Mortality and morbidity among heart transplant recipients in Sweden. Limitations of a life with a transplanted heart.

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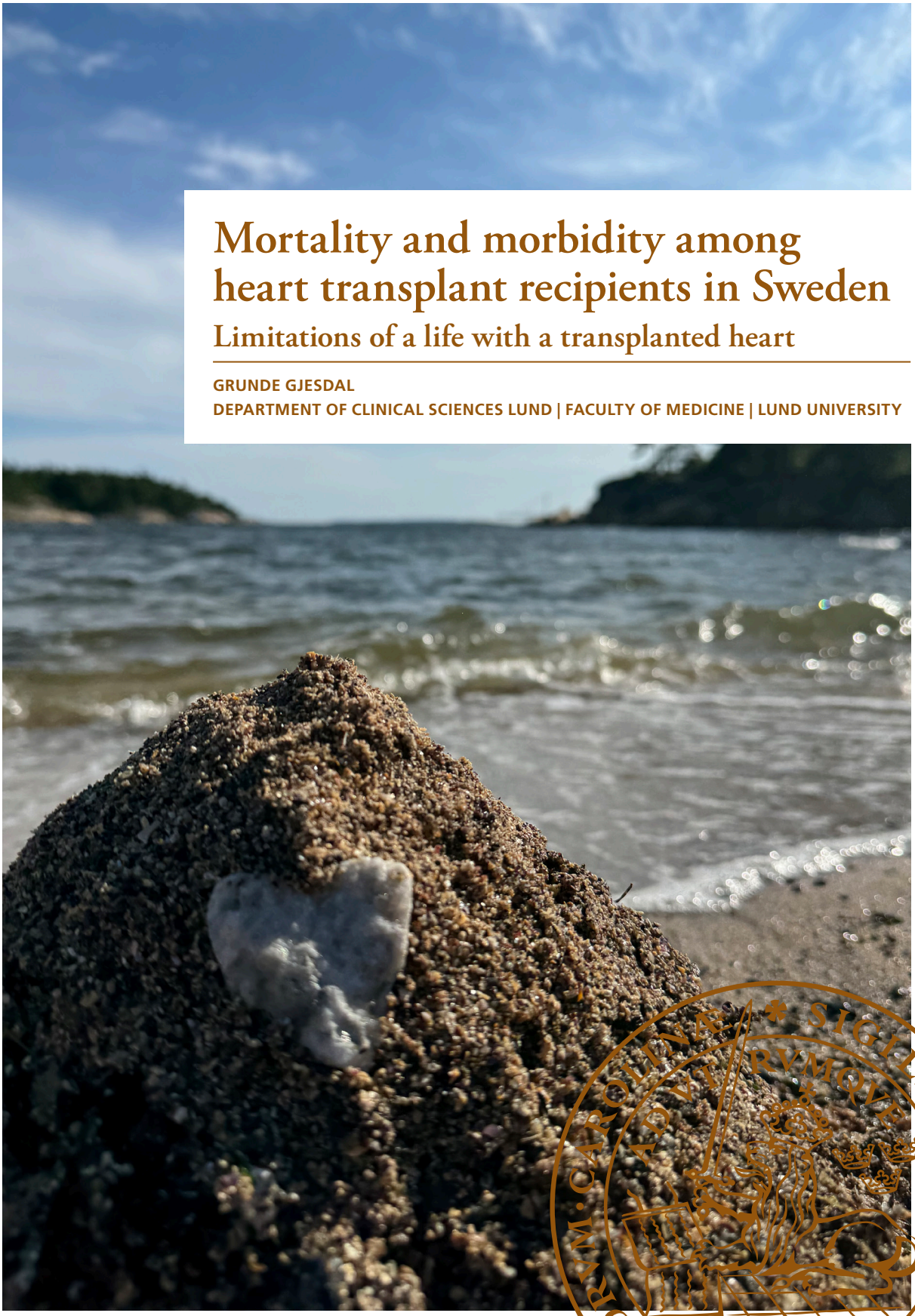

Mortality and morbidity among heart transplant recipients in Sweden

Limitations of a life with a transplanted heart

GRUNDE GJESDAL
DEPARTMENT OF CLINICAL SCIENCES LUND | FACULTY OF MEDICINE | LUND UNIVERSITY

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GRUNDE GJESDAL was born in Oslo, Norway, in 1979. In 2000 he started his medical education at Syddansk University in Odense, Denmark. After completing his internship at Bærum Hospital outside Oslo in 2008, he moved to Skåne, Sweden, where his career began as a resident of emergency and internal medicine at Skåne University Hospital in Lund. After completing his residency in internal medicine, he transferred to the Department of Cardiology. Since 2016, he has worked as a cardiologist with a focus on advanced heart failure and heart transplantation.

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Grunde Gjesdal

LUND
UNIVERSITY

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Abstract:

Background

For carefully selected patients with advanced heart failure, heart transplantation is the optimal treatment to improve survival (1) and quality of life (2). Nevertheless, morbidity within the group is substantial (3). In the present thesis, we aimed to explore outcomes among Swedish heart transplant recipients regarding mortality, comorbidity, and physical limitations related to the physiology of a transplanted heart.

Methods

Retrospective data from local and nationwide Swedish registries were used to analyze mortality and psychiatric comorbidity. Patient records were reviewed to determine death causes and to collect background characteristics of included patients treated at Skåne University Hospital. Cardiac magnetic resonance imaging in combination with cardiopulmonary exercise testing (CPET) was used for the mechanistic studies.

Results

Although medical treatment has improved and survival after heart transplantation in Sweden is both excellent and continuing to improve, acute rejections of transplanted hearts are still responsible for the loss of many patient life-years. Psychiatric comorbidities are common both before and after transplant surgery. Exercise capacity in heart-transplanted patients is lower than in healthy controls and may be restricted by the transplant recipients' reduced longitudinal heart function and limited ability to increase myocardial perfusion.

Conclusions

The thesis presents a broad glance into the limitations of a life with a transplanted heart and may contribute to identifying areas needing further investigation.

Key words: Heart transplantation, mortality, morbidity, centralization, life years lost, psychiatric comorbidity, cardiac magnetic resonance, left ventricular atrioventricular plane displacement, myocardial perfusion

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Dedicated to my two favorite girls
and the little guy who commands all of our attention

Against the background of this research and with our own experience in the experimental laboratories, backed by the knowledge of the surgical management and post-operative care of patiwents undergoing major cardiac surgery, the time arrived when a cardiac transplant could be contemplated with hope of success.

Christiaan N. Barnard. *The operation*. South African Medical Journal, 1967

Table of Contents

Abstract

Background

For carefully selected patients with advanced heart failure, heart transplantation is the optimal treatment to improve survival (1) and quality of life (2). Nevertheless, morbidity within the group is substantial (3). In the present thesis, we aimed to explore outcomes among Swedish heart transplant recipients regarding mortality, comorbidity, and physical limitations related to the physiology of a transplanted heart.

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Conclusions

The thesis presents a broad glance into the limitations of a life with a transplanted heart and may contribute to identifying areas needing further investigation.

Populärvetenskaplig sammanfattning

Bakgrund

För noggrant utvalda patienter med avancerad hjärtsvikt är hjärttransplantation den optimala behandlingen för att förbättra överlevnad och livskvalitet. Men trots detta är sjukligheten fortfarande betydande inom gruppen. Med avhandlingen ville vi undersöka utfallet bland hjärttransplanterade patienter i Sverige med fokus på dödlighet, samsjuklighet och fysiska begränsningar som är relaterade till det transplanterade hjärtats fysiologi.

Metodik

Retrospektiva registerdata från flera stora båda lokala och rikstäckande register användes för analys av dödlighet och psykiatrisk samsjuklighet. Journaldata granskades för bestämmelse av dödsorsaker och inhämtning av bakgrunds-information gällande undersökta patienter lokala till Skånes Universitetssjukhus. Magnetisk resonanstomografi av hjärtat i kombination med ergospirometri användes för de fysiologiska studierna.

Resultat

Även om den medicinska behandlingen har förbättrats enormt och överlevnaden efter hjärttransplantation i Sverige är både utmärkt och i förbättring, orsakar akuta avstötningar fortfarande många förlorade levnadsår för patienterna, och psykiatrisk samsjuklighet är vanligt både innan och efter transplantationen. Den fysiska arbetsförmågan hos hjärttransplanterade patienter är fortfarande lägre än hos den friska befolkningen och kan begränsas av både nedsatt longitudinell hjärtfunktion och minskad förmåga att öka hjärtats genomblödning.

Slutsatser

Avhandlingen ger en bred inblick i begränsningarna i livet med ett transplanterat hjärta och kan förhoppningsvis bidra till att identifiera områden som behöver undersökas ytterligare.

List of Papers

Paper I

Gjesdal G, Rylance RT, Bergh N, Dellgren G, Braun OÖ, Nilsson J. Waiting list and post-transplant outcome in Sweden after national centralization of heart transplant surgery. *J Heart Lung Transplant*. 2024 Aug; 43(8), 1318-1325

Paper II

Gjesdal G, Lundgren J, Czuba T, Wareham NE, Gustafsson F, Nilsson J, Smith JG, Braun OÖ. Validation of cause of death classification after heart transplantation and cause-specific life expectancy compared to the general population. *Clin Transplant*. 2022 Sep;36(9), e14756

Paper III

Gjesdal G, Li X, Milos Nymberg V, Smith JG, Sundquist K, Braun OÖ. Depression and Anxiety in Heart Transplant Recipients in Sweden: A Nationwide Study. *Manuscript*.

Paper IV

Gjesdal G, Székely A, Engblom H, Arheden H, Braun OÖ, Steding-Ehrenborg K. Left ventricular longitudinal function is reduced, but partially compensated by increased radial function after heart transplantation. *Manuscript*.

Paper V

Dimovski K, **Gjesdal G**, Steding-Ehrenborg K, Jablonowski R, Xue H, Kellman P, Braun OÖ, Arheden H, Engblom H. Myocardial perfusion reserve is low in heart transplant patients and is related to exercise capacity. *Submitted manuscript*.

Author's contribution to the papers

Paper I

The author participated in the conceptualization, methodology development and wrote the original draft of the manuscript.

Paper II

The author participated in methodology development, validation of death causes, and wrote the original draft of the manuscript.

Paper III

The author participated in the conceptualization, methodology development and wrote the original draft of the manuscript.

Paper IV

The author participated in the conceptualization, methodology development, analysis of CMR investigations, and statistical analyses, and wrote the original draft of the manuscript.

Paper V

The author participated in the conceptualization and editing of the manuscript.

