV consists of a deep layer of longitudinal muscle fibres and a superficial layer of circumferential fibres. Longitudinal shortening accounts for at least 70 % of the RV SV [29].

Heart failure

Heart failure (HF) is a chronic progressive condition where the heart is unable to deliver adequate CO to meet the needs of the organs. Rather than a single pathological diagnosis, HF is clinical syndrome consisting of cardinal symptoms such as breathlessness, ankle-swelling, fatigue and peripheral oedema. The syndrome is caused by structural and/or functional abnormality of the heart causing elevated intra-cardiac pressures and/or inadequate CO [30]. The definitions of HF have lacked standardisation but the new *Universal Definition and Classification of Heart Failure* provides a definition that is clinically relevant and simple but conceptually comprehensive [31]. The new definition enables sub-classification of HF within ejection fraction (EF) groups and provides revised classification of stages of HF. HF can be further divided in LV vs. RV failure, acute vs. chronic HF, forward vs. backward HF and systolic vs. diastolic HF.

The term HF usually refers to LV failure since the LV most often is affected initially. HF from LV dysfunction can result from a variety of pathologies such as coronary ischemia, hypertension, valvular heart disease or primary heart-muscle disease. LV induced HF can secondarily also lead to RV failure as congestion of blood back to the pulmonary circuit occurs. Isolated RV dysfunction is less common but may occur secondary to pulmonary diseases (e.g. pulmonary hypertension due to chronic obstructive pulmonary disease, lung fibrosis or pulmonary arterial hypertension), as a result of coronary ischemia, as a negative effect of congenital heart disease or be related to RV arrhythmias [28, 32].

Acute HF is broadly defined as rapid onset of new or worsening signs and symptoms of HF. However, guidelines often refer to patients with established chronic HF where the symptoms can be classifying in the clinical extent of HF and graded using the New York Heart Association (NYHA) classification (**Figure 13**). The system classifies patients in four different categories based on their limitations during physical activity. Higher NYHA class score is correlated with more symptoms and worse outcome.

Class I	No limitation of physical activity. Ordinary physical activity does not cause undue breathlessness, fatigue, or palpitations.
Class II	Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in undue breathlessness, fatigue, or palpitations.
Class III	Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity results undue breathlessness, fatigue, or palpitations.
Class IV	Unable to carry on any physical activity without discomfort. Symptoms at rest can be present. If any physical activity is undertaken, discomfort is increased.

Figure 13. New York heart association (NYHA) classicfication of heart failure [30].

The subdivision of HF based on the terms forward and backward failure is complex and has been debated. The term forward failure refers to that the heart is not pumping out enough blood to satisfy the needs of the organs. Thus, excess fluid retention result in the occurrence of oedema. Backward failure occurs when any of the ventricles fails to pump, whereby blood is stagnated in the ventricle resulting in increased ventricular filling pressure and systemic or pulmonary oedema.

Lastly, HF can be divided into either systolic or diastolic dysfunction or a combination of both. In the normal aging process stiffening of the ventricles occurs, resulting in impaired LV relaxation which ultimately may cause LV diastolic dysfunction with increased filling pressures due to inadequate filling. Diastolic dysfunction often presents before systolic dysfunction with decreased myocardial contractility and impaired pump function (i.e. heart failure with preserved ejection fraction; HFpEF). Conversely however, chronic systolic dysfunction is almost always accompanied by diastolic dysfunction.

Left ventricular assist device – LVAD

A LVAD is a mechanic circulatory assist device; a pump designed to support the failing LV in maintaining adequate CO [11]. The treatment is applicable as bridge to transplant in patients with severe HF awaiting OHT, and in selected cases as

bridge to recovery, or to improve quality of life as end stage HF treatment (i.e. destination therapy). The pump is surgically implanted outside the heart and connected to the patient's own circulation through two cannulas (i.e. inflow and outflow cannula) connected to the apex of the LV and the ascending aorta respectively. Blood is thereby largely passively transported from the LA, through the LV via the pump and returned to the ascending aorta. The pump is connected to an external device, used to adjust the speed of the pump to achieve optimal unloading of the LV, through a driveline in the abdomen (**Figure 14**).

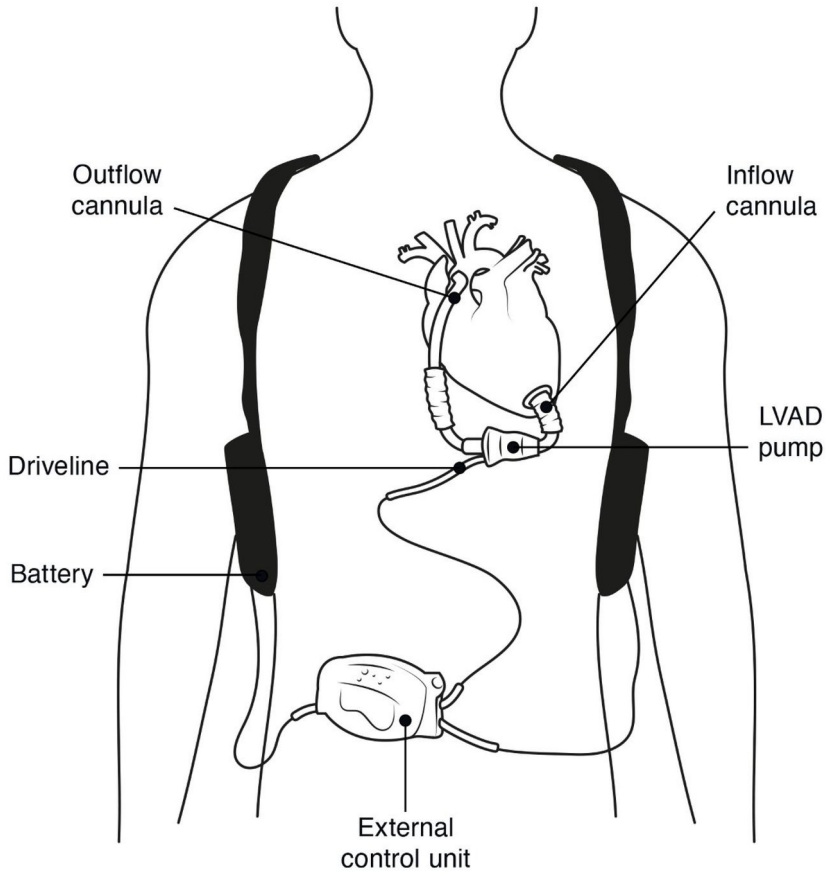


Figure 14. Drawing showing the different components of the left ventricular assist device (LVAD).
The LVAD is connected through cannulas to the left ventricular apex and ascending aorta. A driveline through the abdomen is connected to the external control unit that is driven by portable battery packs.
Illustration by Sandra Persson

Physiologically, LVAD-treatment also accounts for unloading of the LV and thereby reduced LV filling pressures (i.e. pulmonary arterial wedge pressure; PAWP). Consequently, the positive effect on pulmonary artery pressure reduces RV afterload [33]. It is well known that high pulmonary pressure may cause structural changes in the pulmonary vessels (i.e. endothelial damage and hypertrophy of the media) which additionally increases the RV afterload through increased pulmonary vascular resistance (PVR) [34]. Therefore, in patients awaiting OHT preconditioning with LVAD may be beneficial since physiological conditions can be held more constant before transplantation. Furthermore, patients that were previously considered non eligible for OHT due to significant pulmonary hypertension (PH) or high PVR may achieve remodelling of the pulmonary vasculature and thereby attain a functional status that entitles them as OHT candidates [35].

Heart transplantation

Advanced HF represents a challenging aspect of HF patients. Standard treatments may be inadequate, and the condition is associated with a worsening of clinical symptoms, re-hospitalization, and high mortality. Thus, these patients are in need of additional treatment options. OHT is considered as the final treatment option when medical or surgical treatment are not sufficient or possible [36]. Among conditions that eventually may require heart transplantation can be mentioned severe ischemic heart disease, different cardiomyopathies, valvular diseases, treatment refractory ventricular arrhythmias, and complex congenital heart disease [17]. Males are more often affected earlier in life than females which partly accounts for the skewed distribution between genders seen among OHT recipients.

Since the first OHT, significant improvements in operative techniques, postoperative therapy along with the introduction of cyclosporine have led to reduced operative mortality and increased long-term survival [18]. OHT surgery is a complex surgical procedure that takes several hours. Two separate surgical approaches exists: biatrial and bicaval (**Figure 15a and b**). In the older biatrial technique, large parts of the native atria in the recipient are spared, and the donor heart is sutured on to the native atria with only two anastomoses. This reduces the technical challenge of implantation and shortens the ischemic time but has the potential disadvantage of putting the sinoatrial (SA) node at risk of injury. Furthermore, redundant atrial tissue causing LA enlargement may affect atrial hemodynamic function and increase the risk of atrial arrhythmias postoperatively. In the more novel bicaval technique, the donor heart is connected through bicaval anastomosis. This technique offers physiologic benefit by preserving the anatomic configuration and is superior in maintaining hemodynamic function [37, 38]. Using

this technique, only the upper part of the atrium including the pulmonary veins are retained from the recipient. The heart is further connected to the aorta and the pulmonary artery.

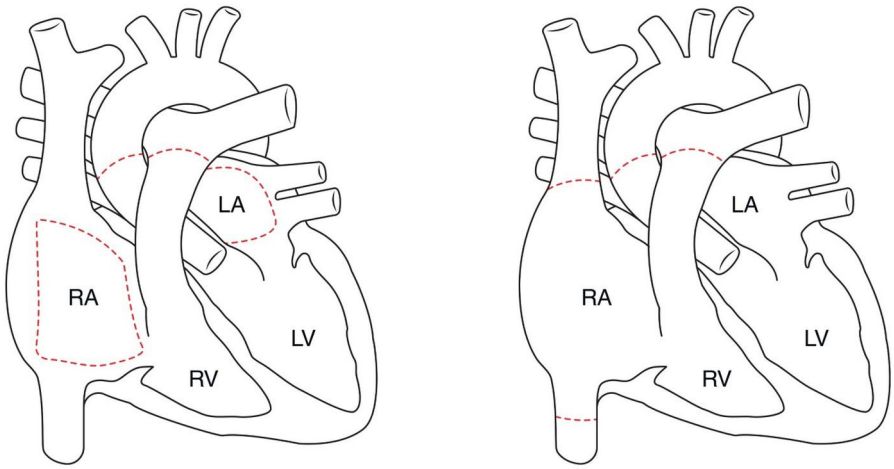


Figure 15a. Sketch illustrating the two separate surgical techniques used for orthotopic heart transplantation. Red dotted line represent the suture lines. On the left the older biatrial technique sparing large parts of the recipients native atrias and thereby leaving the recipient with elongated "double" atrias post transplantation. On the right the, nowadays commonly used, bicaval technique were the donor heart is connected to the remnant rooft of the left atrium with pulmonary veins from the recipients native heart. The donor heart is then connected to the aorta and the pulmonary trunk.

LV = left ventricle, RV = right ventricle, LA = left atrium, RA = right atrium

Illustration by Sandra Persson

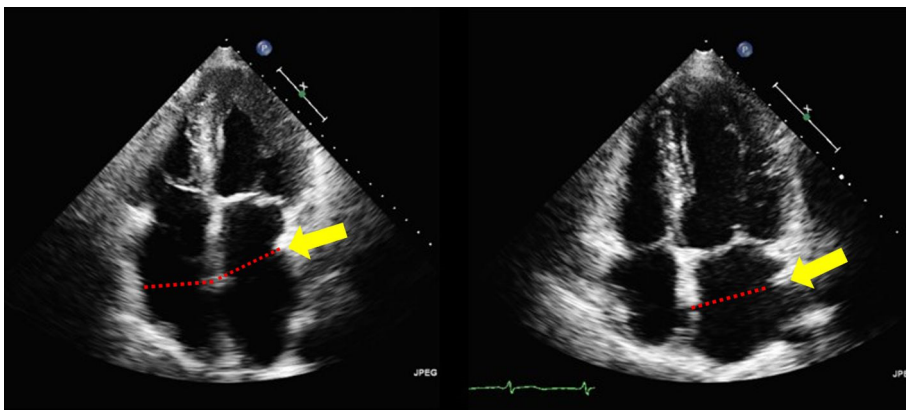


Figure 15b. Echocardiographic four chamber view illustrating the two separate surgical techniques used for orthotopic heart transplantation.

On the left the biatrial technique with elongated atria and on the right the bicaval technique. The part of the donor heart that is spared with the different techniques is seen below the red dotted line, and the yellow arrow indicate the suture line of the left atrium to the allograft. Photo by Annika Ingvarsson

Although OHT is nowadays a standard treatment option, it is still very physiologically complex. There are countless concerns involved in the OHT process that may impact on heart physiology post transplantation. Factors that have been suggested to negatively affect cardiac function involve donor age and the presence of hypertension (which is relatively common among donors suffering from cerebrovascular insult). Furthermore, different preservation of the allograft and cold ischemic time has been suggested to affect ventricular function [39, 40]. It is well known that the RV as well as the interventricular septum is sensitive to pericardiotomy, and postoperative RV function has also been shown to correlate to cause of donor death (i.e. donors suffering from cerebrovascular insult) [28, 41-44].

Following OHT, ventricular function may be affected by cardiac allograft vasculopathy (CAV); a diffuse form of vasculopathy and rejection episodes [45-48]. Moreover, the host immune response against the allograft demands lifelong immunosuppressive treatment [18]. Corticosteroids were among the earliest immunosuppressive agents used in transplantation and is remained in use because of their potent and diverse anti-inflammatory and immunosuppressive effects. Optimally, the delicate balance between immunosuppression to prevent rejection while avoiding the adverse effects of immunodeficiency and drug toxicities needs to be fulfilled. Problems related to under- and over-immunosuppression have for many years been well known as one of the most critical limiting factors for long-term survival following OHT, and there is constant ongoing research to deal with this matter. Compared to the general population, many diseases are more common in OHT patients, and several of these are closely linked to the side effects of the immunosuppressive drugs used. Diabetes mellitus (DM), CAV, hypertension, renal dysfunction, malignancy, and osteoporosis are examples of severe complications due to long-term immunosuppressive therapy [18].

