Implications of myocardial dysfunction before and after aortic valve intervention

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To Louise, Olivia and Wilhelm

To the relief of my supervisors!

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ABSTRACT

BACKGROUND

Postoperative heart failure in the setting of aortic valve surgery results in poor long-term survival. We hypothesized that there could be a myocardial factor that is not addressed by risk scores currently available. We speculated that this myocardial factor could be diastolic dysfunction. By evaluating postoperative heart failure, the EuroSCORE, the NT-proBNP level, and diastolic function, we might achieve a deeper understanding of the outcome for individuals with postoperative heart failure.

METHODS

This research project was built upon four cohort studies. The first two studies (I and II) were retrospective in nature, and studies III and IV were prospective, observational, and longitudinal. All work was based on data from clinical and national databases. In Study I, we compared the outcome of patients with or without postoperative heart failure, evaluated according to the preoperative risk score. In Study II, we explored the effect of underlying heart disease on the preoperative level of NT-proBNP and the relationships between NT-proBNP and severe postoperative heart failure and short-term mortality. In Study III, we described the dynamics of NT-proBNP, from a preoperative evaluation to a six-month follow-up, in patients that underwent one of two different procedures: a surgical aortic valve replacement and a transcatheter implantation. We related both pre- and postprocedural NT-proBNP levels to one-year mortality. In Study IV, we evaluated diastolic function in patients that underwent sur-

gical aortic valve replacement and its influence on outcome. We also evaluated NT-proBNP levels and postoperative heart failure as predictors of long-term mortality.

RESULTS

Study I

This study included 397 patients that underwent isolated surgical aortic valve replacements. Of these, 45 patients (11%) were treated for postoperative heart failure. With an average follow-up of 8.1 years (range 5.2-11.2), among patients at low risk (EuroSCORE $\leq$ 7), the crude five-year survival rates were 58% in patients with postoperative heart failure and 89% in those without postoperative heart failure ($p<0.001$). Among patients with postoperative heart failure, those classified as low risk had the same poor long-term prognosis as those classified as high risk (EuroSCORE >7). In the high risk group, survival rates were similar between patients with or without postoperative heart failure (57% vs. 64%; $p=0.60$).

Study II

This study included a cohort of 2978 patients with coronary artery disease, aortic stenosis, and mitral regurgitation. Preoperative NT-proBNP levels were found to be 1.7-fold higher in patients with aortic stenosis than in patients with coronary artery disease and 1.4-fold higher in patients with mitral regurgitation than in patients with coronary disease. The power of preoperative NT-proBNP for predicting severe postoperative heart conditions was good among patients with coronary heart disease and patients with mitral regurgitation, but not as good among patients with aortic stenosis. NT-proBNP also showed good discriminating power for short-term mortality among patients with coronary artery dis-

ease. Moreover, NT-proBNP was found to be an independent predictor for both severe postoperative heart failure and short-term mortality in patients with coronary artery disease.

Study III

This study included 462 patients that underwent preoperative evaluations for aortic valve disease. Aortic valve interventions elicited a rise in NT-proBNP that was more pronounced in patients undergoing surgical aortic valve replacement compared to patients undergoing transcatheter valve implantation. No deterioration in NT-proBNP was observed during the waiting time before the intervention, despite a median duration of four months. At six months after the intervention, NT-proBNP levels had decreased to or below the preoperative levels in all groups. Among patients that received surgical aortic valve replacements, pre-and early postoperative NT-proBNP levels showed good discriminatory power for one-year mortality. This discriminatory power was not observed among patients that had undergone a transcatheter procedure; those patients had higher levels of both pre- and postoperative NT-proBNP compared to patients that had undergone surgery.

Study IV

We evaluated 273 patients that underwent aortic valve surgery. High left ventricular filling pressure was present in 22% (n=54) of patients at the time of surgery. At six months after surgery, diastolic function deteriorated in 24/193 (12%) patients and improved in 27/54 (50%) patients. Diastolic dysfunction was not found to be associated with long-term mortality. However, both postoperative heart failure and preoperative NT-proBNP levels were associated with increases in long-term mortality. In a multivariable Cox analysis, NT-proBNP remained predictive of long-term mortality.

CONCLUSION

Postoperative heart failure contributed to long-term mortality, even in patients considered to be at low risk preoperatively. Our results suggested that pressure overload, followed by a volume overload led to a NT-proBNP response that was more pronounced than the ischemia response. Elevated levels of NT-proBNP were associated with both short- and long-term mortality. In these studies, we could not corroborate the notion that high left ventricular filling pressure was associated with long-term mortality.