Abbreviations

ACR	acute cellular rejection
AMR	antibody-mediated rejection
APC	antigen presenting cells
ATG	anti-thymocyte globulin
AVPD	atrioventricular plane displacement
AZA	azathioprine
BPM	beats per minute
C3b	complement factor 3b
CAV	cardiac allograft vasculopathy
CMR	cardiac magnetic resonance
CMV	cytomegalovirus
CNI	calcineurin inhibitor
CPET	cardiopulmonary exercise test
CR1	complement receptor 1
CyA	ciclosporin
DAMPs	damage-associated molecular patterns
DBD	death by brain death
dd-cfDNA	donor-derived cell-free DNA
DSA	donor-specific antibody
ECG	electrocardiogram
ECV	extracellular volume
ECMO	extracorporeal membrane oxygenation
ED	end-diastole
ES	end-systole
FDA	US Food and Drug Administration
G1/2	cell cycle gap phases 1 and 2
GEP	gene expression profiling
GFR	glomerular filtration rate
HLA	human leukocyte antigen
IL2	interleukin 2
IL2RA	interleukin 2 receptor antagonist

ISHLT	International Society of Heart and Lung Transplantation
IVUS	intravascular ultrasound
LGE	late gadolinium enhancement
LVAD	left ventricular assist device
LVAVPD	left ventricular atrioventricular plane displacement
LVEF	left ventricular ejection fraction
M	cell cycle mitosis phase
MAC	membrane attack complex
MHC	major histocompatibility complex
MMF	mycophenolate mofetil
MP	myocardial perfusion
MPA	mycophenolic acid
MPR	myocardial perfusion reserve
MR	magnetic resonance
mTOR	mammalian target of rapamycin
NEJM	New England Journal of Medicine
NFAT	dephosphorylated nuclear factor of activated T-cells
peakVO_2	peak oxygen consumption
PRR	pattern recognition receptor
RPP	rate pressure product
S	cell cycle synthesis
STE	steroids
STRAX	Swedish Thoracic Transplant Register
SV	stroke volume
SWEDEHEART	Swedish Web-system for Enhancement and Development of Evidence-based care in Heart disease
TAPSE	tricuspid annular plane systolic excursion
TNF	tumor necrosis factor
UNOS	United Network for Organ Sharing

Introduction

Since starting my medical career with a residency in emergency medicine and general internal medicine 16 years ago, I have considered myself a clinician, and believed that my abilities are better suited to interact with patients rather than scientific research. On a few occasions I was given the option of becoming a PhD student, but I always felt content focusing on my clinical career.

After completing my internship in cardiology, I was offered the opportunity to work with advanced heart failure and transplantation. A field where I felt that I could benefit from my broad clinical background. For the first time, I got the opportunity to explore research inspired by clinical curiosity. Today, I see myself as a combination of an advanced heart failure specialist and primary care physician for some 150 heart transplanted recipients.

This thesis, driven by curiosity awakened in the meetings with these patients in the non-pretentious environment of our heart failure and transplantation team, is dedicated to all those who make my days both rewarding, challenging, and most of all, enjoyable.

To my patients, my combined colleagues, scientific supervisors, and friends, and most of all - to my family.

Heart transplantation 1967 to 2024

Dr. Christiaan Barnard and the first heart transplant

The first human heart transplant was performed by Dr. Christiaan Barnard and his colleagues at Groote Schuur Hospital in Cape Town, South Africa in December 1967 (4) (Figure 1). The patient, 55-year-old Louis Washkansky, suffered from terminal heart failure. The donor, a 25-year-old woman named Denise Darvall, was the victim of a car accident and had been proclaimed brain-dead by neurologists (5). The heart transplant surgery went well, and post-transplant immunosuppression was managed using a combination of intravenous hydrocortisone, prednisone, azathioprine, and local irradiation of the heart using a one curie source of cobalt. The transplant recipient Mr. Washkansky lived for a total of 18 days after the surgery, but ultimately died of sepsis, which was initially misinterpreted as acute rejection. Dr. Barnard later explained at the Dick Savett Show (6, 7) that he believed the source of sepsis to be an infection in Mr. Washkansky's leg that was caused by needles used for fluid drainage and present at the time of transplantation.

Figure 1: News of the first heart transplant in December 1968 (8). Reprint with permission of Elsevier©, license 5770080049939.

The work that paved the way

That Dr. Barnard, not residing in the US, was the one to perform the first heart transplant somewhat surprised the medical community. However, the timing was not coincidental. Leading up to the surgery, progress had been made at several pivotal points and Dr. Barnards achievement would not have been possible without the work of many other pioneers. The French surgeon Alexis Carrel won the Nobel Prize in Medicine 1912 for his work on vascular anastomoses (9). The Russian scientist Vladimir Dhemikov performed several canine heart transplants as early as in the 1940s and 1950s (10), and the US surgeon from Mississippi James Hardy attempted the first xenotransplantation of a chimpanzee heart into 68-year-old Boyd Rush in 1964. Rush died a mere hour after the transplant (11).

Dr. Norman Shumway

The US surgeon Norman Shumway at Stanford has since been widely regarded as the "father of heart transplant" (12), and was expected by many to be the one to perform the first human heart transplant. Together with his colleague Richard Lower, Shumway developed the surgical technique that is still widely used today (13). Shumway performed the fourth-ever human heart transplant in early January 1968. Later the same year, over 100 heart transplants would be performed worldwide (12). Despite early enthusiasm, disappointing patient survival caused by a high incidence of life-threatening acute rejections soon dampened the interest (Table 1a-b). By the early 1970s, only a few transplants were performed yearly.

Table 1a: Survival of the first 60 heart transplant recipients (14)

	Duration of Survival					
	<1 day	1 day – 1 month	1 month – 1 year	1-2 years	>2 years	Total
Number	11	19	19	7	4	60

Table 1b: Cause of death of the first 60 heart transplant recipients who survived < 2 years (14)

	Cause of Death				
	Rejection	Infection	Cardiac	Other	Total
Number	11	19	19	7	56

The 1970s - Stanford in the lead

Rejections constraining outcome

In 1971, Shumway and his colleagues at Stanford reported that they had performed 26 heart transplants. Six-month survival was 42%, one-year survival 37%, and two-year survival 26% (15). Early graft rejection was still the main obstacle. Routine post-transplant follow-up consisted of monitoring the blood pressure and auscultation for the presence of gallop-rhythm. Echocardiograms were performed in order to assess for potential thickening of the left ventricular wall or increasing right ventricular diameter, and repeated electrocardiograms (ECG) were evaluated for decreasing QRS voltage, arrhythmias, right axis shifts, and ST-T wave changes.

The first immunosuppressant regimes

Around the same time, Scottish surgeon Philip Caves who was visiting Stanford came up with a technique for sampling small pieces of myocardial tissue using a bioptome (Figure 2) accessed through the right jugular vein (16). Together with the coinciding discovery of anti-thymocyte globulin (ATG) (17), this laid the foundation for histological assessment, diagnosis and treatment of early and sometimes even asymptomatic rejection. A year after publishing the new technique of obtaining biopsies, the team at Stanford reported successfully reversing 35 out of 37 biopsy-detected acute rejections by using augmented immunosuppression (18). The immunosuppressive protocol consisted of a combination of intravenous methylprednisolone, anti-thymocyte globulin (ATG), and the transcription inhibitor (chemotherapeutic drug) actinomycin D (19).

Figure 2: The author G. Gjesdal holding a cardiac bioptome designed by colleague Øyvind Reitan

Declining interest in heart transplants among peers

The available long-term use of the combination of azathioprine and prednisone was too ineffective to provide adequate immunosuppression. By adding ATG induction, the immunosuppressive effect was augmented, but the induction also caused increased rates of infections, which constrained outcomes. Interest in the procedure declined, and by the late 1970s, only a handful of surgical centers across the world were performing heart transplants. However, Shumway and his team at Stanford continued to slowly but steadily improve their results using their ever-growing experience and dedicated research. The hunt was on for improved immunosuppression.

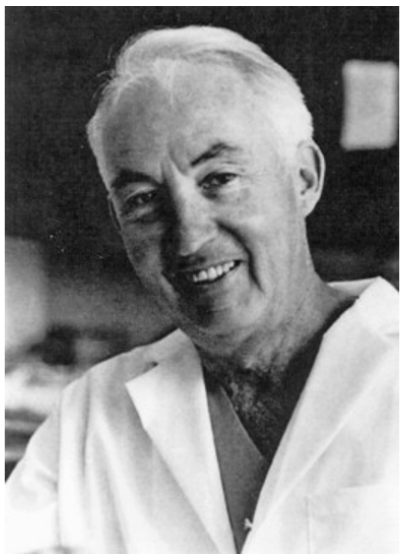


Figure 3: U.S. surgeon Norman Shumway at Stanford (20). Reprint with permission of Elsevier©, license 5770070181477

The immune system at a glance

The innate and adaptive immune system

The human immune system has several pathways able to detect and respond to unfamiliar cells and tissue. The first protective response the donor's heart is subject to, is that of the innate immune system. Cells of the innate immune system express a wide range of pathogen-associated pattern recognition receptors (PRRs) able of being activated by a variety of markers of tissue injury named damage-associated molecular patterns (DAMPs); reactive oxygen species, heat shock proteins, heparin sulfate, and fibrinogen that are exposed from damaged tissue. The DAMPs in turn activates a cascade of proinflammatory cytokines, interleukins, tumor necrosis factor (TNF), among others, facilitating inflammation. Consequently, the surgically removed and partly ischemic transplanted donor heart meets the first line of the transplant recipient's response regardless of their tissue factor differences and similarities (21).

The second line of the immune defense consists of the adaptive immune system and its recognition of alloantigens. T-cells are vital to the immune response, and research has shown that T-cell-depleted mice can tolerate deliberately non-matching organ grafts without resulting organ rejection (22). Allorecognition occurs when antigen-presenting cells (APCs) bind to donor cell surface membrane-bound glycoproteins called major histocompatibility complex (MHC) molecules. The APC may be of donor origin (direct pathway) or recipient origin (indirect pathway). MHCs, called human leukocyte antigens (HLAs) in humans, are divided into two major clinically relevant classes: class I (A, B, C) and class II (DR, DQ, DP) (23).

The APC presents HLA to the T-cell, and, co-stimulated by the binding between glycosylated proteins CD80/86 (B7) on the APC and the CD28-receptor on the T-cell, a cascade is launched, starting with calcium-influx and ultimately leading to the activation, differentiation and proliferation of T-cells (Figure 4).

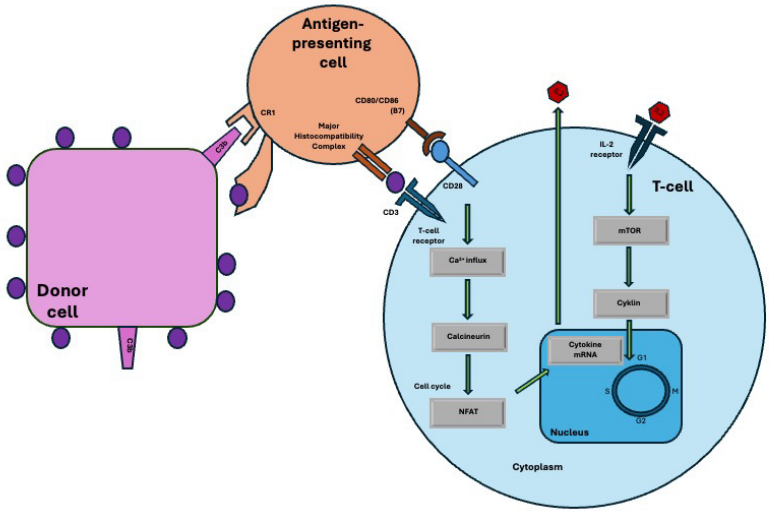


Figure 4: Initiation of the T-cell response through complement activation of antigen-presenting cells. Complement activation of APC which recognizes HLA from the donor cell and present it to the T-cell. By co-stimulation in the form of interaction between glycoproteins B7 on the APC and CD28 on the T-cell, T-cell activation and proliferation are initiated. Abbreviations: C3b = Complement factor 3b; CR1 = Complement receptor 1; G1/G2 = Cell cycle gap phase 1 and 2; M = Cell cycle mitosis phase; mTOR = Mammalian target of rapamycin; NFAT = Dephosphorylated nuclear factor of activated T-cells; S = Cell cycle synthesis

Allograft rejection

Donor allograft rejection may be classified as hyperacute, acute, or chronic (24). Hyperacute rejections occur within minutes or hours after graft reperfusion. They are caused by preformed recipient antibodies directed toward HLA or ABO-blood group antigens. The recipient antibodies attach to the endothelial cells of the donor organ, fixing complement and initiating a cascade resulting in cell damage, platelet aggregation, and vascular occlusion (25).