Aims

The overall aim of this doctoral dissertation was to echocardiographically assess ventricular size and function in relation to invasive hemodynamic evaluation following OHT. The specific aims of each paper were:

Paper I:

The purpose of paper **I** was to investigate if and how stable OHT patients differed in TTE parameters compared to published normal values. Secondly, the study also aimed to establish specific echocardiographic reference values for this unique patient population. Thirdly, the study were designed to evaluate the possible impact of previous rejection, and time since transplant, on ventricular size and function.

Paper II:

The purpose of paper **II** was to identify differences in TTE findings based on OHT recipient gender. Moreover, the study also aimed to assess the possible influence of donor gender and donor recipient mismatch.

Paper III:

The purpose of paper **III** was to describe the adaptation of ventricular size and function during the first year following OHT. The study was also designed aiming at comparing echocardiographic data with invasively measured hemodynamic parameters obtained in conjunction at one-, six- and twelve- months follow up.

Paper IV:

The purpose of paper **IV** was to evaluate the conceivable impact of bridging with LVAD on early LV- and RV- function following OHT. Echocardiographic data and hemodynamic data from the healthy controls at one-, six- and twelve- months were compared between OHT patients with and without prior LVAD treatment.

Material and methods

Study population and design

All studies were performed prospectively utilising a specified extended protocol designed to coincide with the time-points when the patients conducted their routine echocardiographic and hemodynamic evaluations. Apart from exclusion following pre-defined criteria patients were enrolled consecutively. All echocardiographic examinations were performed by senior sonographers and offline evaluation and measurements were performed by the main author of the thesis.

In paper **I-II** patients transplanted both with the biatrial and bicaval technique were included, whereas paper **III-IV** were limited to patients transplanted with the bicaval technique. In paper **III-IV** mPAP >25 mmHg at rest [49, 50] was regarded as a simplified indicator of PH and elevated PAWP was defined as >15 mmHg.

Paper I-II

A total of 137 patients were prospectively enrolled and examined with 2D TTE as they arrived for their yearly routine control between 2012 and 2015. Each patient was only enrolled once. After exclusion, 124 patients (n=23 biatrial, n=90 males) remained available in study **I**. Re-evaluation of data when analysing the material for paper **II** resulted in additional loss of one patient due to possible previous underestimation of aortic regurgitation, leaving 123 patients (n=89 males) in study **II** available for analysis (**Figure 16a and b**).

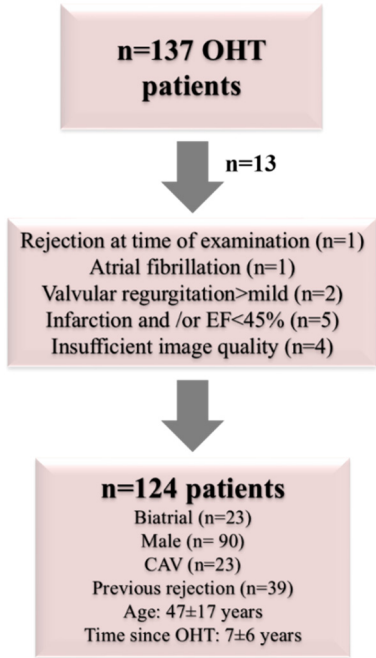


Figure 16a. Schematic illustration of the patient population in study I.
Data are presented as mean ± SD or as numbers (n). OHT = orthotopic heart transplantation, CAV = cardiac allograft vasculopathy

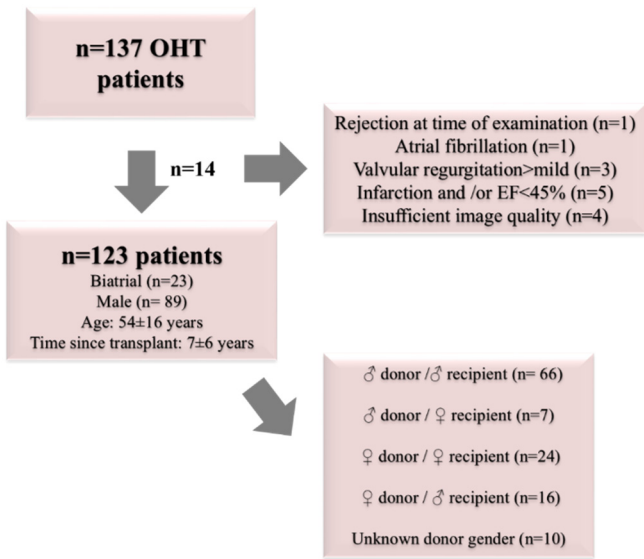


Figure 16b. Schematic illustration of the patient population in study I.
Data are presented as mean ± SD or as numbers (n). OHT = orthotopic heart transplantation

Paper III

Fifty-seven patients were recruited in the years 2013-2018. Due to exclusion criteria (presented in **Figure 17**) or death during follow up a total number of seven patients were excluded. In the final study cohort (n=40 males), 13 patients were bridged to transplant with an LVAD. At RHC, when assessed and listed for OHT, 36 patients had PH according to definition above and 41 patients had PAWP >15mmHg. Echocardiographic assessment was performed at 1-, 3-, 6- and 12- months and correlated to RHC performed at 1-, 6- and 12- months according to clinical practice.

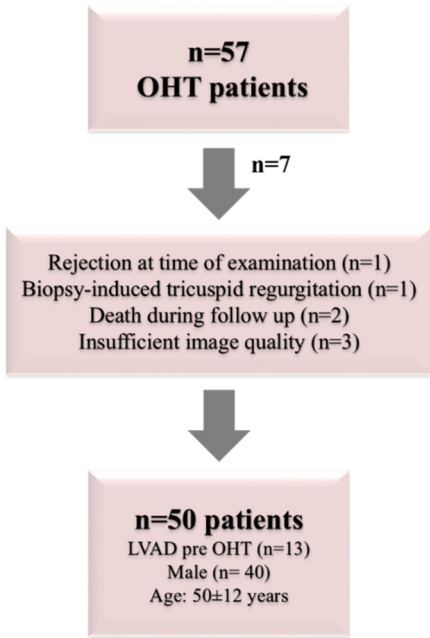


Figure 17. Schematic illustration of the patient population in study I.
Data are presented as mean ± SD or as numbers (n). OHT = orthotopic heart transplantation

Paper IV

From 2014 to 2020 the study enrolled 66 patients. During one year of follow up after OHT two patients died and additionally five patients were excluded based on pre-defined exclusion criteria (**Figure 18**). The remaining 59 patients were distributed as 20 pre-treated with LVAD (n=18 males) vs. 39 with no LVAD pre-treatment (n=25 males). When RHC evaluation occurred before acceptance for OHT, 44 patients (LVAD n= 16) had PH according to definition above and in 46 patients (LVAD n= 18) PAWP was above 15mmHg. TTE and RHC were performed in conjunction at 1-, -6- and 12- months follow up.

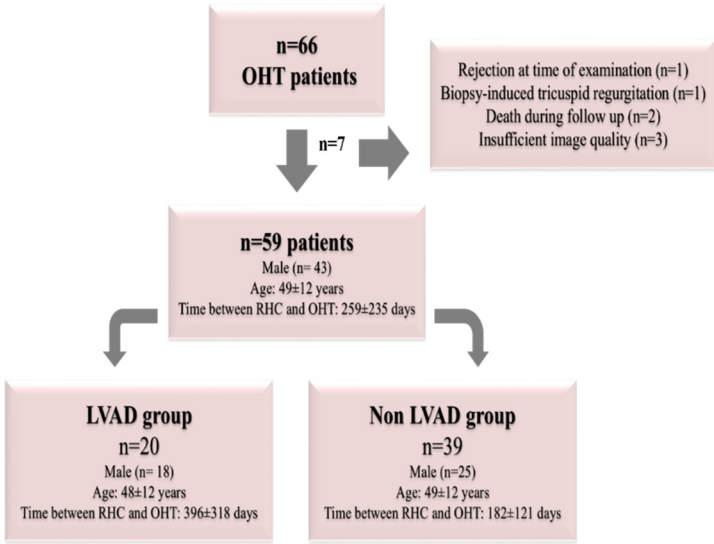


Figure 18. Schematic illustration of the patient population in study I.
Data are presented as mean ± SD or as numbers (n). OHT = orthotopic heart transplantation, LVAD = left ventricular assist device, RHC = right heart catheterization

Image acquisition

Echocardiography

*Two-dimensional image acquisition, paper **I-IV***

Commercially available echocardiographic system equipped with a 1-5 MHz transducer, S5-1 (Philips iE33, Philips Healthcare, Eindhoven, NL) were used for all TTE examinations. The examinations were performed by experienced senior sonographers according to the prevailing guidelines (at the study-time) from the American Society of Echocardiography [51]. Offline measurement and calculations were performed by the author of the thesis. Three consecutive beats were recorded for 2D and tissue doppler cine loops. When applicable, loops were obtained with the patients in an unforced end-expiratory apnoea. All loops were recorded, with the patient positioned on their left side, from standard parasternal, apical, or RV-focused apical four-chamber view [51-53].

Standard LV volumes were traced through outlining of the interface between the compacted myocardium and the LV cavity, and LVEF were calculated according to the biplane Simpson´s method (**Figure 19**).

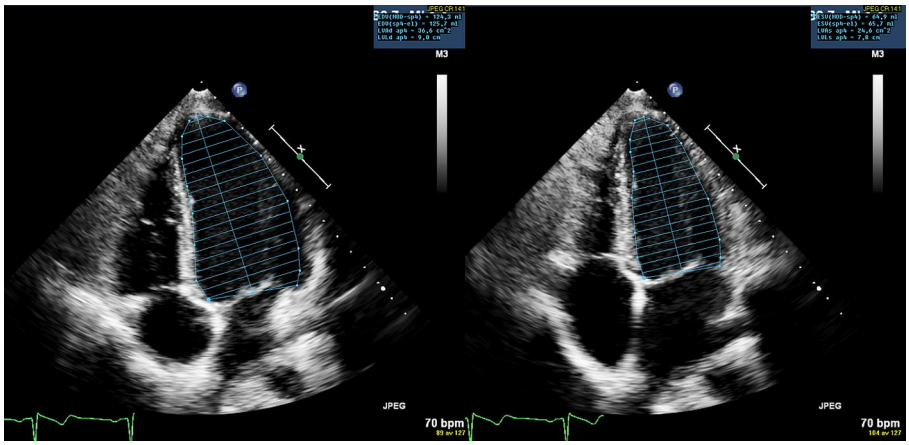


Figure 19. Apical 4-chamber view with delineation of the left ventriclular end diastolic volume (EDV) seen to the left and left ventricular end systolic volume (ESV) seen to the right. Ejection fraction (EF) is calculated through the formula: (EDV-ESV)/EDV.
Photo by Annika Ingvarsson

Atrial volumes were measured from a non-for shortened four-chamber view using the biplane method of discs, avoiding pulmonary veins and LA appendage. Volumes were indexed to body surface area (BSA). RV dimensions were measured from a RV-focused four-chamber view according to recommendations (**Figure 20)**.

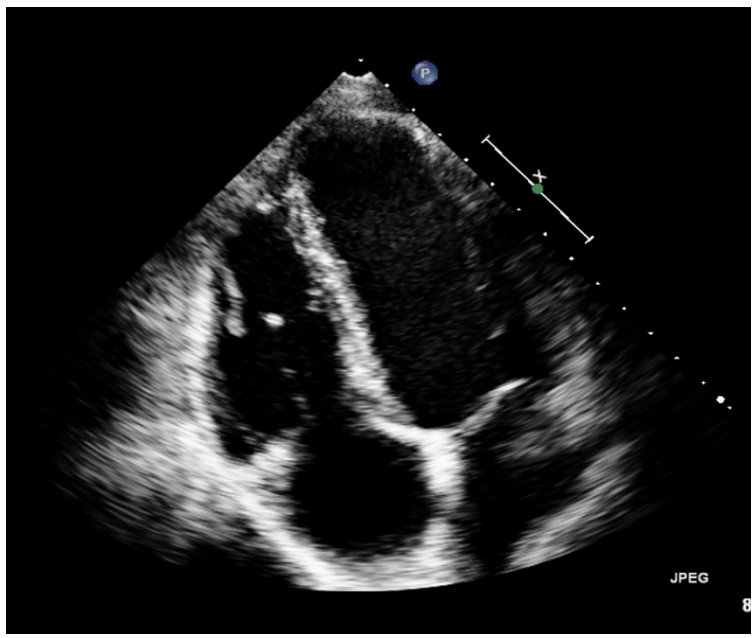


Figure 20. Tilted apical four chamber view with right ventricular focus.
Photo by Annika Ingvarsson

For STE analysis routine 2D- grey scale imaging was used, and frame rates was optimized to >50 Hz. Sector width and gain were adjusted to allow complete myocardial and endocardial visualization. The region of interest (ROI) was traced along the LV or RV endocardium at end-diastole, and manual correction was applied if necessary, after visual assessment during cine-loop playback to ensure appropriate tracking. Global longitudinal strain (GLS) was assessed from apical views while global circumferential strain (GCS) was obtained from parasternal short axis (SAX) views. Since strain is expressed as the percentage change in length, shortening of the myocardial fibres in systole will generate negative values; more negative values account for "better" strain. Henceforth, in this thesis a more negative strain value is considered to be higher. The software used for strain analysis was CMQ, Q-lab version 10.1 in paper **I-II** and version 10.3 in paper **III-IV** (Philips Healthcare, Eindhoven, NL).