SVENSK SAMMANFATTNING

Betydelsen av hjärtdysfunktion vid aortaklaffkirurgi

Aortaklaffsjukdomar (förträngd och/eller läckande klaff) är vanliga i västvärlden och ökar med stigande ålder, särskilt åldersrelaterad förträngning av aortaklaffen. Vid läckande aortaklaff måste hjärtat arbeta med en allt större blodvolym. Vid aortaklaffsförträngning krävs att hjärtat genererar ett högre tryck än normalt för att pumpa blodet genom den förträngda klaffen. Båda typerna av klafffel leder till att hjärtat kompenserar för den ökade belastningen och det kan gå många år innan symtom uppträder. Till slut räcker inte kompensationsmekanismerna till och hjärtat börjar svikta och typiska symtom som andnöd, kärlkramp och svimning tillstår. Någon effektiv medicinskt botande behandling finns inte varför enda alternativet är att ersätta eller reparera klaffen. Idag finns två metoder för detta, öppen hjärtkirurgi och kateterburen insättning av aortaklaffen. Båda typerna av ingrepp har risker som kan påverka utfallet efter ingreppet. Inför varje ingrepp görs en riskvärdering för att om möjligt optimera behandlingen. Inte sällan utgörs den största riskbelastningen av hjärtats funktion som i olika grad kan vara påverkad av underliggande hjärtsjukdom. Tidigare forskning har visat att hjärtsvikt i samband med operation av aortaklaffen är relaterat till sen överdödlighet och i det här avhandlingsarbetet ville vi närmare studera faktorer som kan vara del av den överdödligheten vid aortaklaffintervention.

Vi har valt att studera betydelsen av postoperativ hjärtsvikt hos patienter som före operation bedömdes ha låg respektive hög risk att inte överleva ingreppet. Resultaten visar att lågriskpatienter som efter operation drabbas av hjärtsvikt har en lika starkt reducerad långtidsöverlevnad som den hos högriskpatienter med hjärtsvikt. I avhandlingen visar vi att förträngning av aortaklaffen med tryckbelastning på hjärtat ger ett större svar av

hjärtsviktshormonet NT-proBNP i jämförelse med patienter med volymsbelastat hjärta och de med kranskärslssjukdom. Vidare visar vi att hjärtsviktshormonet NT-proBNP med hög grad av säkerhet kan identifiera kranskärslspatienter med ökad risk för svår svikt och död på kort sikt.

Vi beskriver också det dynamiska förloppet av hjärtsviktshormonet NT-proBNP hos patienter med förträngning av aortaklaffen samt det svar som de två operationsmetoderna har på hormonet. Öppen hjärtkirurgi leder till en kraftig stegring med en topp vid tredje dagen efter operation. Kate-terburen insättning av klaffen ger ett lägre svar och en tidigare topp redan dagen efter klaffinsättningen. Efter 6 månader har de förhöjda värdena sjunkit till eller under de värden som fanns innan ingreppet. Vi visar även att förhöjda värden av hjärtsviktshormonet före operation och tidigt efter operation är kopplat till ökad dödlighet under det första året efter operation. Den kopplingen sågs inte vid kateterburen klaffinsättning. Tjugotvå procent av patienterna som opererades för förträngd aorta klaff uppvisade tecken på nedsatt diastolisk hjärtfunktion med förhöjda fyllnadstryck. Efter operation hade hälften av dessa förbättrats och uppvisade inte längre tecken till förhöjda fyllnadstryck vid ultraljudsundersökning av hjärtat. Hos en mindre andel, 12 % sågs en försämring av den diastoliska funktionen 6 månader efter kirurgi. Både postoperativ hjärtsvikt och förhöjda värden av hjärtsviktshormonet NT-proBNP visade sig vara kopplade till reducerad överlevnad på lång sikt. Vi kunde dock inte finna att förhöjda fyllnadstryck i sig hade någon koppling till reducerad överlevnad på lång sikt.