Acute cellular rejection (ACR) may occur soon after the transplant (<10 days) or at any later point, but the risk is greatest during the early postoperative period, and decreasing with time (26). ACR is driven by T-cell activation, causing inflammation and ultimately leading to myocytolysis and tissue necrosis if left untreated (27).

The presence of antibody-mediated rejections (AMR) was described as early as in the late 1980s (28), but was not formally recognized until the 21st century (29). The pathological mechanism of AMR is still not completely understood (30). The most dramatic form of AMR is hyperacute rejection, but AMR may, as ACR, develop at any point post-transplant, and the underlying mechanism is likely to be a contributing factor in patients with chronic rejection.

AMR is caused by HLA antibodies directed against the donor graft endothelium (donor-specific antibodies, DSA) (28). DSA binding results in complement activation by the classical pathway of the complement cascade (31). Antigen-antibody complexes bind to complement C1q, and in a cascade of amplified steps, complement components form a membrane attack complex (MAC), leading to donor cell lysis. Active complement fragments C3a and C5a exert direct effects on endothelial cells and have chemotactic properties, recruiting both neutrophils and macrophages to the transplanted organ (32) (Figure 5).

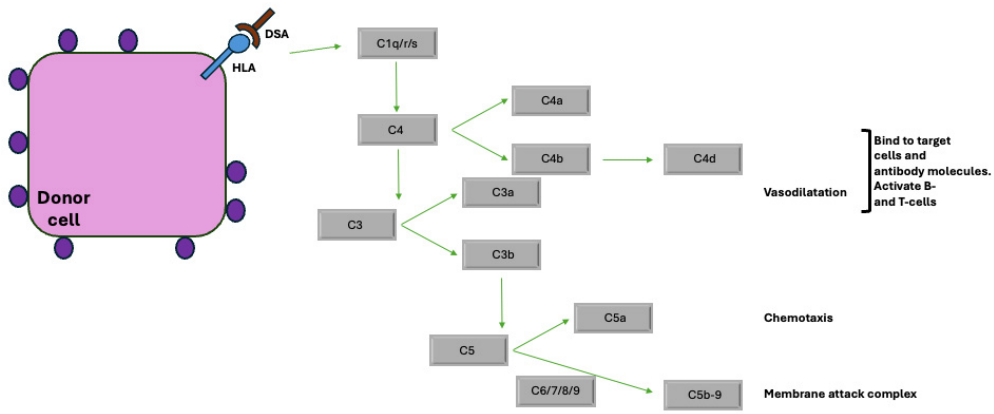


Figure 5: HLA-DSA activation of the classical complement pathway cascade. Complement C1 is activated by the HLA-DSA complex, causing a cascade of amplification and resulting in vasodilatation, migration of inflammatory cells, and ultimately myocytolysis. Abbreviations: C = Complement factor; DSA = Donor specific antigen; HLA = Human leukocyte antigen

The mechanisms behind chronic allograft rejection have not been completely mapped. They are likely multifactorial. Histological and immunohistochemical signs of AMR with complement deposition may be found in over 50% of patients who develop clinical rejection more than seven years post-transplant (33). These signs of AMR have been linked to increased long-term mortality (34). Diffuse and repeated alloimmune attacks result in a clinical picture called cardiac allograft vasculopathy (CAV). The CAV process targets the epithelium, the arteries, the arterioles, as well as the capillaries. The resulting inflammation of the vessel intima layer leads to concentric narrowing of the complete vasculature, ultimately causing vessel obliteration, myocytolysis and development of fibrous scar tissue (35).

The 1980s - The Golden Era

The ISHLT and the multidisciplinary approach

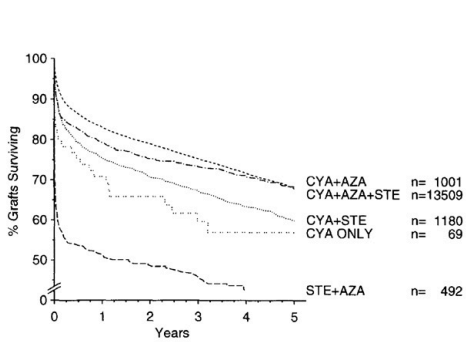
In March 1981, the newly formed International Society of Heart and Lung Transplantation (ISHLT) had its first meeting in San Francisco, California, USA. The organization sought to aid in research and education on heart and lung transplantation, and to collaborate on improving outcomes. At the time of foundation, the organization reported a 5-year mortality rate of about 50% (36). The ISHLT brought together surgeons, cardiologists, pulmonologists, immunologists and infection disease specialists, and was a driving force in developing the multidisciplinary team approach that has since become a common practice in medical decision making in general (12).

Since its formation, the ISHLT registry has gathered information on patient, donor, and transplant characteristics and post-transplant outcomes of over 100,000 heart transplants worldwide (37).

Ciclosporin shifting the mood

In 1972, ciclosporin, an inhibitor of T-cell calcineurin (38), was first isolated from *Ophiocordyceps sessilis,* a fungus collected by the Swiss biologist Hans Peter Frey working for *Sandoz* pharmaceuticals while vacationing at Hardangervidda in Norway (39). Ciclosporin was first used in a heart transplant patient in 1980 (40), and was approved by the Food and Drug Administration (FDA) for clinical use (41) three years later.

Although ciclosporin use was limited by a narrow therapeutical window, common side effects, and vulnerability to infections, its impact on survival rates was paradigm-changing (42) (Figure 6a). By 1985, Shumway's team at Stanford University reported a 1-year survival rate of 80% (43). From a low of 187 heart transplants a year in 1982 worldwide, the 1980s saw a steady increase in heart transplants, growing more than 20-fold, to 4,528 heart transplants, in 1990 (44) (Figure 6b).



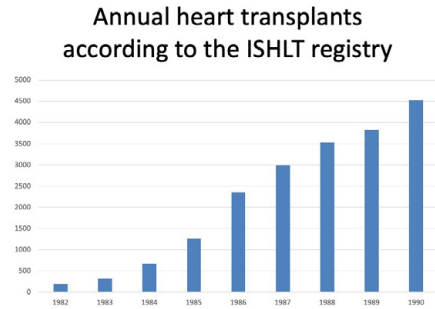


Figure 6a: Post-transplant survival according to the immunosuppressive induction regimen (42). Reprint by permission of Professor Gerhard Opelz, University of Heidelberg, Germany. Abbreviations: CYA = Ciclosporin; AZA = Azathioprin; STE = Steroids.
Figure 6b: Annual worldwide heart transplants according to the ISHLT registry. Adapted from the 2015 ISHLT Adult Heart Transplantation Report (44).

Prophylactic anti-microbial and anti-viral therapy

Prior to 1980, two-thirds of solid organ transplant recipients developed at least one infectious complication during the first post-transplant year (45). While the change to ciclosporin-based immunosuppression resulted in fewer infections than the alternative combination of ATG induction followed by azathioprine and prednisone, bacterial, fungal, and viral infections still caused considerable limitations to both post-operative and long-term survival. During the early 1980s, regimens of standardized prophylactic antibiotic treatment were developed at most transplant centers, primarily based on broad-spectrum antimicrobials such as a cephalosporin (46) in combination with trimethoprim-sulfamethoxazole to counteract pneumocystis carinii infection (47).

However, while antibacterial treatment options were improving, cytomegalovirus (CMV) infections were an ongoing problem. Some transplant centers reported up to a 100% CMV infection rate (48). Prophylactic acyclovir treatment was attempted but showed no effect (49). In the late 1980s, ganciclovir, the first treatment with proven effect toward CMV, was finally approved by the FDA and was soon incorporated as both prophylactic and infection treatment (50).

Development of the bicaval operating technique

The original biatrial surgical technique used by Barnard during the first heart transplant remained essentially unchanged during the 1970s and 1980s. In 1974, Barnard and his colleague Losman experimented with heterotopic transplantation, in which the donor's heart was transplanted with the recipient's heart still in place

(51). In its original form, the procedure resulted in the donor heart serving, by principle, as a left ventricular assist. Barnard later modified the technique to include biventricular support (52, 53), but soon abandoned the modification due to inferior survival rates (12).

In 1989, Yacoub and Banner published a new surgical technique in which the right atrium was explanted together with the rest of the recipient's heart, and anastomoses were constructed between the inferior and superior vena cava (54) (Figure 7). While this technique was more time-consuming than the previous techniques, and hence resulted in greater donor graft ischemic times, it has since been associated with lower right-sided filling pressures, a decreased burden of atrial arrhythmias, and improved survival rates (55).

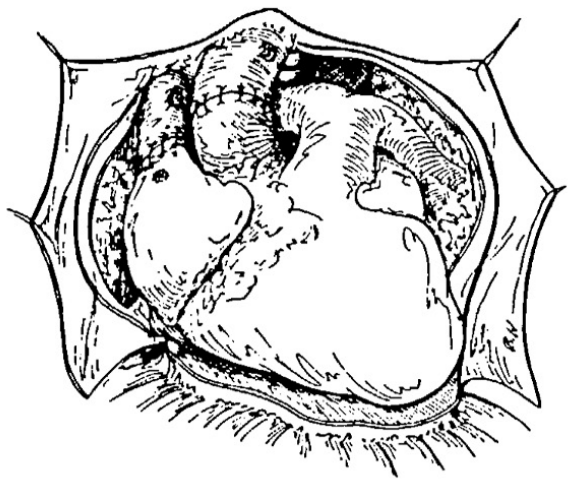


Figure 7: Bicaval operating technique developed by Yacoub and Manner 1989 (54). Reprint with permission of Elsevier©, license 5770040868055.

The dawn of heart transplantation in Sweden

In Sweden, the introduction of heart transplant surgery was delayed compared to many other countries, as the definition of brain death was not integrated into Swedish law until 1988. As a result, the first Swede who underwent heart transplantation in 1980, had the procedure performed at Stanford. When the first heart transplant on Swedish soil was performed at Sahlgrenska University Hospital in 1984, the donor heart was collected and flown in from Germany. During the following years, a handful of heart transplants were performed at both Sahlgrenska

University Hospital in Gothenburg and Karolinska Institute in Stockholm, all using non-domestic hearts. Also during the mid-1980s, several Swedish patients were referred to and were operated on at Harefield Hospital in England, where Swedish surgeons were trained while awaiting permission to use domestic organs. After the concept of brain death was formalized in Swedish legislation, Sahlgrenska, Karolinska, and Lund University hospitals soon launched local heart transplant programs (56).

The 1990s - Standardized follow-up and improved survival rates

Margaret Billingham and the standardization of rejection grading

In 1990, the ISHLT published a grading scale for cellular rejection (57). The scale was based on the work of the Stanford pathologist Margaret Billingham (18, 58), and soon became the gold standard for assessing graft rejection.

The new grading system was a helpful aid in communication between various transplant centers regarding research and standardization of rejection treatment. However, inconsistencies were soon noticed in interpreting biopsy findings and clinical outcomes between centers. To combat these inconsistencies, and in view of the emerging understanding of changes caused by AMR, a special ISHLT committee was formed. The committee published a revision of the original grading scale in 2004 (59) (Table 2).