In paper **I-III**, LV- and RV- function was evaluated both using conventional echocardiographic parameters and STE, while paper **IV** focused on assessment of RV function. The amount of size and function parameters chosen for validation differ slightly between the studies. Further clarification of echocardiographic parameters assessed to evaluate size and function throughout the studies (**I-IV)** are presented below.

Evaluation of left heart size

LA size was assessed volumetrically according to guidelines [51]. When used, 2D lineal internal diameter measurement was obtained from a parasternal long axis view (PLAX) in atrial diastole. LV volumes was obtained from an apical two- and four-chamber view as described above. Linear measurements of LV inner diameter and LV wall thickness was performed in PLAX with care taken to perform the measurement perpendicular to the LV (**Figure 21**).

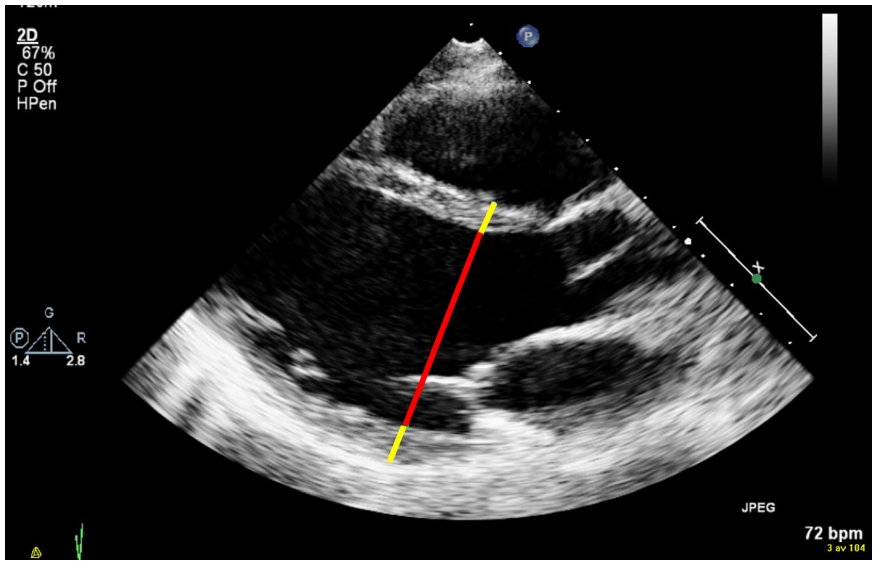


Figure 21. Parasternal long axis view with measurement of septal and posterior wall thickness (yellow lines) and diastolic inner diameter (red line).
Photo by Annika Ingvarsson

Conventional Assessment of LV function by Echocardiography

LV function was evaluated by fractional shortening (FS), i.e. the percentage change between linear cross-sectional measurement of the LV cavity in systole and diastole, and by EF. Furthermore, SV was assessed utilising the diameter of the LVOT to calculate the LVOT area, that were multiplied by the tracing of the velocity time integral (VTI) of the pulsed wave (PW) doppler curve in LVOT. Moreover, in paper **I-II**, systolic tissue doppler velocities (S´) from the septal, lateral anterior and inferior wall of the LV were recorded in apical view.

A few parameters conventionally used to assess diastolic function were measured; LV early- and atrial- filling (MVE and MVA respectively) was measured by PW doppler registration at the tips of the mitral leaflets in diastole, whereby E/A ratio could be calculated [54]. Deceleration time of the MVE-slope was measured and tissue doppler assessment of early (é) velocity was recorded from the LV lateral wall and used in calculation of E/é. For diastolic parameters please refer to **Figure 22**.

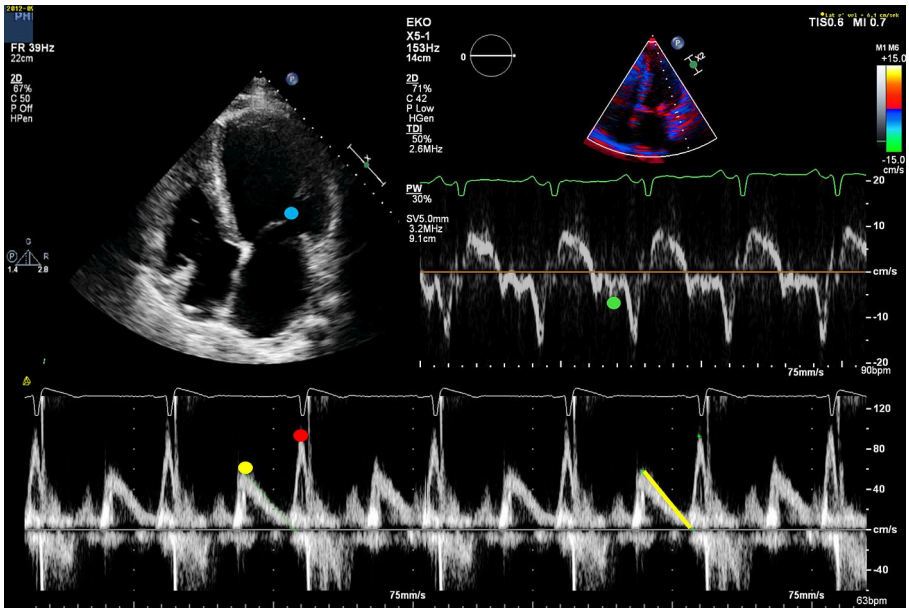


Figure 22. Measurements of echocardiographic parameters of diastolic function.
Upper left is apical 4 chamber view with blue dot indicating the location of pulsed waved doppler position seen below. On the upper right is tissue doppler image with green dot indicating lateral é velocity. Yellow dot indicate E-wave velocity and red dot A-wave velocity of the mitral inflow. Yellow line illustrate E deceleration time.
Photo by Annika Ingvarsson

Evaluation of right heart size

RA volume was obtained through measuring of RA area in a four-chamber view. RV size was assessed from a RV focused four-chamber view and included linear measurements of the inflow-, midventricular- and longitudinal- diameter respectively along with tracing of the RV area in systole and diastole (**Figure 23**).

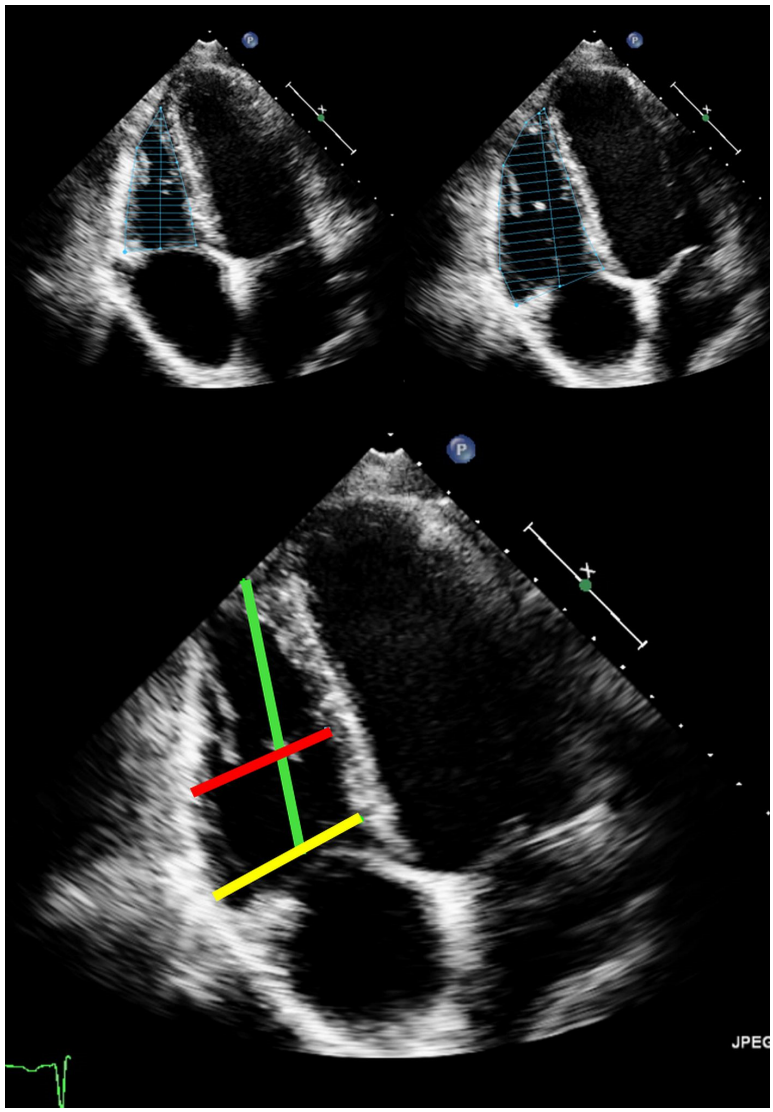


Figure 23. Apical pictures of right ventricular size parameters.
Upper images shows right ventricular systolic and diastolic area measurements. Image below illustrates measurements of right ventricular inflow diameter (yellow line), right ventricular mid diameter (red line) and right ventricular length (green line). All measurements are obtained in a right ventricular focused view. Photo by Annika Ingvarsson

Conventional Assessment of RV function by Echocardiography

Function parameters of the RV shown in **Figure 24a** included: tricuspid annular plane systolic excursion (TAPSE) measured with M-mode, systolic tissue doppler velocity (S´) from the lateral wall of the RV, fractional area change (FAC) obtained

from calculating the percentage change between RV systolic and diastolic volumes. Right index of myocardial performance (RIMP) measured by PW and continuous wave (CW) doppler **(Figure 24b)** and isovolumetric acceleration time (IVA) are depicted in **Figure 24c**.

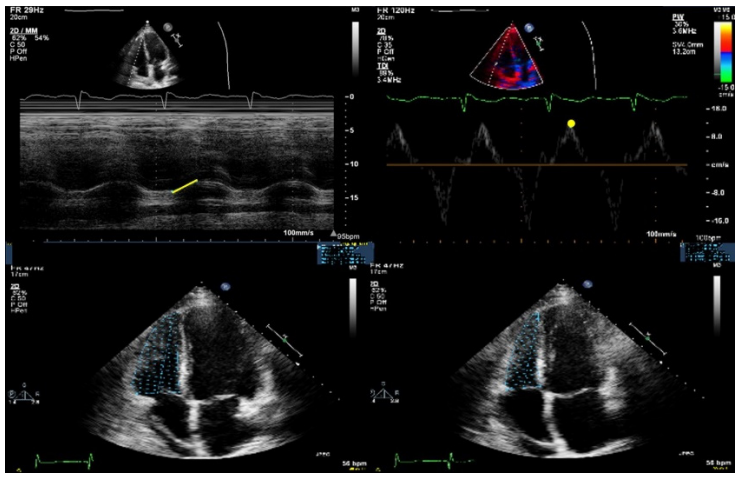


Figure 24a. Conventional right ventricular function parameters.
Upper left (yellow line) shows tricuspid annular plane systolic excursion (TAPSE). Upper right illustrates peak systolic tissue doppler velocity (S´) (indicated by yellow dot). Below from the left is diastolic and systolic delineation of the right ventricular area used to calculate fractional area change (FAC). Photo by Annika Ingvarsson

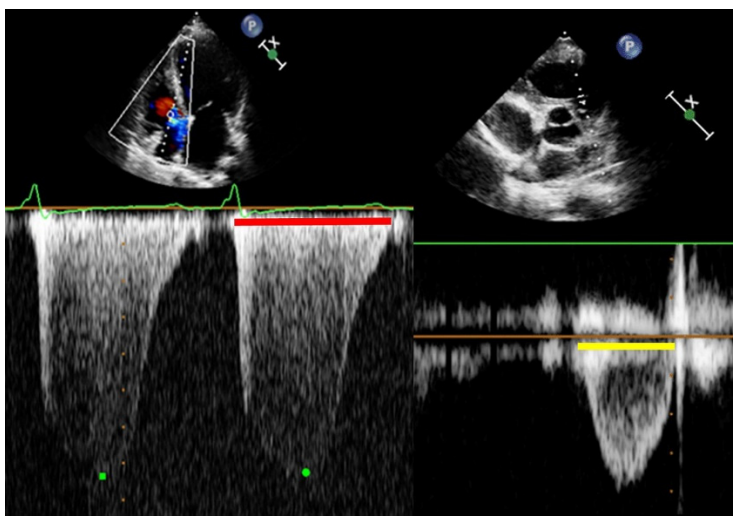


Figure 24b. On the left continous doppler registration of the tricuspid regurgitation and on the right pulsed waved doppler from the right ventricular outflow tract. Registrations of tricuspid valve ejection time (TVET) indicated by red line and right ventricular ejection time (RVET) indicated by yellow line are used to calculate right index of myocardial perfomace (RIMP) through the following formula: (TVET-RVET)/RVET.
Photo by Annika Ingvarsson

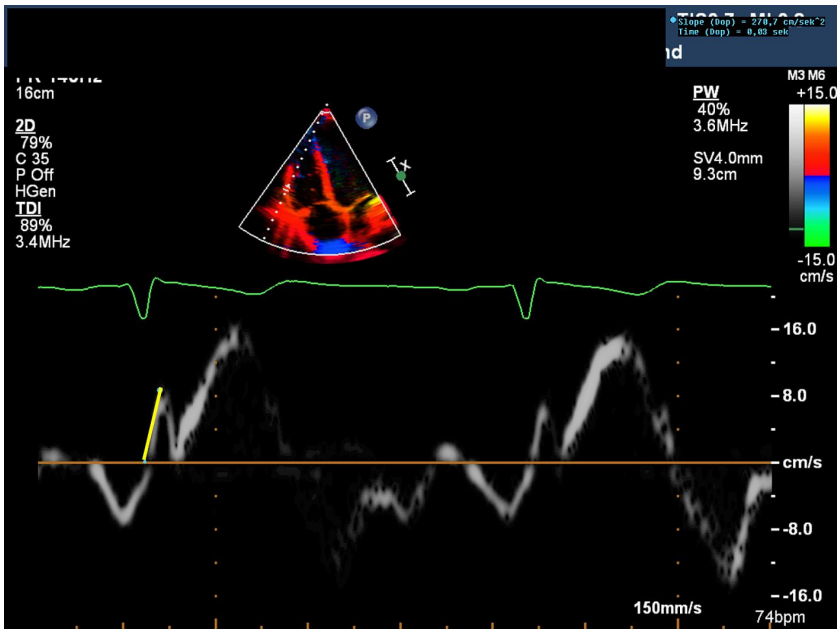


Figure 24c. Tissue doppler from the right ventricualr lateral wall. The slope illustrated by the yellow line indicate measure of isovolumetric accelation time (IVA).
Photo by Annika Ingvarsson

Assessment of LV function by speckle tracking echocardiography

2D STE was used to conduct LV strain measurements both longitudinally and circumferentially (**Figure 25a and b**).