Sammanfattningsvis visar avhandlingsarbetet att postoperativ hjärtsvikt fortsatt är av stor betydelse för prognosen av hjärtopererade patienter. Vi visar att hjärtsviktshormonet NT-proBNP har god prediktiv förmåga för såväl kort- och långtidsprognos och därför bör vara en del av den preoperativa riskevalueringen. Vi har visat att den diastoliska funktionsnedsättningen kan förbättras efter aortaklaffkirurgi men att en del även försämras. Vi kunde inte visa att diastolisk funktionsnedsättning med förhöjda fyllnadstryck är kopplat till död på lång sikt.

LIST OF PAPERS

I Henrik Hultkvist, Farkas Vánky, Rolf Svedjeholm

The Combined Impact of Postoperative Heart Failure and EuroSCORE on Long-Term Outcome after Surgery for Aortic Stenosis
The Journal of heart valve disease. 2011;20(6):633-8.

II Huiqi Jiang, Henrik Hultkvist, Jonas Holm, Farkas Vánky, Yangi Yang, Rolf Svedjeholm

Impact of underlying heart disease per se on the utility of preoperative NT-proBNP in adult cardiac surgery
PloS one. 2018;13(2):e0192503.

III Henrik Hultkvist, Jonas Holm, Rolf Svedjeholm, Farkas Vánky

Rise and fall of NT-proBNP in aortic valve intervention
Open heart. 2018;5(1):e000739.

IV Henrik Hultkvist, Eva Nylander, Éva Tamás, Rolf Svedjeholm, Jan Engvall, Jonas Holm, Eva Maret, Farkas Vánky

Evaluation of left ventricular diastolic function in patients operated for aortic stenosis, an observational study
Manuscript

ABBREVIATIONS

A	Late diastolic filling velocity
AF	Atrial fibrillation
AP	Angina pectoris
AR	Aortic regurgitation
AS	Aortic stenosis
AUC	Area under the curve
AVR	Aortic valve replacement
BMI	Body mass index
BSA	Body surface area
CABG	Coronary artery bypasses grafting
CAD	Coronary artery disease
CCS	Canadian Cardiovascular Society Functional Classification of Angina
CCT	Cross clamp time
CHF	Congestive heart failure
COPD	Chronic obstructive pulmonary disease
CPB	Cardiopulmonary bypass
DM	Diabetes mellitus
E	Early diastolic filling velocity
é	Early diastolic myocardial velocity
ECC	Extra corporeal circulation
EDV	End diastolic volume
EF	Ejection fraction
EOA	Effective orifice area
EuroSCORE	European System for Cardiac Operative Risk Evaluation

GFR	Glomerular filtration rate
IABP	Intra Aortic Balloon Pump
ICU	Intensive care unit
IVRT	Isovolumic relaxation time
LAA	Left atrial area
LV	Left ventricle/ ventricular
LVEDD	Left ventricular end diastolic dimension
LVEDV	Left ventricular end diastolic volume
LVESV	Left ventricular end systolic volume
LVOT	Left ventricular outflow tract
MR	Mitral regurgitation
NT-proBNP	N-terminal fragment of brain natriuretic peptide
NYHA	New York Heart Association
PAD	Peripheral artery disease
PHF	Postoperative heart failure
PHT	Pulmonary hypertension
PMI	Perioperative myocardial infarction
PPM	Prosthesis-patient mismatch
PVL	Paravalvular leakage
Redo	Reoperation
ROC	Receiver operating characteristic
SAVR	Surgical aortic valve replacement
SvO ₂	Mixed venous oxygen saturation
TAVI	Transcatheter aortic valve implantation

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Louise, Olivia and Wilhelm, the love of my life.

INTRODUCTION

Myocardial dysfunction is not uncommon in aortic valve disease, and postoperative heart failure is a major contributor to mortality in this setting ¹. Aortic valve interventions are among the most frequently performed cardiac procedures in the Western world today ². The incidence of degenerative calcific aortic valve disease increases with age and, due to the aging of the world population, it is expected to increase even more in future ³. When the disease is severe and patients are symptomatic, life expectancy is substantially reduced in the absence of a valve disorder correction ⁴. Patients that become symptomatic are often older with comorbidities, and the valve disorder has led to adaptive, and eventually, maladaptive changes, which result in myocardial dysfunction. The only efficient treatment available is aortic valve replacement. Although life expectancy is nearly normalized after an aortic valve replacement ⁵, the procedures themselves can cause intraoperative trauma, which affects the outcome in both the short and long runs ⁶⁻⁹.