Table 2: 1990 vs 2004 ISHLT grading of rejection (57, 59)

1990 ISHLT grading of rejection		2004 ISHLT grading of rejection	
0	No ACR	0R	No ACR
1A	Focal, mild ACR	1R	Mild, low-grade ACR
1B	Diffuse, mild ACR		
2	Focal, moderate ACR		
3A	Multifocal, moderate ACR	2R	Moderate, intermediate ACR
3B	Diffuse, moderate ACR	3R	Severe, high-grade ACR
4	Severe ACR		
		AMR0	No histologic or immunopathologic features of AMR
		AMR1	Histologic features of AMR and/or immunofluorescence staining for AMR

Pravastatin and improved 1-year outcomes

During the early 1990s, attention to cholesterol's effect on coronary arteriosclerosis was peaking (60-62), and awareness of CAV was rising. Hypercholesterolaemia, which had been associated with CAV (63), was common in heart transplant recipients. In addition, in animal models, statins had been shown to reduce coronary vasculopathy by a mechanism that seemed independent of the cholesterol-lowering effect (64). As other available statins were fat soluble, and therefore feared to increase the risk of rhabdomyolysis caused by interaction with ciclosporin, Jon Kobashigawa and his colleagues chose to use pravastatin when designing an open-label single-center trial of 100 heart-transplanted patients randomized to pravastatin or no statin treatment in addition to standard post-transplant treatment. The study, published in the New England Journal of Medicine (NEJM) in 1995, showed that the pravastatin group had lower cholesterol levels, a reduced incidence of rejections accompanied by hemodynamic compromise, a lower incidence of coronary vasculopathy, and improved survival rates one-year post-transplant (65).

Antimetabolites - Mycophenolic acid replaces azathioprine

Mycophenolic acid (MPA), a purine antagonist that inhibits inosine monophosphate dehydrogenase, was first discovered by the Italian scientist Bartolomeo Gosio towards in late 19th century. Gosio isolated a species of fungus from spoiled corn and named it *Penicillium glaucum*. In 1893, Gosio found that the fungus had antibacterial properties against the anthrax bacterium, making it the first antibiotic to be isolated in its pure form. MPA has since been proven to have antiviral, antifungal, as well as antitumorous effects (66).

The use of MPA and its modified ester derivative mycophenolate mofetil (MMF) was first approved by the FDA for use in kidney transplant recipients in 1995 (67). MMF selectively targets proliferating T- and B-lymphocytes, as they are solely dependent on the de novo pathway of purine synthesis (12). In 1998, a large double-blind multicenter randomized trial of MMF as it compared to azathioprine in addition to cyclosporine and corticosteroids showed that MMF reduced both the number of rejections and the 1-year post-transplant mortality in heart transplanted patients (68). Later in 1998, MMF was approved by the FDA for clinical use in heart transplantation (67).

The challenge of improved survival

By the turn of the 21st century, long-term post-heart transplant survival rates greatly improved. The 10-year survival was now around 45-50% (69, 70). With improved long-term survival, the side effects related to long-term use of immunosuppression gained greater focus. In 1999, Fraund and her colleagues published their findings

on long-term outcomes among heart-transplanted patients at the time, noting that moderate renal impairment was common. Chronic rejection in the form of cardiac allograft vasculopathy ultimately caused death in up to 39% of recipients, and infection and malignancy was the death cause in 11% of patients, respectively (70).

The millennium and beyond – Focus on long-term constraints

The CNI-switch – Tacrolimus taking over

Tacrolimus, a calcineurin inhibitor (CNI) like ciclosporin (Figure 8), was first described in the late 1980s (71) but was first approved for routine use in solid organ transplants in the mid-2000s (72). Early trials of tacrolimus were conducted at the Presbyterian University Hospital in Pittsburgh, Pennsylvania, USA in the early 1990s and showed promising results in reducing the number of rejections (73). In addition, tacrolimus was not associated with such common side effects of ciclosporin as hirsutism, gingivitis, and facial bone growth (74).

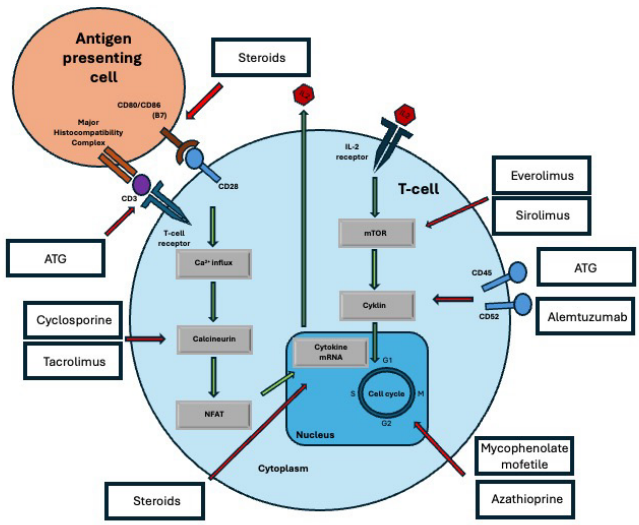


Figure 8: Overview of immunosuppressant cellular mechanism of action

The results of the first randomized trial of tacrolimus were published in 1996. Of the 243 patients randomized to tacrolimus or ciclosporin-based immunosuppression, freedom of rejection was more common in the tacrolimus group. Additionally, 18 patients in the ciclosporin group who suffered from refractory rejection improved after switching to tacrolimus (75). The trial was unfortunately marred by inconsistent use of induction therapy (72).

While subsequent trials demonstrated no difference in short vs. long-term survival, treatment with tacrolimus was associated with decreased rates of rejection (76, 77), hypertension (76-80), hypertriglyceridemia (76, 77, 79, 80), and improved renal function (80, 81). One study, however, indicated an association between tacrolimus and an increased burden of new-onset diabetes mellitus (77).

As cellular rejection instances decreased and long-term survival increased, focus among researchers shifted from rejection to the many side effects of immunosuppression. Seeking to minimize immunosuppression, the 2011 TICTAC trial randomized 150 clinically stable, newly transplanted patients without biopsy-proven AMR to either single-agent treatment with tacrolimus or a combination of tacrolimus and MMF. Even though prednisone was tapered off within 8 weeks post-transplant in all patients, no difference in the primary endpoints of rejection, allograft vasculopathy, or 3-year survival was observed (82).

Antibody-mediated rejection gaining attention

At around the same time, focus on AMR was growing. The 2004 ISHLT consensus report on rejection included diagnostic criteria (59), but inconsistencies in interpretation and reporting were widespread and created frustration. At the end of the 20th century, more than half the transplant centers were basing their AMR diagnosis solely on cardiac dysfunction in the absence of cellular infiltrates (83). Inconsistencies were likely partly due to the absence of standardized treatment (84).

In 2010, the ISHLT held a consensus conference on antibody-mediated rejection (83). An updated definition of the criteria (85) was formulated (Table 3). Initially, routine monitoring of DSA to assist in the diagnosis was only recommended for the first post-transplant year, but after the 2018 ISHLT update on managing antibodies, annual monitoring of DSA has been recommended (86). To date though, there is no consensus on exactly how to best treat AMR.

Table 3: 2013 ISHLT grading of antibody-mediated rejection (AMR) (85)

Grade	Definition	Substrate
pAMR 0	Negative for pathologic AMR	Histologic and immunopathologic studies are both negative.
pAMR 1 (H+)	Histopathologic AMR alone	Histologic findings are present and immunopathologic findings are negative.
pAMR 1 (I+)	Immunopathologic AMR alone	Histologic findings are negative and immunopathologic findings are positive.
pAMR 2	Pathologic AMR	Histologic and immunopathologic findings are both present.
pAMR 3	Severe pathologic AMR	Interstitial hemorrhage, capillary fragmentation, mixed inflammatory infiltrates, endothelial cell pyknosis, and/or karyorrhexis, and marked edema and immunopathologic findings are present.

CAV and the mTOR-inhibitors

Previous AMR has been associated with an increased risk of CAV development (87), and CAV has been shown to be a main cause of long-term mortality in heart transplant recipients (44, 88). Inhibitors of mammalian target of rapamycin (mTOR) have been hypothesized to reduce the onset and progression of CAV by inhibiting fibroblast and smooth muscle cell proliferation. Compared to the alternatives, mTOR inhibitors have also been thought to reduce the development of renal impairment, rates of CMV infection, and malignancy (89).

In 2003, Howard Eisen and his colleagues reported that the combination of the mTOR inhibitor everolimus, was superior to azathioprine when combined with a combination of ciclosporin and prednisone, in reducing the severity and incidence of CAV (90). Soon, several studies showed similar results for both everolimus (91-93) and the closely related drug sirolimus (94). The positive trend remained even when withdrawing the CNI instead of the antimetabolite (95-99).

Today, mTOR inhibitors are generally believed to be superior to CNI and antimetabolites regarding the development of CAV and renal impairment (100).

Even with the supposed reduction in CAV development, a recent large retrospective review of the United Network for Organ Sharing (UNOS) database of patients treated with mTOR inhibitors between 2010 and 2018 showed no long-term effects regarding survival, rates of infection, malignancy, or renal transplantation (89). Several studies have also pointed to an increased risk of non-fatal cellular rejection with regimens primarily based on mTOR-inhibition (92, 99, 101). This risk may be reduced by combining mTOR-inhibition with a low dose of CNI (102).

Induction or no induction, that is the question

Since the beginning of heart transplantation, hyperacute and early graft rejections have been feared. To minimize the risk of rejection and to spare initial renal damage caused by the combination of surgery-related issues and CNI toxicity, several induction protocols have been developed over the years. Specific antibody preparations may be used alone or in combination with high-dose corticosteroids.

Anti-thymocyte globulin has been widely used since the first organ transplantations in the 1960s. By the late 1980s, induction with OKT-3®, an antibody directed against CD3, became an alternative. While the first randomized trial of OKT-3®showed fewer rejection episodes in early post-operative settings, no difference could be seen regarding the number of rejections at 6 months (103). At the same time, an increased risk of uncontrollable cytokine release associated with the treatment dampened the enthusiasm toward the late 1990s (104).

During the same time, two new monoclonal antibodies directed against the interleukin 2 (IL-2) receptor; daclizumab and basiliximab, showed promising results. In two trials of using daclizumab compared to no induction, the rate of early rejections was decreased (105, 106). However, in one of these two studies, an increased risk of death was observed among patients who had received daclizumab and were later treated for acute rejection. Even though, there was no difference in the total mortality between the groups. In another study, basiliximab was shown to decrease the risk of early renal failure by delaying CNI introduction, without increasing the risk of rejection or infection (107). Despite these discrepancies, the use of IL-2 antibody induction steadily increased through the 2000s (108).

To date, no single induction therapy has improved survival in any randomized trial (109). However, induction therapy with ATG or IL-2 receptor antagonists continues to be used in approximately half of transplant centers. A 2013 Cochrane review concluded that there were no significant differences in mortality, infection, CMV infection, post-transplantation lymphoproliferative disorder, cancer, adverse events, chronic allograft vasculopathy, renal function, hypertension, diabetes mellitus, or hyperlipidemia between the induction strategies (110). An extensive review of data from the ISHLT register covering a 13-year timespan between 2000 and 2013 also showed no difference in survival of patients who received no induction, as compared to patients treated with ATG or basiliximab., The use of ATG was also associated with increased malignancy-related mortality in patients as compared to patients who received no induction, even though the total mortality rate was the same for these two groups (111). However, the results of a 2021 retrospective review conflicted with the earlier findings, discovering that of almost 29,000 transplant recipients from the UNOS database who received transplants in the US between 2010 and 2020, patients who received induction therapy had lower mortality and fewer rejections. According to this study, induction using ATG seemed to be associated with the lowest risk (108). There is no need to say; that randomized trials are warranted.