Global strain for each view was presented by the software system in a bullseye-plot (**Figure 26c**). LVGLS was automatically generated by the software-algorithm from the apical 2-, 3- and 4- chamber view. LVGCS was measured in SAX view striving to visualize three different levels of the LV; basal, papillary muscle and apical.

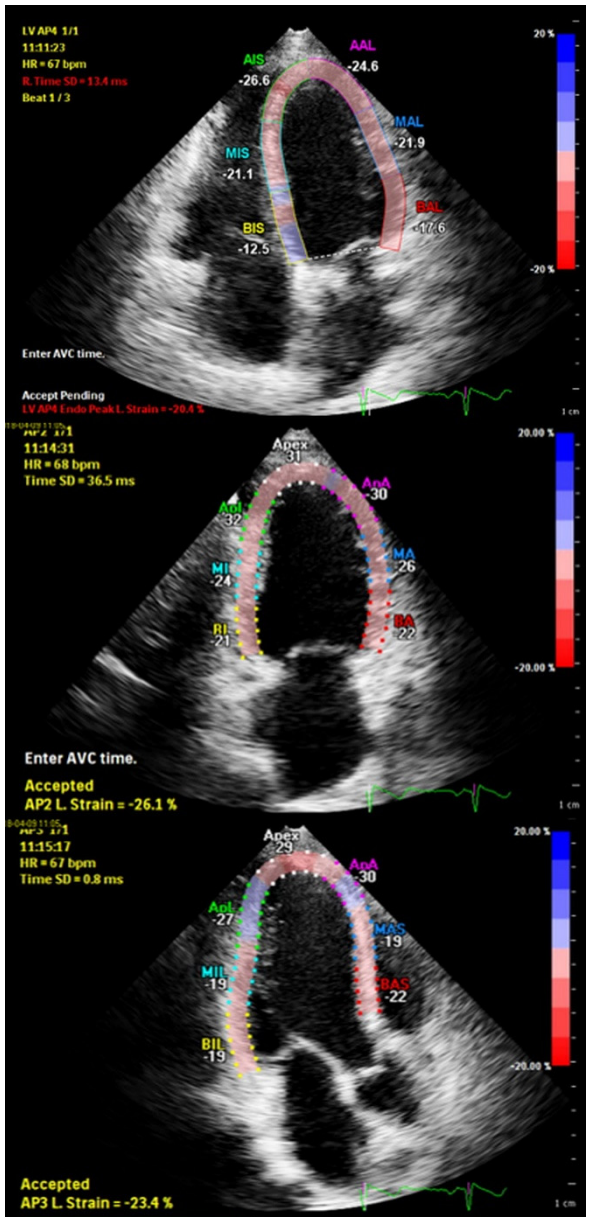


Figure 25a. Longitudinal strain measurements obtained from apical 4-, 2- and 3- chamber view.
Photo by Annika Ingvarsson

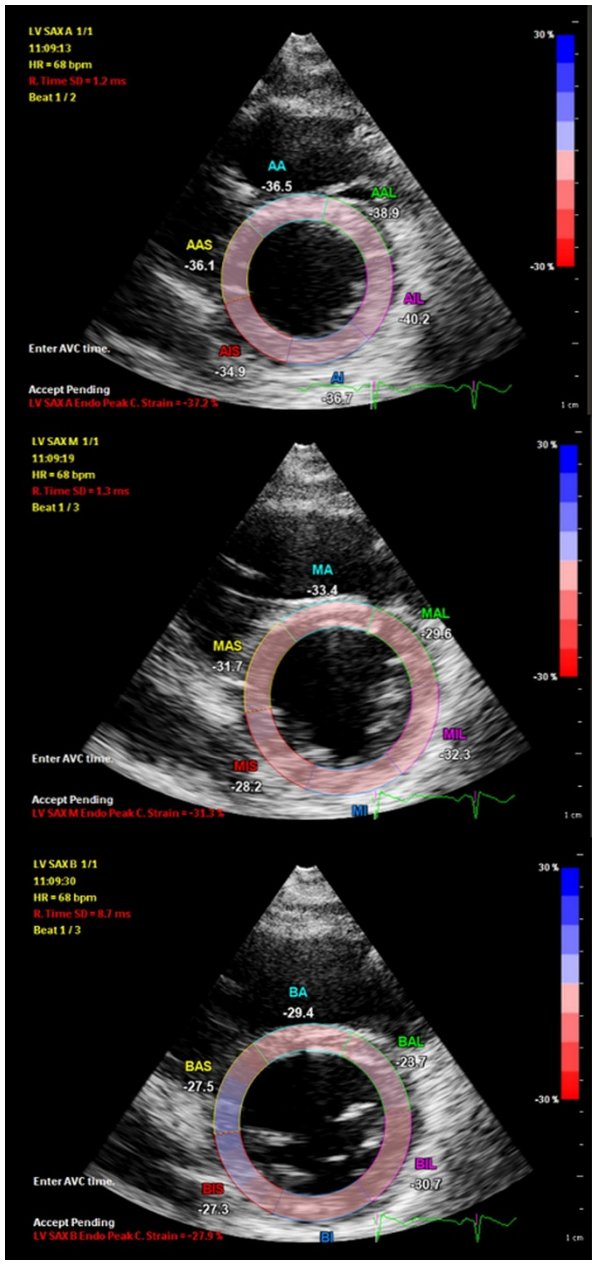


Figure 25b. Circumferential strain measurements obtained from the three different levels; apical-, mid- and basal-, in short axis view.
Photo by Annika Ingvarsson

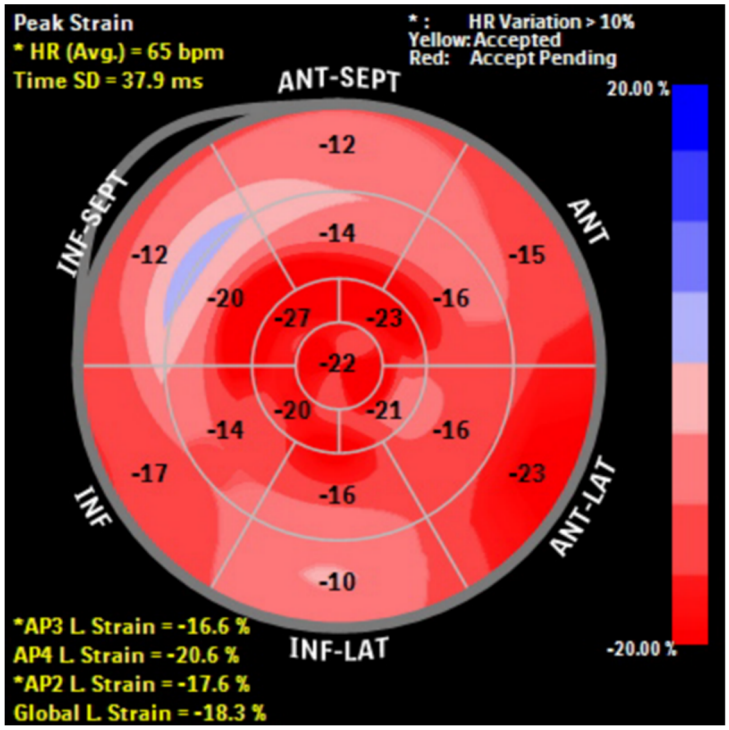


Figure 26c. Bullseyeplot showing global longitudinal strain from a 17 segment model. The bullseye is authomatically generated by the software from strain measurements from the three apical views.
Photo by Annika Ingvarsson

Assessment of RV-function by speckle tracking echocardiography

The RV longitudinal strain by 2D STE was obtained from an RV-focused apical view using the LV-dedicated software. The ventricle was automatically divided into seven standard segments. Longitudinal strain from a four-chamber view (RVGLS) was calculated by the software as a mean of the peak systolic strain of all seven segments (**Figure 27)**.

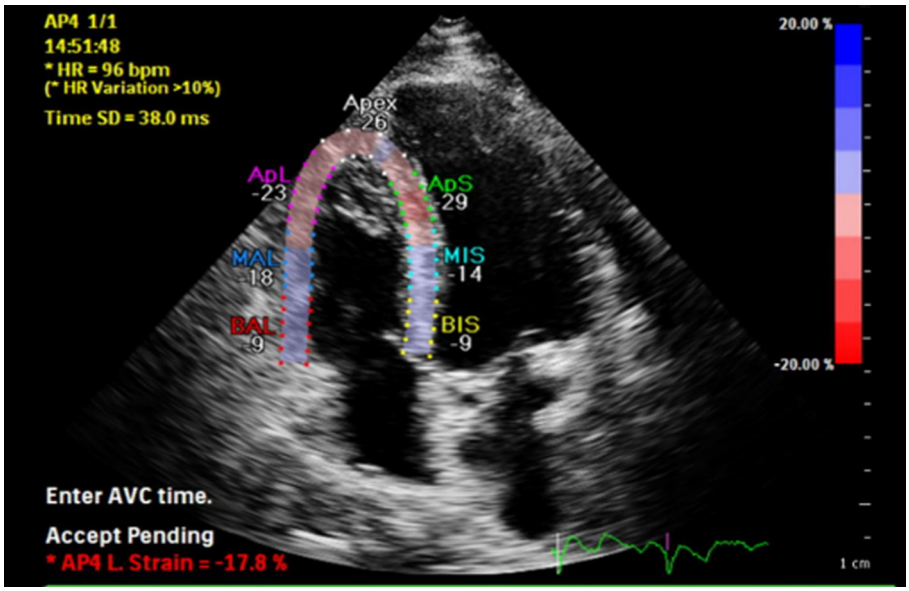


Figure 27. Global longitudinal strain analysis of the right ventricle (RVGLS).
Photo by Annika Ingvarsson

Strain of the RV lateral free wall (RVfree) was manually calculated by averaging the three regional peak systolic strains along the RVfree wall (**Figure 28)**.

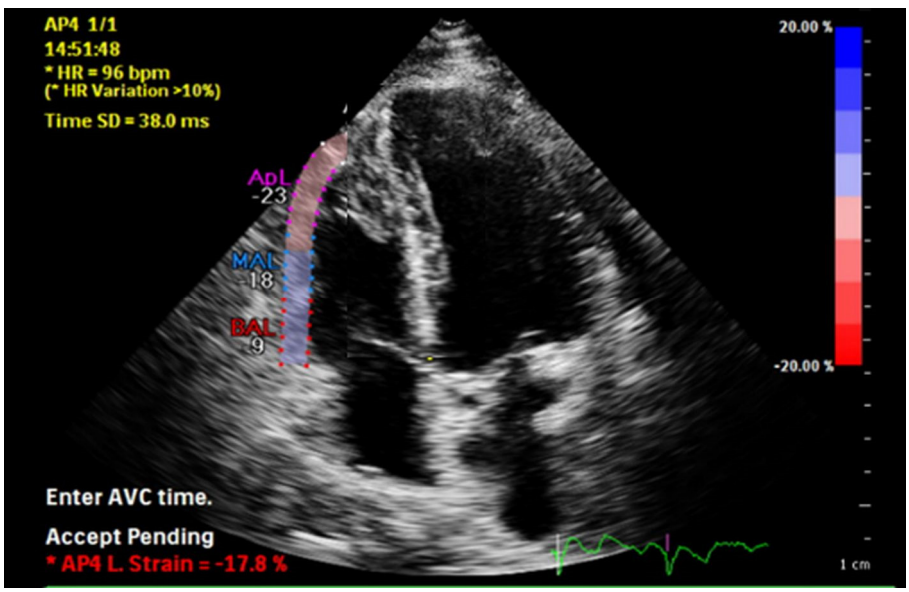


Figure 28. Strain analysis of the three segments of right ventricular lateral wall (RVfree).
Photo by Annika Ingvarsson

Right heart catheterization

*Paper **I**, **III** and **IV***

RHC was conducted under local anaesthesia in supine position at rest. Seldinger technique was used to insert an 8 French sheath, predominantly via the right internal jugular vein. A triple lumen Swan-Ganz catheter was introduced and passed through the heart to the pulmonary arteries, facilitated by its flow directed tip balloon (**Figure 29)**.