The concept of this dissertation emerged from the recognition that patients with heart failure after surgery for aortic valve stenosis had a dire prognosis after a few years, even when the initial course was apparently benign. We speculated that postoperative heart failure (PHF) might unmask a previously unknown myocardial factor that has not been addressed by currently available risk scores.

In cardiac surgery, evaluating risks is pivotal, and those risks are, to a high degree, dependent on the patient's condition, preoperative comorbidities, and cardiac function, in addition to the type of surgery. Historically, much attention has been paid to left ventricular (LV) systolic function. One of the most commonly used risk scores, the European System for Cardiac Operative Risk Evaluation (EuroSCORE), uses the ejection fraction (EF) to evaluate LV systolic function, among other parameters ¹⁰.

However, in addition to systolic function, other aspects of heart function might impact prognosis. We hypothesized that a subtle, preclinical myocardial dysfunction, which is not revealed in classic risk evaluations, might play a role before systolic dysfunction becomes apparent.

In this project, we studied myocardial dysfunction in different aortic valve interventions, with special references to PHF, NT-proBNP (N-terminal pro B-type natriuretic peptide), and diastolic dysfunction.

BACKGROUND

The heart and the valves

The normal heart acts as a pump, constantly providing our cells with oxygenated blood and nourishment. The cardiac cycle is divided into diastole, when the heart relaxes and fills, and systole, when the heart contracts and empties. Effective pump function is possible through the intricate orientation of the muscle fibers in the heart, which was explained by Torrent Guasp in 1957 ¹¹. According to T-G, the myocardial fibers are oriented in inner longitudinal layer, circumferentially in the middle and spiral in the outer layer, forming a myocardial band. This can be seen as a statistical distribution of cells and does not have to be physically reproduced in the real world. The middle circumferential layer reduces the intraventricular lumen during contraction. The apical portion of the ventricle contracts before the basal portion, which drives the blood towards the aortic valve. The longitudinal and spiral muscles pull the mitral valve towards the apex. The three different orientations of muscle fibers provide a highly efficient way for the heart to pump and receive blood during each cardiac cycle. This structure allows rotation and torsion, followed by recoiling, with each cardiac cycle ^{11, 12}. However, the concept of a myocardial band has recently been questioned, and a new model that involves a three-dimensional (3D) myocardial mesh has been suggested ^{13, 14}. With the aid of high resolution microcomputed tomography, it was shown that cardiomyocytes are arranged within a supportive fibrous matrix, which constitutes a 3D mesh ¹⁴. The concept of a myocardial band was assumed to be a simplification to facilitate our understanding of the structure and function of the ventricles.

In each heart cycle, the right side of the heart pulls blood out of the veins and pumps the blood to the lungs. Then, the left side of the heart simulta-

neously pulls the blood out of the lungs and pumps it into the systemic circulation ¹⁵. To accomplish these tasks, the competencies of the heart valves are of utmost importance. The valve leading into the right ventricle is called the tricuspid valve, and the valve leading into the left ventricle is called the mitral valve. The outlet valves of the heart normally have three cusps (tricuspid valves). The two outlet valves are the pulmonary valve, which allows blood to pass into the lungs, and the aortic valve, which allows blood to pass into the aorta. When a valve begins to leak, the heart must deal with increasing volume overload; when a valve becomes stenotic, the heart must compensate for flow obstruction. Initially, the heart adapts to these changes, but further volume or pressure overload will eventually lead to a failing heart, when left untreated.

Chronic aortic regurgitation

In aortic regurgitation, the aortic valves do not close normally, and blood leaks back from the aorta into the ventricle. This condition can be caused by diseases that affect the valve apparatus or by pathology that affects the aortic root ¹⁶. As the end-diastolic volume increases, the left ventricular dimensions increase to compensate for excessive volume overload and also pressure overload ¹⁷. In aortic regurgitation there is a widened pulse pressure (systolic blood pressure-diastolic blood pressure) due to the extra volume being pumped into the aorta during systole. The pressure overload is caused by the systolic hypertension as a result from increased stroke volume ¹⁷. The ventricle compensates by dilating, through eccentric hypertrophy. In eccentric hypertrophy, sarcomeres replicate in a serial pattern. Conversely, in aortic stenosis, the heart compensates with concentric hypertrophy, where sarcomeres replicated in a parallel pattern ¹⁸. Over time, the compliance of the ventricle adapts, and the ventricle can handle a larger volume, which leads to a decrease in diastolic pressure. Although not fully understood, this sequence of events might explain why

the ventricle eventually decompensates. Indeed, an imbalance between a high LV stroke volume (observed in aortic regurgitation) and a reduced diastolic pressure can lead to reduced subendocardial perfusion and repeated episodes of ischemia ⁹. Ventricular dilatation and hypertrophy can compensate for the volume overload for years before symptoms arise, but eventually, ventricular remodelling occurs, in both systolic and diastolic dysfunctions ¹⁹.