Human leukocyte antigen: optimizing the donor-recipient match

In the late 1980s, there were first reports that a mismatch between donor and recipient HLA was associated with an increased risk of early allograft rejection (112-115). In 1994, Gerhard Opelz and colleagues published a retrospective report of more than 8,000 heart transplants, showing that heart transplant recipients with one or less HLA (A, B, or DR) mismatch had significantly better 3-year survival than those who had two or more HLA discrepancies (116). Since then, HLA matching has become routine in transplants of organs such as bone marrow and kidney. However, with thoracic organ transplants, many transplant centers perform routine HLA matching only in previously highly immunized transplant recipients (117).

There is currently some conflicting evidence regarding the association between HLA matching and long-term survival of transplant recipients. A retrospective report published in 2015 of over 25,000 patients in the ISHLT registry who received transplants between 1988 and 2011 found no difference in survival between HLA-matched and HLA-mismatched patients as a whole (118), while another large retrospective report published in 2019 showed that mismatch between HLA-DR/DQ specifically caused higher rates of late graft loss (119). A recent study from 2014, which analyzed UNOS data collected between 2005 and 2021, reported that there was no association between HLA mismatch and transplant recipient survival, although HLA-mismatched patients had a greater incidence of reported rejections. Mismatch of the HLA-DR locus was associated with a greater risk of CAV development (117). More studies are needed to gain further insight into long-term effects in the setting of modern immunosuppression and increased long-term survival.

Ticking the boxes: organ preservation in modern day

When Christiaan Barnard performed the first heart transplant in 1967, the ventilator keeping the donor Denise Darvall alive was disconnected, and the team waited until there had been no electrocardiographic activity for 5 minutes before performing the heart explant. Louis Washkansky was prepared for surgery and standing by in the adjacent operating room in order to minimize the length of time of donor heart ischemia (4).

During the 1970s, the definition of death by brain death (DBD) (120) gained attention and debate. During the early 1980s, DBD transplantation became routine at most transplant centers, thus further reducing ischemic times. Together with the introduction of ciclosporin, transplantation of hearts from DBD donors contributed to revitalization of the heart transplantation procedure (121).

Ever since the first heart transplants were performed, the method of preserving harvested hearts has remained largely unchanged. The harvested heart is cannulated,

blood is removed from by infusion of a preservation fluid, then the heart is explanted and chilled to approximately 4°C.

As donors are in short supply, and the focus on the effects of optimal donor-recipient matching is growing, a variety of research is being done on optimizing organ preservation and extending ischemic time without further damage to the graft. Results from ongoing randomized studies on several different heart preservation box solutions showing encouraging results were presented (122-127) at the annual meeting of the ISHLT in April 2024. Also, donations of organs from donors declared dead by circulatory death are gaining greater focus, with the hope of further expanding the potential donor pool (128).

The future of rejection surveillance

Since the beginning of heart transplantation, pathologic assessment of endomyocardial biopsies has been considered the gold standard for diagnosing rejection. However, concordance among pathologists on biopsy interpretation is still reported to be as low as 70% (129).

Fragments of cell-free DNA originating from cancer cells were first described in peripheral blood in 1948 (130). Small fragments of DNA are released into the bloodstream during cell injury and may be identified in the plasma by PCR amplification. In 1998, donor-derived cell-free DNA (dd-cfDNA) was first suggested as a marker of cell injury in solid organ transplant recipients by a team from Hong Kong that investigated dd-cfDNA presence in kidney or liver transplant recipients (131).

A few years later, gene expression profiling (GEP) of mononuclear cells in peripheral blood was suggested as an alternative method of monitoring for rejection. The GEP method uses PCR to identify gene expression in peripheral leukocytes known to be activated during rejection. The GEP method has been shown to have an excellent negative predictive value in ruling out ACR in the 2006 CARGO trial (132), the 2010 IMAGE-trial (133), and the 2016 CARGO II-trial (134) of heart transplant recipients who were more than 2 months post-transplant.

In contrast to GEP, rising dd-cfDNA levels have not only been shown to rise during episodes of ACR (135), but have also been associated with AMR (136). Rising dd-cfDNA levels have furthermore been correlated with mortality (137).

Several high-volume US heart transplant centers currently use the combined negative predictive value of GEP and dd-cfDNA technique as part of their standard surveillance program to monitor for heart transplant rejection, thus minimizing the need for invasive endomyocardial biopsies (138).

In addition to these laboratory methods of post-transplant surveillance, there is currently growing interest in cardiac magnetic resonance (CMR) imaging as a tool

to diagnose rejection. The presence of myocardial fibrosis detected by late gadolinium enhancement (LGE) has been associated with decreased long-term survival (139, 140), and several studies have shown that modern CMR techniques using combinations of T1 and T2 imaging, estimation of extracellular volume (ECV) and LGE have excellent sensitivity and specificity for identifying acute rejections (141-143).

The high cost and low availability of GEP, dd-cfDNA, and CMR limit their use in some transplant centers. In the future, however, their use will likely grow, and routine biopsies will likely become much less frequent.

So what about morbidity?

In the 57 years that have passed since the first heart transplantation, post-transplant survival has improved (1) (Figure 9) and patient-reported quality of life has been shown to be better after than before transplantation (2). Still, a transplanted heart is not the same as a healthy original heart, and the life of a heart transplant recipient has many limitations. Psychiatric comorbidities such as post-traumatic stress disorder and major depression are common in heart-transplant recipients (144, 145), and somatic co-morbidities, as well as mortality, are significantly higher than in the general population (146). Advanced heart failure with peak oxygen consumption (peakVO_2) below 12 ml/(kg*min) is considered to be the main criterion for listing a patient as a candidate for heart transplantation (147). However, while a healthy 50-year-old has a peakVO_2 of around 40 ml/(kg*min) (148), stable and well-functioning heart transplant recipients younger than 40 years of age have peakVO_2 as low as 23.3 ml/(kg*min) (149).

Working with the follow-up of heart transplant recipients, one sees the immense effect of transplantation on mortality and morbidity, but also the struggles that many patients go through. The background of this thesis was the curiosity awakened by these experiences. Are outcomes after heart transplantation in Sweden adjacent to that of other countries? To what extent does the transplant solve the accompanying psychiatric challenges? And how do the transplanted heart pumping mechanics differ from that of a normal one? Could the emerging technique of cardiac magnetic resonance imaging help us understand the physiological restraints of transplanted hearts?

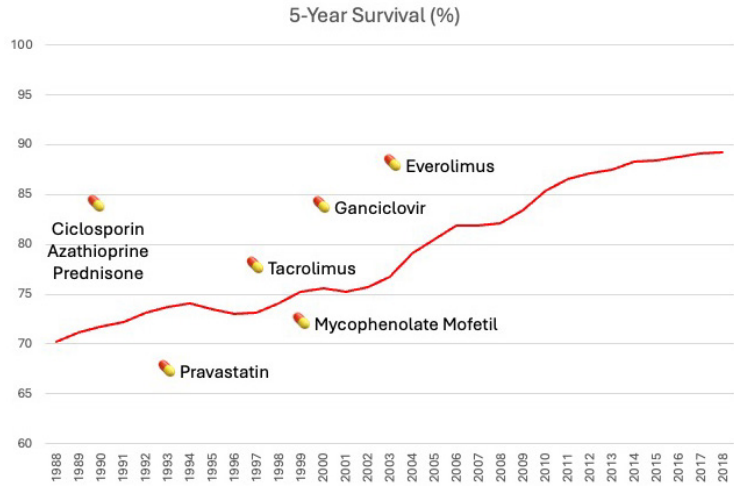


Figure 9: 5-Year Survival of heart transplant recipients in Sweden 1988-2018 and timing of the most important medical treatments. 5-year survival (%) according to the transplant year, with average of the year +/- 4 years to even out yearly variations. Mortality figures according to the Scandiatransplant registry (unpublished data).

Aims

The general aim of this thesis was to gain insight into the limitations facing heart transplant recipients in Sweden, with a broad overview of survival, co-morbidity, and the mechanistic properties of the transplanted heart's that limit the patients in their everyday lives. The focus was on retrospective data gathered from Swedish national registries along with patient record data from the routine post-transplant surveillance program at Skåne University Hospital.

The specific aims of the papers were:

Paper I

To investigate whether post-heart transplant survival rates in Sweden in the modern day were comparable to such survival rates in other countries, and whether there was a significant change in pre- and/or post-transplant survival after the national centralization of heart transplant surgery to Gothenburg and Lund, Sweden in 2010.

Paper II

To investigate and validate registered causes of death in heart transplant recipients who had undergone the transplant surgery and received their follow-up in Lund, Sweden since 1988, and to assess the heart transplant recipients' loss of life-years compared to the general population.

Paper III

To investigate whether heart transplant recipients in Sweden had a greater incidence of depression and anxiety diagnoses than the general population. To examine if there was greater use of anti-depressants and anti-anxiety medication within the heart transplant recipient group, and if there was any correlation between the heart transplant recipients' registered psychiatric diagnoses and mortality.

Paper IV

To describe the longitudinal heart function and the radial and longitudinal pumping mechanics in heart transplant recipients and to assess whether the longitudinal ventricular function was associated with cardiac output at rest or with maximal exercise capacity as measured by cardiopulmonary exercise testing.

Paper V

To investigate whether microvascular function as measured by quantitative cardiac magnetic resonance (CMR) perfusion mapping in heart transplanted patients differed from healthy non-transplanted controls and whether it was related to exercise capacity.

Present investigations

Paper I

Methods

Study sample

Data on patients listed as candidates for heart transplantation in Sweden between January 1, 2001, and December 31, 2020, data on donor organ utilization, donor characteristics, and post-transplant treatment, as well as date and cause of death were collected from the following databases: Scandiatransplant (150), the Swedish thoracic transplant (STRAX) (151), the Swedish web-system for enhancement and development of evidence-based care in heart disease evaluated according to recommended therapies (SWEDEHEART) (152), and the Swedish national cause of death registry (153).

Patients native to Sweden aged ≥18 years at the time of heart transplant were included in the post-transplant survival analysis. Patients with graft dysfunction who underwent re-transplantation were excluded. In the analysis of donor utilization rates, all transplants including pediatric transplants and retransplants were included, as there was no available method to ascertain whether donated organs were allocated to children or adults.

Variations in waiting times and mortality associated with the limited number of patients listed as candidates and undergoing transplant surgery in Sweden, complicate the interpretation of annual data. To minimize these variations, the analyses were performed comparing two 10-year periods: before and after the centralization of 2011. Period 1 (January 1, 2001 to December 31, 2010) was compared to Period 2 (January 1, 2011 to December 31, 2020).

Statistical analysis

Differences in baseline characteristics and complications were assessed using the Wilcoxon rank-sum test for skewed variables and a two-sample t-test for normally distributed variables.

Pearson's chi-square test was used to compare categorical data between groups.

The Wilcoxon rank-sum test was used to compare waiting times between the two 10-year periods.

Using the Fine and Gray method, cumulative incidence curves were plotted. Competing risk regressions were calculated for mortality, transplantation, and delisting from the transplantation waiting list.

Post-transplant survival rates were plotted using the Kaplan–Meier method, and survival between the groups was compared using the log-rank test.

A Cox proportional hazard regression model was utilized to assess differences in mortality rates. Mortality on the waiting list was adjusted for age, sex, height, body weight, blood group, and sensitization. Post-operative mortality was adjusted for diagnosis, donor diabetes, kidney function (glomerular filtration rate [GFR]), recipient and donor age and sex, ischemia time, and pre-transplant treatment with a left ventricular assist device (LVAD). Factors previously associated with post-transplant first-year survival (1). Donor dialysis, mechanical ventilation, and total bilirubin values were excluded from the analysis because of a considerable number of missing values. Missing values for GFR and ischemic time were imputed with the mean, and missing diagnoses were imputed with the mode.