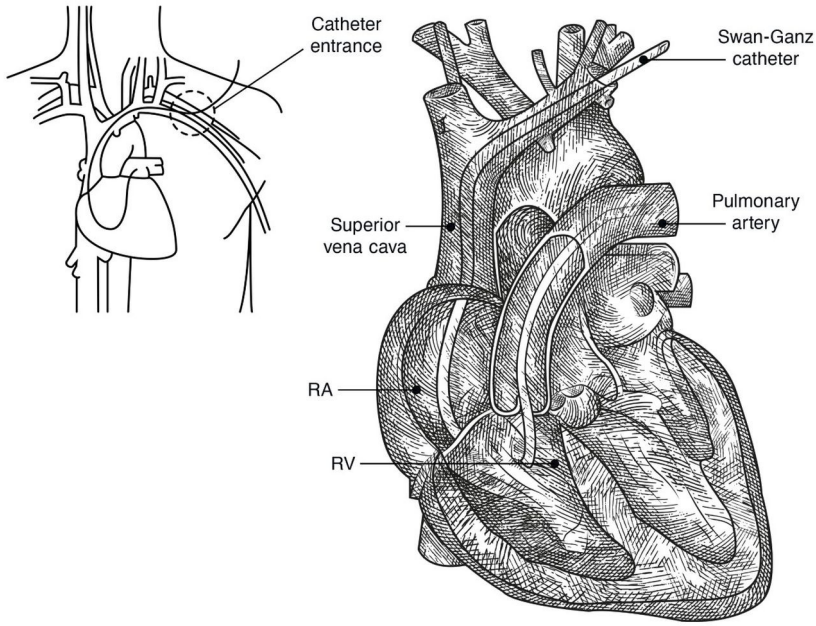


Figure 29. Schematic drawing of the right heart catheterization process.
A Swan-Ganz catheter is inserted through the superior vena cava allowing pressures measurements from the right atrium (RA), the right ventricle (RV), and the pulmonary artery. By inflation of a balloon in the pulmonary artery the pulmonary artery wedge pressures is obtained.
Illustration by Sandra Persson

The pulmonary arterial pressures (systolic PAP, mPAP and diastolic PAP), mean right atrial pressure (mRAP) and PAWP were recorded at free breathing over five heartbeats. Thermodilution was used to calculate CO (i.e. pulmonary blood flow in ml/min), allowing cardiac index (CI) to be calculated by dividing CO by BSA (ml/min/m^2). Stroke volume (SV, ml/beat) was determined by dividing CO by heart rate (HR, i.e. beats/min). SV was also indexed to BSA to calculate stroke volume index (SVI). Right ventricular stroke work index (RVSWI) was calculated by the formula (mPAP-mRAP) x SVI. PVR was defined as (mPAP-PAWP)/CO and

expressed as Woods Units (WU). Pulmonary effective arterial elastance (Ea, mmHg/ml) was calculated as RV systolic pressure divided by SV. Systemic blood pressure (mmHg) was measured using an arm-cuff and sphygmomanometer.

Statistical analyses

General statistics for all papers are described in this section. Comprehensive details for each paper can be found in the attached publications.

Continuous data was expressed as mean ± standard deviation (SD) or median with inter-quartile range, as appropriate according to normal distribution. A 95% confidence interval was used. Categorical data was expressed in absolute numbers and/or as proportion (percentage). Normality was tested by visual inspection of histograms. Differences between groups were analysed with independent sample t-test, or Mann-Whitney U test, as appropriate. Differences in the cohort between time-points were analysed with dependent sample t-test. Findings where considered statistically significant at two-tailed test $P<0.05$. Correlations between parameters where calculated using Pearson´s correlation or Spearman rank correlation coefficients (r-values) as applicable with regard to distribution. The degree of correlation between tests was considered as weak (r = 0.3-0.5), moderate (r=0.5-0.7), strong (r=0.7-0.9) or very strong (r=0.9-1.0) [55]. Data were analysed using SPSS version 22 (paper **I**) or 25 (paper **II-IV**) (SPSS Inc, Chicago, IL, USA). In paper **III** STATA 16 (StataCorp, College Station, TX) was used for linear mixed model regression analysis.

*Paper **I***

Reference range was derived from the 95th percentile. Echocardiographic values obtained were compared to previously published distribution in the reference values using Welch´s unequal-variance t-test since equal variance under these circumstances could not be assumed [56].

*Paper **II***

Dichotomous variables were compared with Chi-2 test and Fisher´s test. Regarding the risk of type II error it is stated that no adjustments for multiple comparisons were made.

*Paper **III***

Intra-observer variability assessment of LV and RV strain parameters were performed in 20 randomly chosen patients, as requested by reviewers when the paper was submitted. Absolute agreement was evaluated using intra-class

correlation with two-way mixed-effect model. The temporal changes in echocardiographic measures and the impact of invasively measured pulmonary pressures were explored by a consulting statistician using linear mixed regression analysis with echocardiographic parameters as dependent variables, time and hemodynamic variables as fixed effects and individual as random effect.

Results

Paper I

Baseline characteristics

The study encompassed a total number of 124 patients after exclusion. Patients were examined when appearing for their yearly routine review. Seventy-eight patients had no history of previous rejection (defined as grade ≥3A). Twenty-nine patients had one episode of rejection and six patients had ≥2 episodes. A majority (n=101) of the patients were transplanted using the bicaval surgical technique. The mean donor age (43±16 years) and recipient age (47±13 years) was close in the total study population. At time of inclusion a total of 41 patients suffered from DM and fifty patients had hypertension according to medical records.

Left ventricular size and function

Compared to reference values presented in the NORRE study [57], we found increased LV wall thickness and consequently higher LV mass ($p<0.0001$). Slightly lower LV diastolic volume were detected in OHT recipients but no difference in systolic volume were noticed, causing slightly lower EF than in a non-transplanted cohort. Global longitudinal strain was reduced (-16.5±3.3% compared to -19.7±1.8%, $p<0.0001$) in reference literature, whereas no difference in circumferential strain were detected (**Figure 30, table 1**) [58].

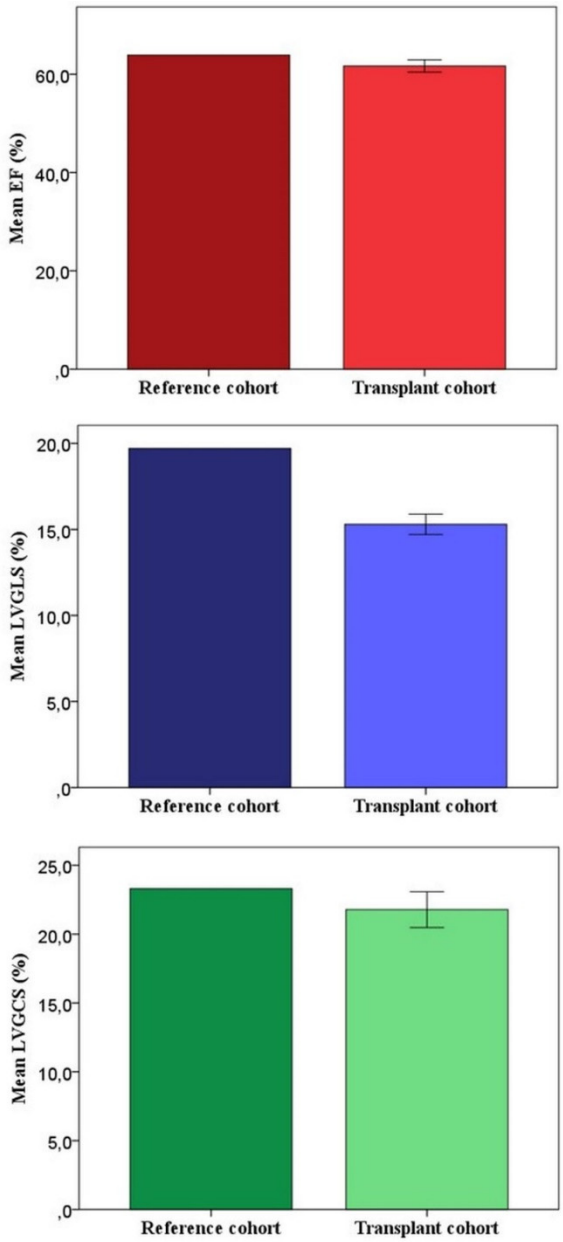


Figure 30. LV function parameters in orthotopic heart transplant (OHT) patients compared with reference values from the normal population [57, 58].

Bars represent mean of the reference population and OHT patients, respectively. Error bars represent 95% CI of the mean in OHT patients. Strain values should be interpreted as negative values.

EF = Ejection fraction, LVGLS = left ventricular global longitudinal strain, LVGCS = left ventricular global circumferential strain

Table 1.
Left ventricular size and function parameters in OHT patients compared to normal reference values [57, 58]

Parameter	OHT patients	Reference value	P
IVSd (mm)	10.9±2.2	8.6±1.6	<0.0001
LVPWd (mm)	10.5±1.9	8.8±1.5	>0.0001
LV mass (g)	160±50	127±37	<0.0001
LVEDV (ml)	88±24	93±25	<0.05
LVESV (ml)	35±12	34±11	n.s.
EF (%)	62.1±7.0	63.9±4.9	<0.01
LVGLS (%)	-16.5±3.3	-19.7±1.8	<0.0001
LVGCS (%)	-22.9±6.3	-23.3±1.3	n.s.

The values are expressed as mean±SD. OHT = ortothopic heart transplantation, IVSd = interventricular septum diameter, LVPWd = left ventricular posterior wall diameter, LV mass = left ventricular mass, LVEDV = left ventricular end diastolic volume, LVESV = left ventricular end systolic volume, EF = ejection fraction, LVGLS = left ventricular global longitudinal strain, LVGCS = left ventricular global circumferential strain

Right ventricular size and function

Both linear measurements of RV diameters and tracing of RV area revealed larger RV size in OHT patients compared to reference values from non-transplanted cohort (p<0.0001) [57]. Conventional measures of RV function; TAPSE, S´ and FAC, were significantly decreased (p<0.0001) in OHT patients [51]. Moreover, RVfree was also much lower than previously published reference values (-16.9±4.2% vs. -29.0±4.5%, p<0.001) [51]. Measures of RV function are depicted in **Figure 31** and shown in **Table 2**.

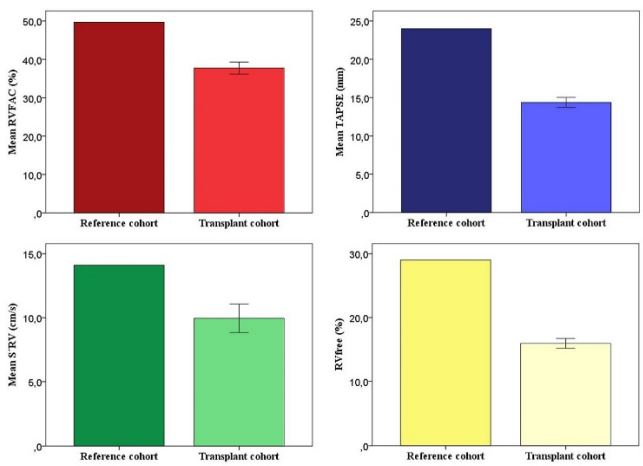


Figure 31. Right ventricular function parameters in orthotopic heart transplant (OHT) patients compared with reference value from normal cohort [51].
Bars represent mean for the reference populationand OHT patients, respectively. Error bars represent 95% CI of the mean for OHT patients. RVfree should be interpreted as negative value.
RVFAC = right ventricular fractional area change, TAPSE = tricuspid annular plane excursion, S´ = systolic tissue velocity of the lateral right ventricular wall, RVfree = right ventricular lateral wall strain

Table 2.
Right ventricular size and function parameters in OHT patients compared to normal reference values [51, 57]

Parameter	OHT patients	Reference value	P
RV basal (mm)	37±6	34±6	<0.0001
RV mid (mm)	33±6	28±6	<0.0001
RV length (mm)	68±12	68±8	n.s.
RVEDA (cm^2)	20±5	17±4	<0.0001
RVESA (cm^2)	12±3	9±3	<0.0001
TAPSE (mm)	15±4	24±4	<0.0001
RV S´(cm/s)	9.7±6.0	14.1±2.3	<0.0001
FAC (%)	40±8	49.7±8	<0.0001
RIMP	0.29±0.18	0.26±0.01	n.s.
RVfree (%)	-16±4.2	-29.0±4.5	<0.001

The values are expressed as mean±SD. OHT = ortothopic heart transplantation, RV basal = right ventricular basal diameter, RV mid = right ventricular mid diameter, RV long = right ventricular length, RVEDA = right ventricular end diastolic area, RVESA = right ventricular end systolic area, TAPSE = tricuspid annular plane systolic excursion, RV S´ = right ventricular systolic tissue doppler velocity, FAC = fractional area change, RIMP = right index of myocardial performance, RVfree = right ventricular strain of the lateral wall

Impact of surgical technique and allograft age

Biatrial enlargement compared to guidelines derived from healthy subjects were detected. Both absolute and indexed LA and RA volumes were larger in the biatrial group than in the bicaval group ($p<0.001$). A weak positive correlation between allograft age and BSA-indexed LA-volume ($R=0.36$, $p<0.001$) was found. When subdividing the material based on surgical technique the correlation only remained for the bicaval group ($R=0.30$, $p<0.01$). All parameters of LV and RV size and function were constant in allografts of varying age.

Impact of previous rejection, CAV and correlation to RHC

As seen in **Figure 32**, previous treatment requiring rejections (defined as ≥3A according to the current classification at time of the study) was shown to negatively affect LVGLS (-14.2±2.8% vs. -15.7±3.4%, $p<0.05$). LVEF was also negatively affected (59±7% vs. 63±7%, $p<0.05$) but remained within normal range. The presence of CAV could not be proven to affect ventricular function. No correlations of clinical importance between RHC and echocardiographic findings were detected.