Cox proportional hazard models were checked for proportionality using Schoenfeld residuals, log-log plots for nominal data, and a zero slope test. Similarly, for the Fine and Gray methods, factors were evaluated visually for proportionality with Schoenfeld residuals and a time interaction test.

Main findings

Heart transplants in Sweden (2001-2020)

- During the 20-year period covered in our study, 954 adults were included on waiting lists for heart transplantation. 51 of the 954 patients died prior to receiving a transplant, and 55 were delisted without a transplant.
- 954 heart transplantations were performed. 24 of these patients underwent re-transplantation. Of the remaining 930 patients, 815 were adults (≥18 years).
- The numbers of heart transplants per year and per hospital are illustrated in Figure 10.

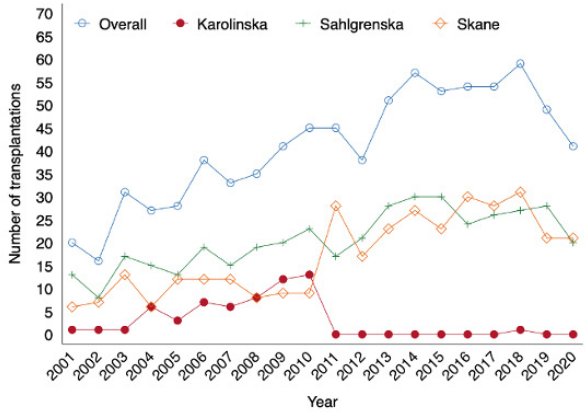


Figure 10: Heart transplants in Sweden 2001-2020

Active waiting time and waiting list mortality

- The median active waiting time was slightly higher (54 vs 71 days) in the second 10-year era (2011-2020).
- The number of heart transplantation procedures increased by more than 50%.
- The organ utilization rate rose (31% vs 35%).
- Despite longer waiting times, the mortality of individuals on the transplant waiting list was lower (8.3% vs 3.2%).

Post-operative mortality

- The 30-day survival rate rose from 90.8% to 97.8%.
- The 1-year survival rate rose from 87.9% to 94.6% (Figure 11a).
- For transplant recipients who survived the first 3 months, there was no difference in 1-year, 5-year, or 10-year survival rates (Figure 11b-d).
- Adjusted for diagnoses of heart failure, kidney function, donor and recipient sex and age, ischemic time, immunization, pre-transplant long-term LVAD, and short-term extracorporeal membrane oxygenation (ECMO), a 63% risk reduction in 1-year mortality was observed.
- Apart from Sahlgrenska, for which the mortality was lower in the second era, no significant difference was observed when analyzing mortality by the referring hospital.

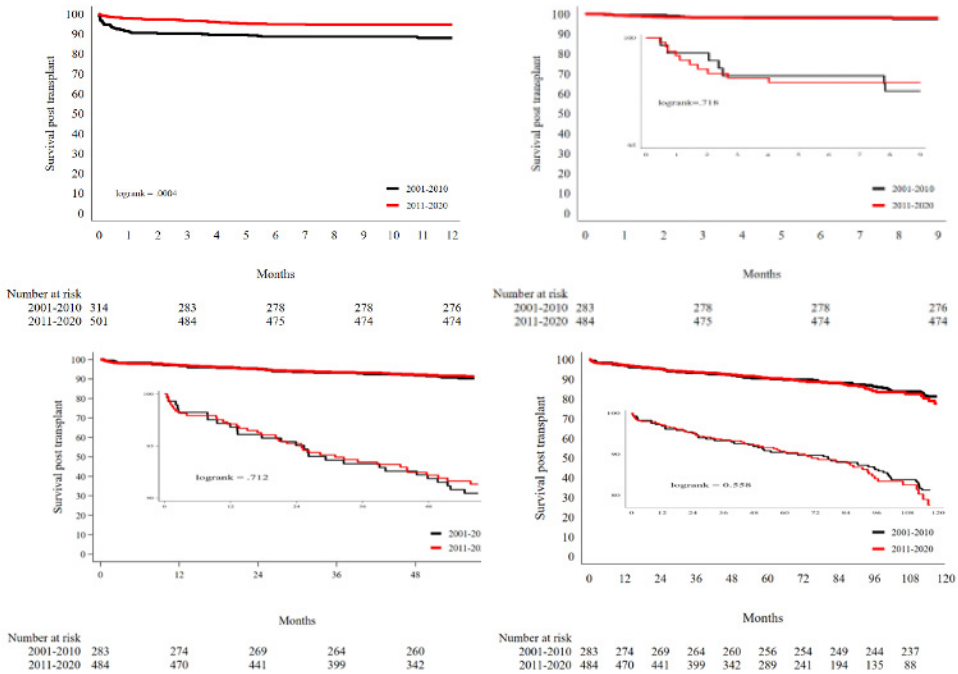


Figure 11: Post-transplant survival comparison for the two 10-year periods

11a (top left): Post-transplant 1-year survival 2001-2010 vs. 2011-2020.

11b (top right): Post-transplant 1-year survival conditional to 3-month survival 2001-2010 vs. 2011-2020.

11c: (bottom left) Post-transplant 5-year survival conditional to 3-month survival 2001-2010 vs. 2011-2020

11d: (bottom right) Post-transplant 10-year survival conditional to 3-month survival 2001-2010 vs. 2011-2020.

Paper II

Methods

Patients who underwent heart transplantation between 1988 and 2019 and received their clinical follow-up in Lund, Sweden, were included in the study. Subjects with unavailable medical records were excluded from the analysis (Figure 12).

Two separate reviewers, authors Lundgren and Gjesdal, independently investigated the hospital records of identified deceased patients. The cause of death was determined according to the CLASS cause of death classification, a classification model specific to transplant recipients developed by a group of Danish colleagues in 2018 (154).

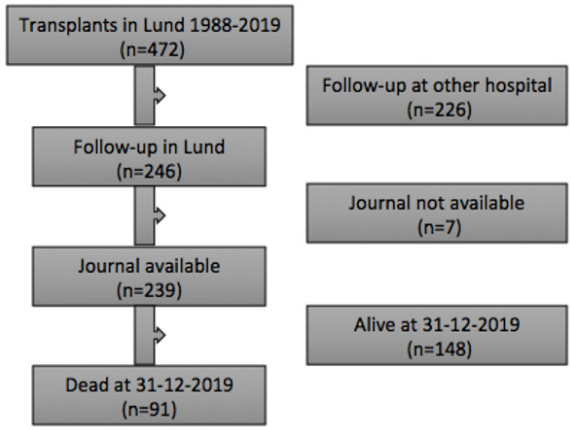


Figure 12: Patient selection for Paper II

Agreement between reviewers was defined as the same death cause (e.g. infection) including sub-group (e.g., bacterial). In the cases where the assessed death cause differed, a board consisting of the two reviewers and a consultant heart failure cardiologist (author Braun) repeated the medical record review and agreed on an adjudicated death cause.

The validated death cause was compared to the registered cause of death extracted from the Scandiatransplant registry. For the classification of death causes, the Scandiatransplant registry uses the ISHLT definition. To overcome this, the death causes from the CLASS system were translated into analogous death causes in the ISHLT classification. The two were further combined to form the new suggested pathophysiologically relevant aggregated death cause (Table 4).

The aggregated cause of death was used to analyze life-years lost. The average life expectancy in Sweden for the period 1988–2019 for male and female Swedish residents aged 0–73 was extracted from the Statistics Sweden database (155). To calculate life-years lost, the life span of transplant recipients was compared to the average life expectancy of the Swedish population, matched by age and sex at year of transplant. The length of time the post-transplant patients survived was subtracted from the expected average lifespan, and the median loss of life-years was calculated overall, per grouped causes of death.

Main findings

Validation of cause of death and the CLASS methodology

- Using the CLASS methodology, we observed moderate (56%) inter-reviewer agreement.
- The validated CLASS death cause had moderate agreement (62%) with the registered ISHLT death cause.
- Combining similar/related diagnoses into aggregated groups according to Table 4, inter-reviewer agreement was increased to substantial (67%).
- The aggregated groups, analyzed separately for each reviewer, had a substantial to almost perfect agreement rate (79% and 85%) with the registered ISHLT death cause.
- The agreement between the validated and grouped CLASS codes and the grouped ISHLT codes remained moderate (67%).

Life expectancy in transplant recipients compared to the matched general population

- Compared to the age and gender-matched Swedish population, heart transplant recipients lost 20 life-years.
- Death caused by acute graft rejection resulted in the most life-years lost.
- Although patients who died of primary graft failure, chronic graft rejection, malignancy, infection, and cerebrovascular events had similar post-transplant survival, the resulting life-years lost compared to the general population was less than in those who died from acute graft rejection, as they were transplanted at an older age.

Table 4: Grouping of validated and registered causes of death

Validated CLASS cause of death	Grouped cause of death	Registred ISHLT cause of death
1.1 Primary (non-function) graft failure	Primary graft failure	2000 Graft Failure: Primary Failure
		2701 Intraoperative (not hemorrhage)
2.1 Acute graft failure	Acute graft rejection	2001 Graft Failure: Rejection, Hyperacute
		2002 Graft Failure: Rejection, Acute
1.2 Non-specific graft failure	Chronic graft rejection	2003 Graft Failure: Rejection, Chronic
		2201 Cardiovascular: Cardiac Arrest
		2203 Cardiovascular: Ventricular Failure
2.2 Chronic graft failure		2299 Cardiovascular: Other
4.1 Bacterial infection	Infection	2100 Infection: Bacterial, Septicemia
4.2 Fungal infection		2101 Infection: Bacterial, Pneumonia
4.3 Viral infection		2109 Infection: Bacterial, Other
4.7 Unknown infectious aetiology		2119 Infection: Viral, Other
5.2 Ruptured vascular aneurysm	Major bleeding	2401 Cerebrovascular: Hemorrhage (non-stroke)
		2500 Hemorrhage: Gastrointestinal
		2599 Hemorrhage: Other
6.1 De-novo malignancy	Malignancy	2600 Malignancy: Metastatic
		2601 Malignancy: Primary
		2602 Malignancy: Post-Transplant Lymphoproliferative Disorder
6.2 Relapse of malignancy		2604 Malignancy: Skin
		2603 Malignancy: Lymphoma
		2699 Malignancy: Other
7.2 Cardiac or vascular failure or dysfunction	Myocardial infarction	2200 Cardiovascular: Myocardial Infarction
	Cerebrovascular accident	2400 Cerebrovascular: Stroke
		2402 Cerebrovascular: Brain Anoxia
	Other causes	2206 Cardiovascular: Rhythm Disorder
7.3 Pulmonary failure or dysfunction		2208 Cardiovascular: Aortic Aneurysm
7.6 GI-tract failure or dysfunction		2708 Amyloidosis
7.7 Pancreas failure or dysfunction		2802 Non-Compliance
9.2 Withdrawal of active treatment		2803 Trauma
10 Accidental death		2998 Other
12 Other causes		2303 Pulmonary: Pulmonary Embolism
14 Unknown cause		
7.8 Multi-organ failure	Multi-organ failure	2705 Multiple Organ Failure

Paper III

Methods

Study sample

The Swedish National Patient Registry (156) was used to identify all individuals with a registered diagnosis of heart transplantation.