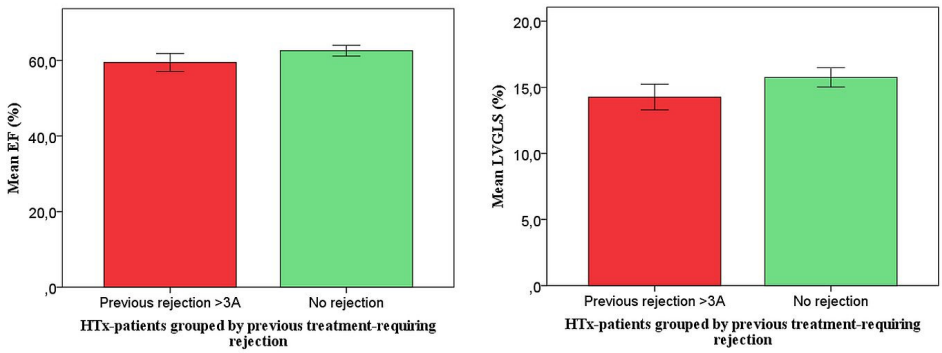


Figure 32. Bars illustrating key echocardiographic differences on the basis of previous rejection.
Error bars express 95% CI of the mean. Both EF and LVGLS were reduced in heart transplant patients with previous rejection. LVGLS is presented in percentage and should be interpreted as negative value.
EF = ejection fraction, LVGLS = left ventricular global longitudinal strain

Paper II

Baseline characteristics

The study consisted of 123 OHT patients (n=89 males) with allograft age varying from one to twenty-four years (median age 4±6 years). Donor age, time since transplant and age at transplant were similar between genders (n.s.), while BSA was higher in male recipients ($p<0.001$). At inclusion 32 patients were diagnosed with CAV, 34 patients had previous treatment requiring rejection, 41 patients had DM and 50 patients had hypertension (n.s. between genders for all parameters). Seventy-three allografts were male (n=66 gender-matched) and 40 allografts were from female donors (n=24 gender-matched). In 10 patients the donor gender was unknown. These patients were excluded from the analysis regarding mismatch.

Impact of recipient gender on LV and RV size and function

LV wall thickness was higher and LV size was larger in male than in female recipients. The difference in size could not be found after indexing to BSA. Most parameters of RV size showed larger RV in male than in female recipients. All statistically relevant parameters pertaining to ventricular size can be found in **Table 3**.

Table 3.
Parameters of ventricular size. P-value refer to the difference between genders

Parameter	Total	Male	Female	P
Left ventricle				
IVSd (mm)	10.9±2.3	11.4±2.2	9.7±1.8	<0.001
LVPWd (mm)	10.7±2.4	10.8±2.0	9.9±1.5	=0.05
LV mass (g)	174±57	185±60	144±32	<0.001
LVEDV (ml)	93±24	100±22	76±19	<0.001
LVESV (ml)	38±12	40±11	30±120	<0.001
Right ventricle				
RV outflow (mm)	31±6	32±6	28±4	<0.001
RV basal (mm)	37±6	38±6	34±6	<0.01
RV mid (mm)	33±6	34±6	30±5	<0.001
RVEDA (cm^2)	18±5	19±6	16±3	<0.05
RVESA (cm^2)	12±3	12±3	10±2	<0.05

The values are expressed as mean±SD. IVSd = interventricular septum diameter, LVPWd = left ventricular posterior wall diameter, LV mass = left ventricular mass, LVEDV = left ventricular end diastolic volume, LVESV = left ventricular end systolic volume, RV basal = right ventricular basal diameter, RV mid = right ventricular mid diameter, RVEDA = right ventricular end diastolic area, RVESA = right ventricular end systolic area

Although both were within normal ranges, female recipients were found to have slightly higher LVEF than male recipients (p<0.05). Apart from this, all conventional parameters of ventricular function were similar between the genders. Regarding longitudinal function assessed with strain, female recipients revealed significantly higher LVGLS (p<0.001), LVGCS (<0.05), RVGLS (p<0.05) and RVfree (p<0.05) than male recipients, **Figure 33 and Table 4**.

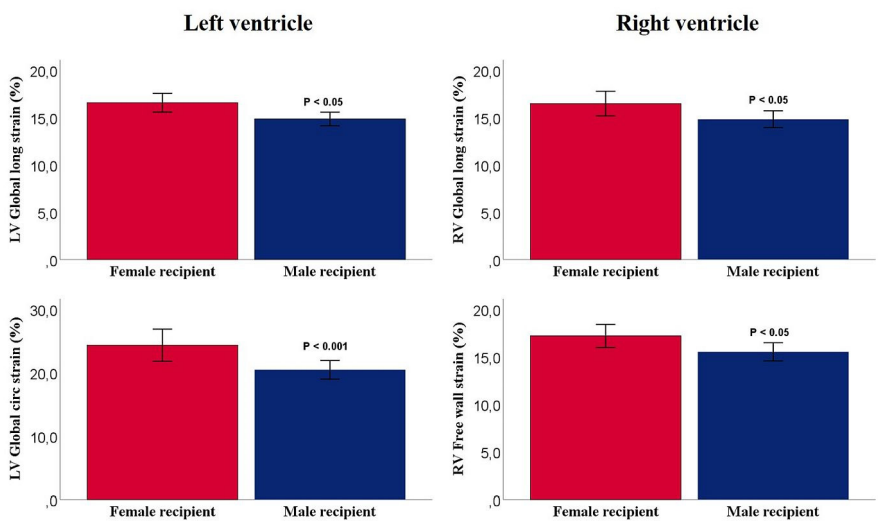


Figure 33. Bargraphs illustrating strain parameters of the two genders.
Red bars represent female recipient and blue bars represent male recipient. Error-bars indicate 95% confidence interval of the mean. All strain values should be interpreted as negative numbers.

Table 4.
Parameters of ventricular function. P-value indicate the difference between genders.

Parameter	Total	Male	Female	P
Left ventricle				
FS (%)	35±9	34±10	36±7	n.s.
EF (%)	62±12	61±7	64±6	<0.05
LVSV (ml)	61±19	62±20	58±11	n.s.
LVGLS (%)	-15.2±3.5	-14.8±3.4	-16.5±2.6	<0.05
LVGCS (%)	-21.8±6.3	-20.4±5.7	-24.5±6.5	<0.001
Right ventricle				
TAPSE (mm)	14.4±3.6	14.0±3.7	15.5±3.0	n.s.
RV S´ (cm/s)	10-0±6.2	10.1±7.2	9.7±2.3	n.s.
FAC (%)	38±4	37±8	40±9	n.s.
RIMP	0.33±0.18	0.31±0.14	0.36±0.25	n.s.
IVA (cm^{-2})	2.2±1.0	2.1±1.0	2.4±0.9	n.s.
RVGLS (%)	-15.3±4.0	-14.8±4.1	-16.5±3.6	<0.05
RVfree (%)	-15.9±4.2	-15.5±4.4	-17.1±3.5	<0.05

The values are expressed as mean±SD. FS = fractional shortening, EF = ejection fraction, LVSV = left ventricular stroke volume, LVGLS = left ventricular global longitudinal strain, LVGCS = left ventricular global circumferential strain, TAPSE = tricuspid annular plane systolic excursion, RV S´ = right ventricular systolic tissue doppler velocity, FAC = fractional area change, RIMP = right index of myocardial performance, IVA = right index of myocarial performace, RVGLS = right ventricluar global longitudinal strain, RVfree = right ventricular strain of the lateral wall

Impact of gender mismatch on ventricular function

Male recipients receiving a female donor heart were found to have LVEF and strain values resembling those of female allograft-matched recipients. The interpretation of this finding is done cautiously given the risk of type II error due to the limited sample size. Comparison of LVEF and strain parameters in male recipients based on donor gender can be found in **Table 5**.

Table 5.
Difference between gender-matched and non-gender-matched male recipients.

Parameter	Total	Matched	Non-matched	P
BSA (m2)	1.98±0.21	2.02±0.21	1.85±0.19	<0.01
Left ventricle				
EDV (ml)	99±23	102±23	88±19	<0.05
ESV (ml)	40±11	41±11	34±9	<0.01
EF (%)	60±9	59±9	64±6	<0.05
LVGLS (%)	-14.6±3.6	-14.3±3.6	-15.9±3.2	=0.08
LVGCS (%)	-20.3±5.7	-18.8±5.4	-24.7±4.3	<0.001
Right ventricle				
RVGLS (%)	-14.5±4.2	-14.0±4.0	-16.5±4.5	<0.05
RVfree (%)	-15.3±4.5	-14.6±4.4	-17.9±2.0	<0.05

The values are expressed as mean±SD. EDV = end diastolic volume, ESV = end systolic volume, EF = ejection fraction, LVGLS = left ventricular global longitudinal strain, LVGCS = left ventricular global circumferential strain, RVGLS = right ventricular global longitudinal strain, RVfree = right ventricular strain of the lateral wall

Paper III

Baseline characteristics

After exclusion, 50 patients remained available for analysis. All patients were transplanted using the bicaval surgical technique and 13 of the patients were bridged to OHT with an LVAD. Median time between listing for OHT and actual transplant was nine months (range 6 days-33 months) and mean-time between initial RHC and OHT were 7±7 months (range 0 days-33 months). One patient had pre-existing DM before OHT. The predominant cause of donor death was brain-death, including all primary brain insults. Echocardiographic evaluation and RHC was conducted within two hours of each other.

Atrial size and left ventricular size and function during the first year

No differences of absolute or indexed LA- and RA-size were detected throughout the study period of one year. Neither were any clinically relevant differences in LV size or function observed between one month and one year after OHT (**Figure 34**).

Right ventricular function the first year following OHT

Mean RV size was within the normal range already by one-month post OHT, and no difference was observed during follow up. Measurements of RV function showed continuous gradual improvement between one and twelve months, with S´ being the sole exception (**Figure 34**).

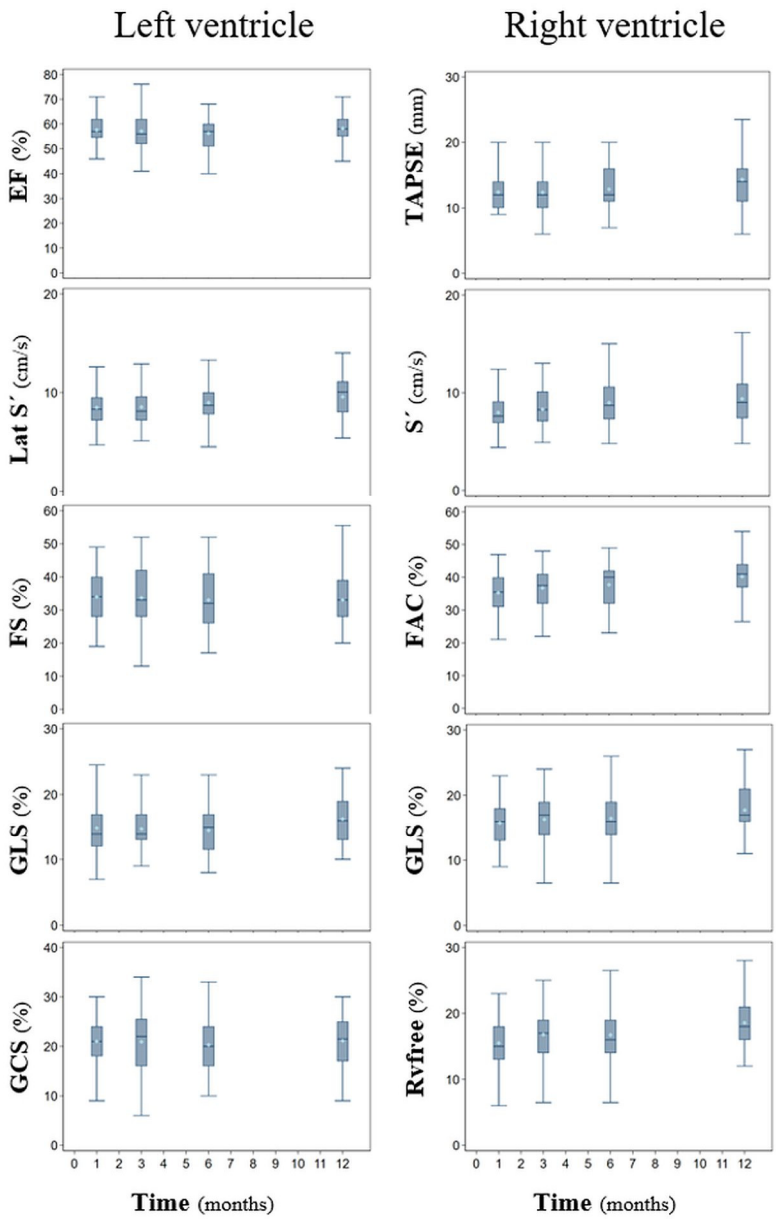


Figure 34. Box plot illustrating unaltered left ventricular function parameters between 1- and 12- months after transplantation and gradual right ventricular function improvement over the first year following OHT.

Dark blue line in the box represents median, light blue dot represents mean, box represents interquartile range (25–75 percentile) and error bars represent the range without regard to outliers. Strain data should be interpreted as negative values.

EF =ejection fraction, S´ =systolic tissue doppler velocity; FS =fractional shortening; lat =lateral, GLS =global longitudinal strain, GCS =global circumferential strain, TAPSE =tricuspid annular plane systolic excursion, FAC =fractional area change, RVfree =right ventricular strain of the lateral right ventricular wall

A complete list of RV size- and function parameters at different time-points can be found in **Table 6**.

Table 6.
Echocardiographic assessment of right ventricular size and function at 1-, 3-, 6- and 12- months following transplantation. P-value indicate the difference between 1 and 12 months.