Data on marital status, geographical region of residence, date of immigration or emigration, educational level, family income, date and cause of death, hospital diagnoses, and dates of hospital admissions (1964-2018), primary care diagnoses, and prescribed medication were gathered from the following databases: The Total Population Registry (157), the Swedish National Patient Registry (156), Statistics Sweden (the Swedish Government-owned statistics bureau) (158), the National Prescribed Drug Register (159), and an almost complete data-set of primary care diagnoses was gathered from 20 of the 21 Swedish regions (160). All linkages were performed using the national 10-digit civic registration number, which was later replaced by serial numbers to ensure anonymity.

Psychiatric comorbidity was assessed by ICD-10 diagnoses for depression (F32 and F33), anxiety, and stress-related disorders including anxiety (F41), phobias (F40), obsessive-compulsive disorders (F42), reaction to severe stress, and adjustment disorders (F43), sleep disorders (G47.0, G47.2, G47.8, G47.9), alcohol abuse disorders (F10, K70) and drug abuse disorders (F11-F19).

Records regarding prescriptions for antidepressant drugs, drugs to facilitate alcohol and opioid addiction, and potentially addictive drugs were extracted from the Swedish National Prescribed Drug Register (26).

Statistical Analysis

Differences in baseline characteristics between the two groups of heart transplant recipients – those with and those without psychiatric diseases at time of transplantation – were examined using Fisher's exact test for categorical variables and Student's t-test for continuous variables.

Logistic regression analyses were performed regarding psychiatric diagnoses, use of antidepressants, anxiety, and sleep medication in the transplant cohort compared to the control group to adjust for the potential confounding factors of age, sex, family income, educational level, immigration status, marital status, and urban vs. rural residence. These factors have been previously associated with the risk of new-onset depression and suicide in heart failure patients in Sweden (4).

A logistic regression model of differences in the use of benzodiazepines and antidepressant medication was performed to examine the association with chosen covariates and known concomitant disease for the heart transplant recipients.

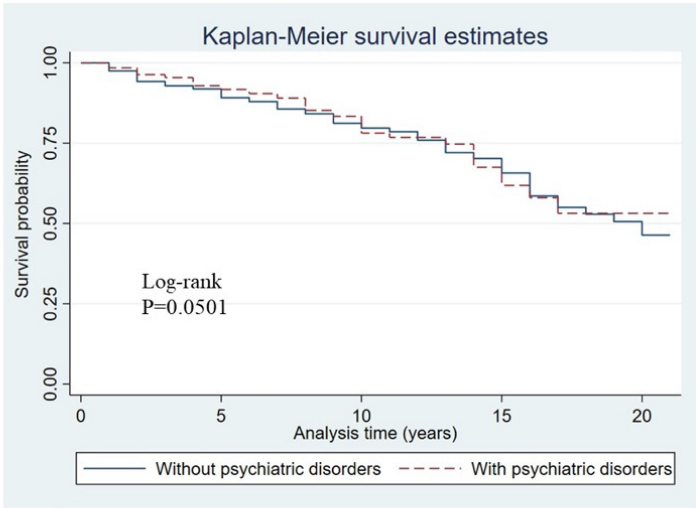
A Cox regression analysis was performed to test whether the length of survival from the time of discharge after transplant surgery was different between the two groups of patients (those with and those without psychiatric disorders). Survival estimates were calculated using the Kaplan-Meier method.

To investigate whether psychiatric diagnoses and prescriptions for psychiatric issues were more frequent before or after the heart transplant, separate analyses were performed comparing heart transplant recipients to the matched general population during 3-year periods immediately preceding and immediately following heart transplant surgery.

Main findings

Survival of the cohort

- 907 heart transplant recipients were identified and compared 1:5 to age and sex-matched controls.
- The mean age was 45 years. 28% were female.
- The mean follow-up time was 16.8 ± 5.8 years.
- We observed a small, non-significant trend toward higher survival for patients with the investigated psychiatric diagnoses compared to patients without a psychiatric diagnosis (HR 0.73, p=0.05) (Figure 13).



	Number at risk				
Without psychiatric disorders	622	597	564	522	462
With psychiatric disorders	285	283	279	261	230

Figure 13: Survival of patients with and without psychiatric comorbidity

Depression, anxiety, stress disorders and substance abuse

- 31.4% of heart transplant recipients were diagnosed with depression or anxiety-related disease, as compared to 25.2% of individuals in the control group.
- Pre-transplant, first-time depression was more common in the transplant recipients than in the control group. Recurrent depression was more common post-transplant.
- There was no difference in identified diagnoses of phobic disease, obsessive-compulsive disorders, or post-traumatic stress disorders.

Antidepressants, anxiety, and sleep medication

- Pre-transplant, patients had a higher prescription rate of anti-depressive, anti-anxiety, and sleep medication.
- Even though both recurrent depression and anxiety were more frequent post-transplant, prescriptions of antidepressants were not equally increased.

Paper IV-V

Methods

Study samples

Patients who underwent CMR and a cardiopulmonary exercise test (CPET) as part of their routine post-transplant surveillance program at the heart transplant unit at Skåne University Hospital, Lund, Sweden, were retrospectively included in the analyses. Control investigations from age- and sex-matched healthy volunteers were collected from a sample of previously available data.

Data collection

Data on time from transplant, prior or current allograft rejection, presence of macroscopic CAV, immunosuppressive medication, other relevant daily medication, blood pressure, and the presence or absence of right bundle branch block at time of CMR were collected from the patient's medical journal.

Cardiac magnetic resonance acquisition

Cardiac MR was performed using Siemens Magnetom Aera 1.5T and Siemens Magnetom Sola 1.5T scanners (Siemens Healthcare GmbH, Erlangen, Germany). Localizers and scout images were acquired to define the left ventricular short-axis and long-axis planes (2-, 3- and 4-chamber views).

T2-prepared steady-state free precision short-axis images covering the left ventricle were acquired. Perfusion maps were obtained during adenosine stress and at rest (161). Stress images were acquired after 3 minutes of intravenous adenosine infusion. Resting images were acquired 10 minutes after the adenosine infusion. Quantitative perfusion and myocardial perfusion maps were generated using Gadgetron inline perfusion mapping software (162).

Late gadolinium enhancement (LGE) images were acquired in the short-axis view covering the entire left ventricle and in the three standard long-axis views 10-15 minutes after an intravenous administration of 0.05 mmol/kg of contrast agent. LGE images were used to assess the presence of myocardial infarction and fibrosis.

All image analyses were performed using Segment v3.3 software (https://medviso.com/segment/) (163).

Calculation of left ventricular atrioventricular plane displacement

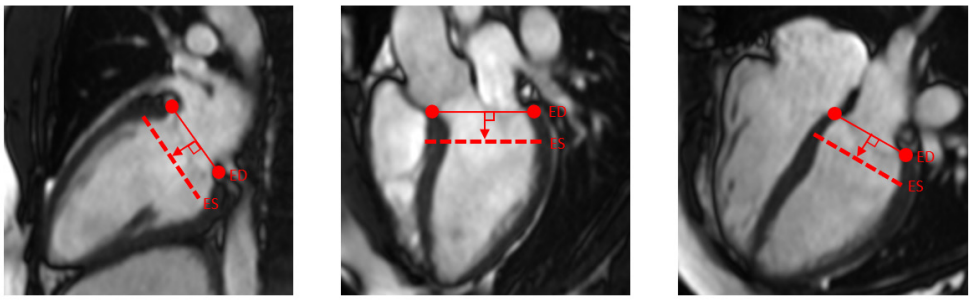
Calculation of left ventricular atrioventricular plane displacement (LVAVPD) was performed using methodology previously described by Carlsson and his colleagues (164, 165), and validated by Seemann et al. (166). The atrioventricular plane was

defined by manually marking the inferoseptal and anterolateral mitral annular hinge in the 4-chamber view, the anterior and inferior points in the 2-chamber view, and the inferolateral and anteroseptal points in the 3-chamber view. If needed, tracking was manually adjusted in end-diastole (ED) and end-systole (ES). Left ventricular AVPD was calculated as the mean shortening distance in millimeters between six markings indicating the atrioventricular plane and the apex (Figure 14a).

Calculation of regional contribution to stroke volume

Short-axis images were delineated in accordance with the Society for Cardiovascular Magnetic Resonance Board of Trustees Task Force protocol to obtain left ventricular mass, volume, stroke volume, and ejection fraction. Trabeculations and papillary muscles were included in the intracavitary volume (167).

Longitudinal contribution to stroke volume as well as radial contribution, divided into septal and lateral contribution, were calculated using methodology previously described (164, 168). Longitudinal contribution to stroke volume was determined by multiplying the LVAVPD with the largest epicardial short-axis area of the left ventricle. This measurement has been shown to better correspond with the volume generated by longitudinal movement than the area of the mitral valve orifice (165). Septal contribution to stroke volume was calculated from the difference between the ED and ES area enclosed by the septal epicardial contours and the insertion of the right ventricle in the short-axis images. Lateral contribution was similarly calculated from the difference between the ED and ES area enclosed by the lateral LV epicardial contours and the right ventricular insertion points in the short-axis images (Figure 14b).



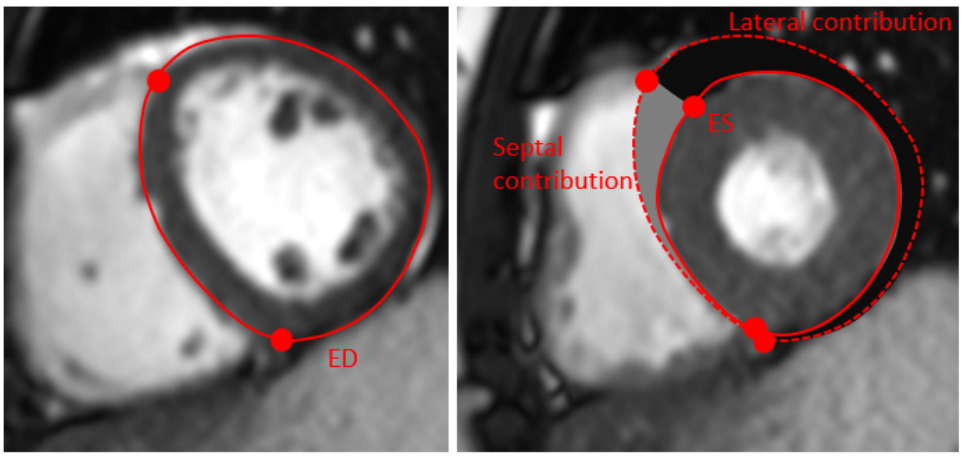


Figure 14a (upper three images). Atrioventricular (AV) plane definition. The solid line shows the AV-plane at end-diastole; the dashed line shows AV-plane at end-systole. The AVPD was defined as the perpendicular mean shortening distance in millimeters between the six markings shown as red dots.

Figure 14b (lower two images). Septal and lateral contribution to stroke volume. The septal part of the left ventricle is defined as the part between the anterior and inferior insertion of the right ventricle, and the lateral part is defined by the remaining free wall. Septal and lateral contribution to stroke volume is calculated by the milliliters of blood displaced by each segment's movement during systole divided by the estimated stroke volume. The gray area shows the septal contribution, and the black area shows the lateral contribution.

Perfusion analysis

Left ventricular mass, volumes, and function were quantified from manual delineations of the epicardium and endocardium of the left ventricle in short-axis cine steady-state free precision images.

The presence of previous infarction and fibrosis was assessed by visual evaluation of late gadolinium hyper-enhancement.

The presence of edema was assessed by visual evaluation of increased signal intensity on T2 weighted images.