Parameter	1 month	3 months	6 months	12 months	P
RV size					
Inflow (mm)	38±6	39±5	37±5	39±5	n.s.
Mid (mm)	33±6	33±5	33±5	35±6	n.s.
Length (mm)	73±12	75±7	73±7	71±14	n.s.
RVEDA (cm^2)	20±4	19±3	20±4	20±4	n.s.
RVESA (cm^2)	12±3	12±3	12±3	12±2	n.s.
RV function					
TAPSE (mm)	12.4±3.3	12.4±3.5	12.9±3.4	14.4±4.3	<0.01
RV S´(cm/s)	8.9±5.7	9.6±8.6	9.0±2.5	9.4±2.7	n.s.
FAC (%)	36±8	37±6	39±8	41±8	<0.01
RVGLS (%)	-15.8±3.4	-16.3±4.0	-16.5±4.5	-17.8±3.6	<0.01
RVfree (%)	-15.5±3.7	-16.8±3.9	-16.8±3.9	-18.6±3.6	<0.001

The values are expressed as mean±SD. Inflow = right ventricular inflow diameter, mid = right ventricular mid diameter, Length = right ventricular length, RVEDA = right ventricular end diastolic area, RVESA = right ventricular end systolic area, TAPSE = tricuspid annular plane systolic excursion, RV S´ = right ventricular systolic tissue doppler velocity, FAC = fractional area change, RVGLS = right ventricular global longitudinal strain, RVfree = right ventricular strain of the lateral wall

Hemodynamic differences between one and twelve months after OHT

Blood pressure increased significantly during follow up, while a simultaneous decrease in HR were detected ($p<0.001$ for both). All measures of pulmonary arterial pressure showed significant decrease along with decrease in mRAP and PAWP (**Table 7**). At one month a weak negative correlation between FAC and PAWP ($R= 0.37$, $p<0.05$) and between FAC and mRAP ($R= 0.35$, $p<0.05$) was found. Linear mixed regression model revealed improvement of all echocardiographic RV parameters over time. A weak negative correlation between S´ vs. mPAP, PAWP and PVR respectively was noted.

Table 7.
Hemodynamic assessment at 1-, 6- and 12- months following transplantation. P-value indicate the difference between 1 and 12 months.

Parameter	1 month	6 months	12 months	P
SAP (mmHg)	120±15	138±14	134±14	<0.001
DAP (mmHg)	73±10	88±10	85±10	<0.001
MAP (mmHg)	89±10	105±10	101±10	<0.001
HR (bpm)	91±10	79±10	80±10	<0.001
PVR (wood unit)	1.5±0.6	1.5±0.6	1.3±0.6	n.s.
mRAP (mmHg)	6.1±3.9	2.7±2.2	2.7±2.2	<0.001
sPAP (mmHg)	28±8	24±6	23±6	<0.01
dPAP (mmHg)	12±4	9±4	8±3	<0.01
mPAP (mmHg)	18±5	15±4	15±4	<0.001
PAWP (mmHg)	10±5	8±3	7±4	<0.05
RVSWI	403±187	459±206	439±148	n.s.
SVi (ml/m^2)	34±9	36±7	37±7	<0.05
CO (L/min)	5.8±1.3	5.5±1.0	5.8±1.1	n.s.
CI (L/min/m^2)	3.0±0.6	2.8±0.5	3.0±0.5	n.s.

The values are expressed as mean±SD. SAP = systolic arterial pressure, DAP = diastolic arterial pressure, MAP = mean arterial pressure, HR = heart rate, PVR = Pulmonary vascular resistance, mRAP = mean right atrial pressure, sPAP = systolic pulmonary arterial pressure, dPAP = diastolic pulmonary arterial pressure, mPAP = mean pulmonary arterial pressure, PAWP = pulmonary arterial wedge pressure, RVSWI = right ventricular stroke work index, SVi = stroke volume index, CO = cardiac output, CI = cardiac index

Intra observer variability

The intra observer variability test performed for strain parameters in 20 patients was 0.98 (95% CI; 0.94-0.99) for LVGLS, 0.99 (95% CI; 0.98-0.99) for RVGLS and 0.99 (95% CI; 0.97-0.98) for RVfree.

Paper IV

Baseline characteristics

A total of 59 patients (n=20 LVAD, n=18 male) were enrolled in the study. Median time between initial RHC and OHT was 146 days, and patients on LVAD support had significantly longer time on waiting-list than non-LVAD patients (396±318 days vs. 182±121 days, p<0.01). Before LVAD support BP was lower in the LVAD group (p<0.05). When evaluated for OHT, 44 patients (LVAD n=16) had mPAP>25mmHg and 46 patients (LVAD n=18) had PAWP>15mmHg. Presence of PH according to above [49], were equally distributed between the groups. On clinical indication a subgroup of eight patients were re-evaluated with RHC while on LVAD support (data shown below).

Impact of bridging with LVAD on early RV adaptation

At one month following OHT echocardiographic parameters of RV longitudinal function were significantly better in patients pre-treated with LVAD: TAPSE 15±3 mm vs. 12±2 mm, RVGLS -19.4±2.1% vs. -14.4±2.8% and RVfree -19.8±2.3% vs. 14.1±2.9% ($p<0.001$ for all parameters). A slightly higher PAWP (11±5 mmHg vs. 9±4 mmHg) and a lower PVR (1.2±0.4 WU vs. 1.6±0.6 WU) was noted in the LVAD group.

RV function during one year follow up

Between one and twelve months all TTE parameters of RV function improved significantly in the non-LVAD group whereas no difference was observed during the same time span in the LVAD group. Consequently, at twelve months differences between the groups were no longer detectable. Echocardiographic parameters for both groups at all time points are listed in **Table 8** and illustrated in **Figure 35**.

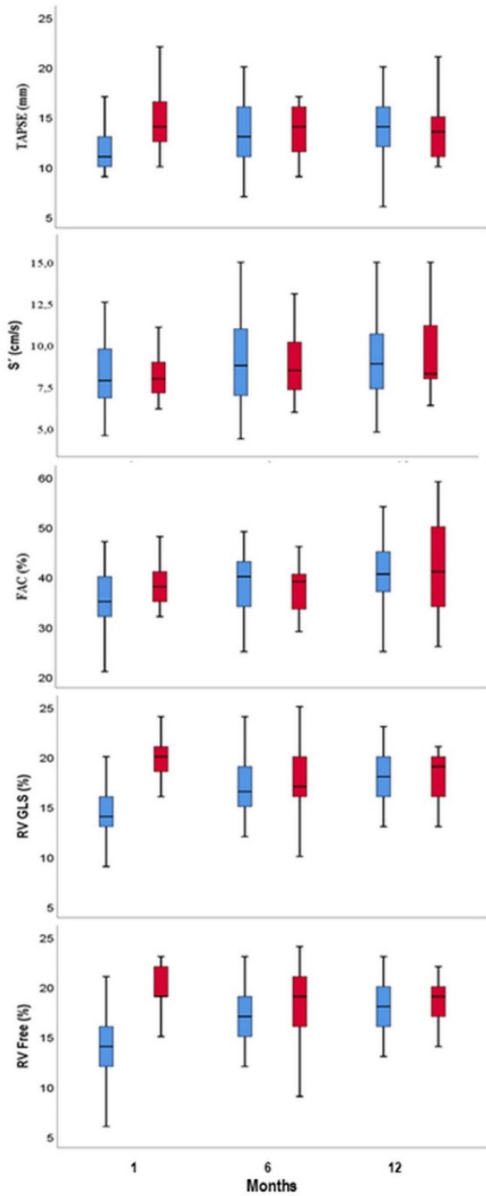


Figure 35. Box-plot illustrating unaltered right ventricular function parameters between one and twelve months after orthotopic heart transplantation (OHT) in the LVAD group compared to gradually improved RV function parameters over the first year following OHT in the non-LVAD group.

LVAD patients are represented by red boxes and non-LVAD group by blue boxes. Black line in the box represent median, box represent interquartile range (25-75 percentile) and whiskers represent the range.

LVAD = left ventricular assist device, TAPSE = tricuspid annular plane systolic excursion, S´ =right ventricular systolic tissue doppler velocity, FAC =fractional area change, RVGLS = right ventricular global longitudinal strain, RVfree =right ventricular strain of the lateral wall

For all patients BP increased between one and twelve months (p<0.001). During follow up a decrease pulmonary artery pressures was observed in the non-LVAD group while the LVAD group only showed a decrease in mPAP and dPAP. Additionally, central venous pressure (CVP) and Ea were lower at twelve months in both groups.

Table 8. Right ventricular function parameters assessed with echocardiography for LVAD and non-LVAD group resprectively at all time-points. P-values represent the difference wtihin the group between one and twelve months. Significant differences between the groups at any time-point is indicated by astrerix in the LVAD column.

	1 month		6 months		12 months		P	P
	LVAD	*Non-LVAD*	*LVAD*	*Non-LVAD*	*LVAD*	*Non-LVAD*	*LVAD*	*Non-LVAD*
TAPSE (mm)	14.5±2.9 ***	11.7±2.4	13.6±2.8	13.2±3.6	14.1±3.8	14.5±4.2	n.s.	<0.001
RV S´ (cm/s)	7.9±1.6	8.2±2.1	8.9±2.0	8.9±2.7	9.2±2.4	9.4±2.6	n.s.	<0.01
FAC (%)	39±5	36±8	38±7	39±7	41±9	41±7	n.s.	<0.05
RVGLS (%)	-19.8±2.1 ***	-14.3±2.8	-17.2±4.4	-17.2±3.1	-18.2±2.4	-18.1±2.8	n.s.	<0.001
RVfree (%)	-19.8±2.3 ***	-14.1±2.9	-17.8±4.3	-17.0±2.9	-18.9±2.2	-18.2±2.9	n.s.	<0.001

The values are expressed as mean±SD. LVAD = left ventricular assist device, non-LVAD = patients not treated with left ventricular assist device, TAPSE = tricuspid annular plane systolic excursion, RV S´ = right ventricular systolic tissue doppler velocity, FAC = fractional area change, RVGLS = right ventricular global longitudinal strain, RVfree = right ventricular strain of the lateral wall. * p<0.05, ** p<0.01, ***p<0.001

Correlation of echocardiographic data with hemodynamic measures

A weak linear correlation was found at one month between RVGLS and RVfree to PAWP (R= -0.28 and -0.31 respectively, p<0.05 for both). RVfree also showed a weak negative correlation to CVP (R=0.28, p<0.05) and TAPSE correlated to PVR (R=0.28, p<0.05). At six and twelve months no correlations were found.

Re-evaluation with RHC while on LVAD support

In a small subgroup (n=8) RHC was performed on clinical indication while on LVAD support (median time since initial RHC was 5 months, range 2-34 months). A significant reduction in pulmonary pressures, PAWP and PVR was detected (p<0.05 for all parameters) in these patients.

Discussion

This doctoral dissertation focused on establishing normal echocardiographic values for OHT patients and assess the possible influence of donor and recipient gender. Moreover, the aim was to describe the ventricular adaptation process during the first year following OHT and evaluate the impact of bridging with LVAD.

Ventricular function in heart failure and OHT

Heart failure, defined as inadequate CO due to impaired ventricular function, can be either chronic or acute and may be caused by both LV- and RV-failure [30, 31]. Chronic LV dysfunction may induce PH with pulmonary vascular remodelling and elevated PVR, thereby increasing the risk of RV failure post OHT [59-61]. Acute RV failure due to increased resistance in the pulmonary circuit and pre-operative PH has been shown to increase early mortality following OHT [62, 63]. Continuous improvements in pre-, peri- and post-operative care has led to increased survival rates [17, 64]. Although PH with vascular remodelling has been considered a relative contraindication for OHT by International Society for Heart and Lung Transplant (ISHLT) [65], the growing use of LVAD support has increased the number of patients eligible for transplantation [35, 66-68]. This is supported by a report from ISHLT that stated that patients who underwent OHT 2004-2015 had comparable survival rate regardless of pre-operative PVR [69].

The surgical procedure of OHT may influence contractility of the heart [70-72]. It is well known that the RV is particularly sensitive to pericardiotomy and that the incision of the pericardial sack immediately affects RV longitudinal contraction as measured by echocardiography. Moreover, pericardiotomy has been shown to disrupt the interdependency of the ventricles [28, 41, 44, 73, 74]. Also, factors related to the donor heart, as well as ischemic time, have been suggested to affect ventricular function [42, 43, 75-80]. Finally, the mandatory immunosuppressive treatment, development of CAV and allograft rejection may influence ventricular function in OHT recipients [18].

Routine clinical follow up after OHT include imaging with echocardiography and although many factors may have influenced the allograft function, data on normal ventricular adaptation and its validation have been sparse [64, 81-86].

Chamber size in OHT recipients

Atrial size and function

The atria have an important role in the ventricular filling process by their three phases (i.e. reservoir, conduit and booster) [20]. When LV remodelling occurs due to aging or relaxation abnormalities this can affect atrial size and extensibility through increased filling pressures [54]. In this thesis, healthy OHT subject, of varying time since transplant (paper **I** and **III**), showed enlargement of both atria compared to guidelines from healthy subjects. Not surprisingly, it was noted that both atria were additionally larger in patients transplanted with the biatrial technique which is explained by the fact that the complete native atria are spared using this technique, leaving the recipient with "double" elongated atria. The LA enlargement found in the bicaval group may partly be explained by the fact that this surgical technique saves the roof of the recipient´s native atrium including the pulmonary veins and suture to the LA of the donor heart.

Re-examination of patients during the first year following OHT revealed no differences regarding absolute or indexed LA and RA volumes between one and twelve months. Nevertheless, in stable OHT patients (allograft age 1-15 years) paper **I** revealed that in the bicaval group atrial size correlated with allograft age, which might indicate that progressive stiffness of the LV accompanied by increased filling pressures are developing. It has previously been demonstrated that CAV, being the most common cause of long-term cardiovascular mortality among OHT recipients, has a prevalence of almost 50% of patients after 10 years from OHT and may induce progressive myocardial fibrosis associated with restrictive filling patterns [45, 87-90].

Although diastolic evaluation was outside the scope of our study it is fair to say that the concept of diastolic assessment remains an echocardiographic challenge also in the normal population, including a large number of parameters that must be weighed to form a conclusion [54]. To further complicate the evaluation in OHT patients, the donor heart is denervated, which leads to mild sinus tachycardia (with reduced HR variability) which in turn may cause fusion of the mitral inflow velocities [91-93]. Pulmonary venous flow is affected by the contraction of the remnant recipient atrial tissue and moreover, a pseudo-restrictive filling pattern may be found in patients with completely normal LV diastolic function as donor hearts are commonly

obtained from healthy young individuals [94-97]. In **paper I** we found no difference between the surgical groups nor correlation with respect to allograft age in conventional parameters of diastolic function. Studies on filling pressures and diastolic dysfunction in OHT patients are sparse and often quite limited in sample size. Others have found that mitral E/A ratio, deceleration time of the E-wave and isovolumetric relaxation time correlate well with PAWP in OHT patients [98]. Moreover, OHT recipients have been shown to have markedly reduced reservoir function. This were more pronounced in subjects with increased LV and RV filling pressure but could also be detected in OHT patients with normal filling pressures [99].

Ventricular size

During the first year following OHT (paper **III**) we could not detect any differences in LV- or RV- size. In paper **I** stable OHT recipients (1-25 years from transplant) had increased LV wall thickness, and slightly lower LV diastolic volume together with larger RV size compared to reference values derived from a normal population were found. In paper **II** comparison between male and female recipients revealed higher LV wall thickness and larger absolute LV volumes in male than in female recipients. However, the difference in size were not detected after indexing to BSA. Moreover, most parameters of RV size showed larger RV in male than in female recipients. The differences in volume and wall thickness may be related to factors such as the immunosuppressive treatment, fibrous atrophy, hypertension, and donor specific features. Loss of pericardial restrain and the surgical procedure of OHT may alter cardiac geometry [100]. These hypothesises are subject to discussion in the separate papers.

Chamber function in OHT recipients

Conventional assessment of ventricular function

Parameters of LV function was normalized by only one month after OHT. In the cohort of patients in steady state, EF remained normal and female recipients had slightly higher EF than male recipients, although both were within normal range compared to reference values [51]. Apart from this, all conventional parameters of LV function were similar between the genders. In paper **II** male recipients receiving a female donor heart were found to have better EF (i.e. comparable to the EF of gender matched female recipients) than males receiving a gender matched allograft. Although we did not conduct a longitudinal study, this finding is rather surprising

since male recipients who receive a female donor heart has been reported to have significantly increased risk of early and late major rejections, with a corresponding increase in CAV. The same authors have also showed this mismatch to be a powerful and independent predictor of major adverse events during long-term follow-up (i.e. higher rates of heart failure and end stage renal failure) [101]. Moreover, it has also been demonstrated that gender mismatch may negatively affect survival in both genders [102]. In paper **I** patients with history of treatment requiring rejection displayed significantly lower EF than the rest of the cohort but remained within normal range. It has previously been reported that EF remained unaltered despite several episodes of rejection, while LV- and RV- GLS were impaired [48]. The authors of this study suggests that this might be related to fibrosis and that strain imaging is useful in detecting early ventricular longitudinal impairment that may later develop to LV dysfunction. In paper **I** no correlation was found between presence of CAV and conventional parameters of LV function. These findings suggest that conventional parameters of LV function poorly reflect subtle changes and possible early LV dysfunction. It has previously been demonstrated that EF may be normal following OHT although interstitial fibrosis is present and exercise tolerance is impaired [90]. Moreover, in a CMR study tissue remodelling and increased extracellular volume (i.e. expansion of connective tissue in the allograft) were detected although EF was preserved, and no clinical allograft dysfunction was present [103]. These findings illustrate the need of constant improvement in imaging techniques to facilitate the early detection of subtle changes. The conventional measures included in the echocardiographic evaluation of LV function following OHT may not be sensitive enough to properly assess early remodelling.

Regarding RV function, TAPSE and FAC improved gradually the first year following OHT (paper **III**). Paper **IV** revealed that patients bridged to transplant with an LVAD had significantly better TAPSE at one month than non-LVAD patients. Nevertheless, in the cohort of steady state patients (paper **I**) all three parameters of RV function; TAPSE, S´ and FAC, were significantly decreased compared to normal reference values. This is an expected finding since longitudinal function is known to be impaired following cardiac surgery. Compensatory mechanism involved in the adaptation process to remain adequate RV function (and SV) remain to be further explored. With regard to RV function, echocardiographically calculated FAC has been reported as the only parameter correlating to CMR [104]. This may reflect an increase in radial contractility compensating for the reduction seen in longitudinal function, and parameters incorporating the radial motion have been recommended to assess RV function following OHT [105].

Speckle tracking assessment of ventricular function

In paper **III** both LVGLS and LVGCS were constant between one and twelve months following OHT, whereas a continuous improvement was seen in RVGLS and RVfree. However, in paper **IV** patients pre-treated with LVAD both RVGLS and RVfree was normalized already by one month after transplantation. This study also found that during the first year, measures of RV contractility improved significantly in the non-LVAD group while no change was observed during the same time span in the LVAD group. Thereby, no difference between the groups was detectable by twelve months post OHT.

One month following OHT a weak linear correlation was found between RVGLS and RVfree and PAWP. RVfree also showed a weak negative correlation to CVP (paper **III**). The correlations between echocardiographic findings and RHC data is of questionable clinical importance and could at most be regarded as indicative for future study designs. Theoretically, presence of pre-existing PH and early postoperative increased afterload might impact on RV mechanics. Though, the expected decrease in PVR following OHT and the near normalization of pulmonary pressures reported in long term follow up [106, 107] require caution when interpreting the importance of single echocardiographic RV function parameters in the light of true RV dysfunction. In a PAH population it has been demonstrated that RVfree correlate to pulmonary arterial systolic pressure (PASP) and that increased RV afterload negatively affect RVfree strain [108]. This is an interesting observation, but the alterations in PASP may differ due to different patient populations and the alteration required to observe these changes may not apply in an OHT cohort. Data on RV mechanics in the OHT cohort are limited [84, 86, 105] and further studies on this subject is warranted.

In stable OHT patients LVGLS was reduced while LVGCS were comparable to normal reference values (paper **I**). Reduction in GLS is in line with what has previously been described in smaller studies following OHT [64, 82, 83, 109] Episodes of treatment requiring rejection were found to negatively affect LVGLS as discussed above. RVfree was significantly lower than reference values derived from a normal population. In paper **II** LVGCS and both LV- and RV- longitudinal strain were significantly worse in male recipients receiving a male donor heart than in female recipients or in male recipients that received a gender mismatched organ.

Hemodynamic features related to LVAD support

OHT patients are known to have slightly elevated HR [92]. In paper **IV** a decrease in HR and an increase in BP between one and twelve months were seen. The physiological impact of LVAD treatment include reduction in left ventricular filling

pressure, mPAP, sPAP and PVR [34, 35, 66] which might account for the difference observed between the groups following OHT.

Another finding was that CVP and Ea were lower at 12 months irrespectively of LVAD pre-treatment. This finding implies that the total RV load is reduced during the first year following OHT. The inclusion of Ea (paper **IV**) as a hemodynamic parameter in the study design may be questioned since its clinical relevance is not fully understood and the simplified calculation is based on several assumptions [110]. However, detection and evaluation of clinically relevant novel measurements that may add value in monitoring RV function following OHT is important. Elevated Ea has been demonstrated to be associated to mortality independent of presence of RV dysfunction. Furthermore, it has been published that Ea, as a novel measure combining resistive and pulsatile component of RV load, adds incremental discriminatory value regarding discriminatory ability of survival among patients with PH due to left heart disease [111]. The same authors have reported that Ea also is superior in reflecting echocardiographically detected RV dysfunction. Conversely, the validity and usefulness of this measurement of the pulmonary circuit has been questioned since the calculation is built on simplified assumptions from the systemic circulation that do not automatically apply to the pulmonary circuit [110]. Nevertheless, Ea remains a promising addition in RV function assessment but needs further validation in various clinical contexts.

In a small subgroup of the LVAD patients in paper **IV**, RHC was performed on clinical indication during LVAD treatment. These patients showed reduction in pulmonary pressures, PAWP and PVR compared to prior to LVAD treatment. This finding is in line with previous studies during and following LVAD support [34, 67, 112] but additional studies with intent to further characterize the hemodynamic impact longitudinally is warranted.

Limitations

For limitations, please refer to the attached papers individually.

Conclusions

The major conclusions of the studies were:

Paper I

OHT affects ventricular size and function rendering the use of values for normality derived from a non-transplanted cohort misleading. Application of normal reference values on this unique cohort may result in underestimation of systolic LV and RV function and false interpretation of reduction in longitudinal contractility. Neither CAV, nor time since transplant were proven to significantly affect ventricular function parameters in this study. However, a slight reduction in EF and LVGLS were noted in patients that previously suffered from treatment requiring rejection. Moreover, OHT patients displayed specific features such as atrial enlargement that is partly related to the surgical procedure as well as slightly increased LV ventricular wall thickness and thereby larger LV mass. Furthermore, RV size was larger than reported in a non-transplant cohort. The results of this paper support having specific reference values that should be applied when assessing OHT patients echocardiographically.

Paper II

Recipient gender may impact on the echocardiographic values used to assess ventricular function. Female OHT recipients were found to have higher values of LV and RV function when evaluated with measures of contractility (i.e. longitudinal strain). Moreover, male recipients receiving a gender mismatched organ displayed the same values as female recipients that received a female donor organ. This suggests that reference values in the OHT cohort could be divided and presented separately for the genders in line with guideline recommendations from a non-transplanted cohort. However, in a clinical context this may be complicated by the lack of information regarding donor gender.

Paper III

Early recovery during the first year following OHT differs for the LV and RV. Echocardiographic evaluation showed normalization of the values assessing LV function already by one-month post OHT. Conversely the values of RV function were decreased at one month but showed continuous improvement during one year follow up, reaching normal range at 12 months post OHT. During the first year

following OHT, BP increased significantly accompanied by a decrease in HR. Also, during follow up PAP, mRAP and PAWP decreased. No clinically relevant correlations between echocardiographic parameters and RHC data were found.

Paper IV

Patients receiving LVAD support before OHT had significantly better RV function one-month post OHT assessed with echocardiography compared to recipients without LVAD as bridge to transplant. The paper also revealed that the RV function was unaltered in the LVAD group during the first one year of follow up, while the non-LVAD group increased their RV function parameters progressively. At one year, no difference between the groups could be detected. Alterations in RHC data between one and twelve months were essentially equal between the two groups. Only weak correlations, with questionable clinical importance, were detected between single echocardiographic values and RHC parameters were detected. Subgroup analysis with limited sample size also suggests that pulmonary pressures, PAWP and PVR are reduced on LVAD support. To conclude, preconditioning with LVAD as bridge to transplant positively impacts the early RV adaptation process and expedites recovery following OHT.

Future perspectives

Survival and ensuring freedom from adverse events following OHT remains a clinical challenge, and there are numerous factors involved in the transplantation process that may affect allograft function following OHT [17]. After OHT the host immune response against the allograft demands lifelong immunosuppressive treatment, leading to issues related to under- and over- immunosuppression, that may limit long-term survival [18, 113, 114]. Moreover, apart from developing CAV and being at risk of developing rejection[45, 115-118], OHT patients are overrepresented regarding DM, hypertension, renal dysfunction, malignancy, and osteoporosis[119-124]. Accurate imaging assessment of ventricular function in OHT recipients in different clinical settings is therefore of outmost importance. Based on the knowledge about normal ventricular adaptation and ventricular function following OHT gained from the studies in this thesis, further studies focusing on improving imaging techniques in different clinical setting are warranted.

Lately several automated and semi-automated methods have been developed by the software suppliers. The technique of 3D echocardiography has expanded with improvements in temporal and spatial resolution along with post-processing that require minimal user input [125-131]. Furthermore, assessment of LV volumes and EF by 3D have been acknowledged in guidelines [51]. These advances require validation in selected cohorts such as OHT recipients but are promising new tools to optimize imaging and increase the understanding about morphology and function.

The heart is a complex organ with the main task to maintain adequate CO, which can be achieved through several different mechanisms. In recent years there has been an increased interest in validating myocardial performance through different myocardial deformation measurements (i.e. strain). OHT patients have been shown to exhibit normal EF but decreased longitudinal function parameters [81-83, 132, 133]. Further studies focusing on adaptation and how the different myocardial components achieve the compensatory mechanism to maintain CO is of great interest. Furthermore, it is well known that OHT induce changes that affect the normal response to increased demands of cardiac CO (e.g. exercise). Medication to normalise BP may also further limit the normal cardiac response [134]. Several studies have been published with the intention to validate ventricular function echocardiographically during physical activity [135, 136]. Combining strain

imaging, 3D echocardiography and physiological stress test may give new insight in the physiology of the transplanted heart. Echocardiography has been evaluated by many as to whether the method can be used to detect rejection with conflicting results [116, 137-142]. To date RHC with endomyocardial biopsies remain the gold standard to make the diagnosis. In the future perhaps with software refinement echocardiographic strain may play a role in detection and monitoring of allograft functional changes related to rejection episodes.

Comprehension of diastolic function is a further complicating factor when evaluating OHT patients. The introduction of LA strain could potentially be a useful measure assisting in LV diastolic evaluation [143-145]. Additionally, studies focusing on physiological stress test echocardiography combined with RHC may also elucidate this topic further.

Lastly the introduction of other imaging modalities such as CMR, considered the gold standard, has in recent years been increasingly clinically used to assess ventricular function in OHT patients [104, 146-148]. CMR has the advantage of being able to detect fibrosis and more accurately assess chamber volumes along with quantifying valvular regurgitation [90, 149]. Nevertheless, TTE has many advantages including accessibility and will most likely remain the first line imaging modality. Therefore, combining studies focusing on comparing the two methods to increase understanding about possible advantages and disadvantages within the methods to further optimize imaging in OHT patients is desirable.

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