The endo- and epicardial borders for the short-axis perfusion maps were manually delineated at stress and rest. The delineations were kept approximately two pixels away from the endo- and epicardial borders to avoid the inclusion of blood pool or extracardiac structures within the myocardial contours. Image artifacts were excluded from the regions of interest.

Myocardial perfusion (MP) was assessed globally and as a 17-segment regional model excluding the apical segment (169). Segments with regional hypoperfusion corresponding to coronary artery stenosis supplying that region were excluded from the analysis of global MP. Segments with LGE patterns consistent with infarction or fibrosis were also excluded.

Myocardial perfusion reserve (MPR) was calculated as the ratio between MP during stress and at rest. The MPR was calculated regionally and globally.

The MP at rest has previously been shown to be related to the rate-pressure product (RPP = heart rate * systolic blood pressure). To adjust for this possible bias, resting MP in each subject was reported corrected for both the individual RPP and for the mean RPP of the group (170). The rate-pressure product corrected MPR was also calculated as the ratio between MP at stress and corrected MP at rest.

CPET

Cardiopulmonary exercise testing (CPET) was performed as part of the routine post-transplant surveillance program. Peak oxygen uptake was measured according to accredited clinical routines. Protocols were individually adapted based on age, sex, and physical activity level, and chosen to yield an exercise duration of 8–12 min (171).

Coronary angiography

A coronary angiogram was performed on 25 heart-transplanted patients according to clinical routine. Cardiac allograft vasculopathy severity was classified according to the International Society for Heart and Lung Transplantation nomenclature (18), where CAV 0 = not significant, CAV 1 = mild, CAV 2 = moderate, and CAV 3 = severe.

Statistical analysis

Normal distribution was tested visually and using the D'Agostino-Pearson test.

Mean values were compared using a two-sided unpaired t-test.

The relationships between continuous variables were assessed using Pearson's linear correlation coefficient.

Single linear regression models were used to analyze potential associations between LVAVPD and transplant status, heart rate (HR), left ventricular volume, body surface area, sex and age.

Multiple linear regression models were used to assess the potential association between factors that were significantly associated in the single linear regression analysis.

Main findings

Left ventricular atrioventricular plane displacement

- Left ventricular AVPD was lower in the transplanted group (10.3mm vs 13.7mm).
- There was no association between LVAVPD and time from transplant or between LVAVPD and previous rejections.
- There was no significant association between LVAVPD and cardiac output at rest.

Regional contribution to stroke volume

- When compared to healthy controls, the transplanted patients had:
    - Lower longitudinal contribution to stroke volume
    - Lower septal contribution to stroke volume
    - Higher lateral contribution to stroke volume (Figure 15).

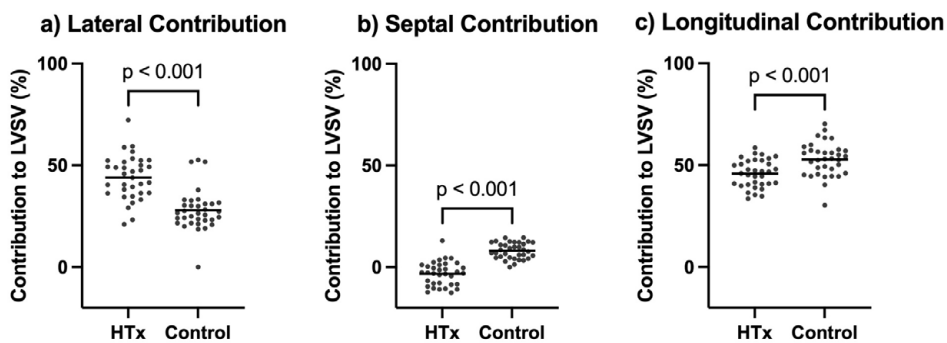


Figure 15: Regional contributions to stroke volume

Ejection fraction, stroke volume and cardiac output

- There was no difference in left ventricular ejection fractions (LVEF) between groups.
- Stroke volumes were lower in the transplanted cohort (90ml vs 100ml).
- Cardiac output was higher (7.2L/min vs 6.4L/min) in the transplanted patients due to higher heart rates (81bpm vs 64bpm).

Association with LVAVPD

- Transplant status, age, left ventricular end-diastolic volume, and heart rate were independently correlated with LVAVPD.
- In the multiple linear regression analysis, only transplant status and age remained significantly associated.
- There was no difference in stroke volume, atrioventricular plane displacement, or septal or lateral contribution to stroke volume between transplanted patients with and without complete right bundle branch block.
- There was no association between the LVAVPD at rest and peak oxygen uptake in the transplanted group.

Myocardial perfusion in heart transplant recipients compared to controls

- There were no differences in the resting myocardial perfusion between the heart-transplanted patients and the controls.
- There were no differences in the myocardial perfusions between the female and male transplanted patients.
- During stress, myocardial perfusion was lower in the heart-transplanted patients (2.9ml/min vs 3.4ml/min).
- The myocardial perfusion reserve was significantly lower in the heart-transplanted cohort (2.7ml/min vs 3.8ml/min).
- We observed no difference in the myocardial perfusion during rest between patients who were less than one-year post-transplant, compared to those who were examined more than 2 years after.

Myocardial perfusion in relation to hemodynamics and CPET values

- The rate pressure product (RPP) (9740bpm*mmHg vs 7687bpm*mmHg) and heart rate at rest (80bpm vs 64bpm) were higher in the heart-transplanted patients. The systolic blood pressure did not differ between the groups.
- No difference in RPP, systolic blood pressure or heart rate was found between heart-transplanted patients and controls during stress.
- The myocardial perfusion reserve corrected for RPP was lower in the transplanted patients than in the healthy controls (2.6ml/min vs 3.7ml/min).
- At rest, myocardial perfusion was correlated with RPP and heart rate, but there was no correlation between the myocardial perfusion and systolic blood pressure or stroke volume.
- Myocardial perfusion reserve in transplanted patients was correlated with the maximal workload, VO2 peak, VO2 at the anaerobic threshold, and O2 pulse.
- There was no correlation between the myocardial perfusion at stress and any measured CPET value.

Conclusion

The thesis aimed to paint a broad picture of outcomes related to mortality, morbidity, and physical limitations facing heart transplant recipients in Sweden.

In **Paper I**, we confirmed that long-term post-heart transplant survival in Sweden is excellent. We showed that, although the time awaiting transplant slightly increased after heart transplant surgery was centralized in Sweden from 2011, both survival both while on the waiting list as well as survival post-transplant was improved. The difference in survival rates between the two analyzed 10-year periods was mainly due to greater early post-operative survival rates. This trend was consistent in patients from all Swedish regions.

In **Paper II**, we showed that survival among heart transplant recipients who were followed up in Lund, Sweden, is excellent compared to survival rates that have been reported internationally (1). The high survival rate is likely due to a broad range of factors, including patient selection, surgery and post-operative medical care, post-transplant follow-up, free medication, free admittance to hospitals and free access to healthcare in general, and quality treatment of comorbidities, availability of psychosocial and physical support, opportunities to work part-time, and governmental financial support for those unable to work.

As previously learned from other patient groups (172, 173), the study confirmed that registry data on cause of death should be interpreted cautiously, and a less meticulous classification system may improve validity. We also analyzed the number of life-years lost to different causes of death, and showed that while causes of death such as cancer, infection, and chronic rejection are common within the heart transplant recipient group, acute rejection affects younger patients more and results in a greater number of life-years lost.

In **Paper III**, we identified Swedish heart transplant recipients using national patient registries and personal identification numbers. We were able to extract information regarding diagnoses from primary and specialist care, prescribed medication, and data on the patient's socioeconomic background. By comparing the heart transplant recipient group with a control group, we showed that heart transplant recipients have a greater incidence of anxiety- and depression-associated diagnoses, but do not receive more antidepressants post-transplant. Our findings showed no clear trend toward fewer psychiatric diagnoses post-transplant than pre-transplant.

In **papers IV and V**, we investigated the mechanistic properties of transplanted hearts using CMR. Transplant vasculopathy (CAV) is a leading cause of long-term mortality in heart transplant recipients (1) and has previously been associated with decreased longitudinal function measured by tricuspid annular plane systolic excursion (TAPSE) (174) and decreased myocardial perfusion as measured by CMR (175).

In **Paper IV**, we showed that the cohort of heart transplant recipients had lower longitudinal heart function as measured by the left ventricular atrioventricular plane displacement (LVAVPD) and lower longitudinal contribution to stroke volume than the control group. Longitudinal motion has previously been shown to be the most energy-efficient way for the heart to pump (176), and our result may help explain the decreased exercise capacity in heart transplant recipients as compared to healthy individuals (148, 149).

In **Paper V**, global myocardial perfusion in the same cohort of heart transplant recipients was demonstrated to be maintained at rest but decreased during stress. The myocardial perfusion reserve was decreased, and there was an association between the reserve and the maximal workload, VO_2 at anaerobic threshold, and the O_2-pulse.

To summarize, the present thesis shows that while survival after heart transplantation in Sweden is excellent and continues to improve, heart transplant recipients continue to face psychiatric and physical challenges. This merits further research and focus.

Future perspectives

The papers referred to in this thesis raise several questions that should be investigated further.

Exactly what parts of pre-operative, operative, and post-transplant treatment contributed to the higher survival rates in the early post-operative period? Is the same rise in survival rates perceived in other countries or hospitals that have not observed the same increase in heart transplant numbers? Previous studies have shown that transplant facility size may play a role (177-180), and better overall results have been reported at the larger transplant facilities (181). However, there are no nationwide studies that enable comparison. An analysis of Scandiatransplant data from other comparable Scandinavian countries would be of interest.

Are issues related to the validity of registered causes of death limited to our heart transplant center, or is this a national or international problem? Several studies have noted low validity of data in the cause of death registry (182-184). Would a simplified system of classification increase the validity? Conducting a limited-size prospective trial of a simplified classification could help gain more knowledge. Confirmation of the result from other equivalent disease groups or from other Scandiatransplant or ISHLT-registry-connected countries would strengthen the result.

As depression and anxiety were shown to be common among heart transplant recipients, would responsive interaction and early treatment of psychiatric ailments improve symptoms? Is post-transplant psychiatric illness associated with working ability and sick leave? Would an intervention with medication, psychotherapy, or both, affect work capacity and possibly even long-term survival?

Is the observed rise in recurrent depression and anxiety post-transplant, and the coincident lack of increase in prescriptions for antidepressants and anxiety medication during the same period, a result of symptom relief, or is it due to medical practitioners' fear of the complexity of psychological disease and possible interactions of antidepressants/anti-anxiety medicines with immunosuppressants, or are there other contributing factors? Are there other medical diagnoses common to the transplanted group that are either undertreated or undiagnosed?

Is the reduced longitudinal heart function that we observed only an issue at rest, or are the longitudinal myocardial fibers recruited during exercise? A follow-up study

on working mechanics, by echocardiography or CMR would be of interest. Are the altered pumping mechanics a result of the properties of the transplanted hearts in itself, or could similar findings be seen in other post-thoracotomy patient groups? A comparison with patients who have undergone valve surgery, and in the absence of ischemic heart disease, could be of interest.

Finally, would the decreased myocardial perfusion reserve be even more apparent in a larger cohort, including a larger proportion of patients who have had their transplanted heart for a longer time? Also, is the reduced myocardial perfusion reserve primarily a result of microvascular CAV, or do other mechanisms play a role, e.g. ischemic damage from surgery or chronic rejection?

The possibilities for further studies seem endless, and I can't wait to dig in.

Tack!

Det är så många man vill tacka, och flera som förtjänt uppmärksamhet än de jag nämner vid namn här. Ett stort tack till er alla!

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