Aortic stenosis

In aortic stenosis, the valve does not open as expected, and the leaflets become stiff and non-compliant. Three major processes are associated with aortic valve stenosis: degenerative calcification of the aortic valve, calcific degeneration of congenital bicuspid valves, and rheumatic valve stenosis.

The incidence of calcific degenerative aortic stenosis, with or without concomitant regurgitation, is increasing due to the growing older population in Western cultures ². Globally, the incidence of rheumatic fever and its effects on the heart has exceeded the incidence of degenerative calcification and its effects on aortic valve stenosis ²⁰. Calcific degeneration of the aortic valve occurs in two phases. The first is an inflammatory phase with lipid deposition, not unlike atherosclerosis; the second is a later phase with calcific mineralization, not unlike bone formation ^{21, 22}. To overcome the resistance of a stenotic valve, the heart compensates with left ventricular concentric hypertrophy, which reduces the wall stress in the left ventricle ²³. Ultimately, this initial compensatory hypertrophy hampers LV relaxation and compliance, and the LV cannot fill at low atrial pressures. When this condition remains untreated, survival rapidly declines in symptomatic patients ²⁴. Typical symptoms consist of shortness of breath, angina, and syncope; however, the variability between patients is large, particularly among older individuals. In older patients, it might be diffi-

cult to detect a transition from asymptomatic to symptomatic stages, due to a gradual decline in the patient's physical activity and the slow progression of symptoms. Therefore, clinical guidelines have recommended that the patient's symptoms should be recorded, a thorough evaluation of the circulatory and respiratory systems should be conducted, and the heart should be evaluated via echocardiographic examinations ^{25, 26}. Left untreated, a progressive narrowing of the aortic valve will lead to a failing heart, and ultimately death, due to the increased workload imposed on the heart. The only option is to replace the valve, because no effective medical treatment is currently available.

Echocardiography

Echocardiography has become a cornerstone in the evaluation and surveillance of patients with aortic valve disease ²⁵⁻²⁷. Echocardiography allows the visualization of heart anatomy and function. With echocardiographic analyses, the degree of valvular lesions can be quantified and both systolic and diastolic functions can be assessed ²⁸. In medical ultrasound, a high-frequency energy beam of 2-10 mega Hertz (MHz), which is not audible to humans, is sent through the body and reflected (echoed) back to the generating transducer, which produces an image. Two-dimensional (2D) echocardiography generates very short bursts of ultrasound in 2-3 wavelengths, which generates an image of the heart. This technique enables us to see, for example, the aortic valve and the cavities of the heart. It generates a real-time image of the moving heart. This approach facilitates evaluations of valvular pathology and the extent of ventricular hypertrophy or dilation, in addition to systolic function. When ultrasound is reflected against moving objects, it changes frequencies. When the object moves towards the transducer, the frequency of the reflecting sound will increase; conversely, when an object moves away from the transducer, the frequency of the reflecting sound will decrease. This principle is used in

Doppler echocardiography. With Doppler echocardiography, blood erythrocytes are the moving objects, and by assessing the velocity of blood flowing through the valve, it is possible to calculate the aortic valve area and the severity of aortic stenosis.

Natriuretic peptides

The natriuretic peptide family consists of three peptides: atrial natriuretic peptide (ANP), brain natriuretic peptide (BNP), and C-type natriuretic peptide (CNP) ²⁹. Accordingly, three natriuretic peptide receptors (A, B, and C) have been identified in mammalian tissues. Natriuretic peptide receptors A and B are linked to the cGMP-dependent signalling cascade. These receptors mediate many of the effects of natriuretic peptides on the cardiovascular and renal systems. In addition, BNP binds to natriuretic peptide receptor C, which is involved in the clearance of natriuretic peptides. BNP is an endogenous hormone that is mostly produced in cardiac tissue. It was first found in brains of pigs in 1988, hence the name BNP (B for brain) ³⁰. Its main functions are to maintain cardio-renal function and to counteract some features of heart failure. Its effects include diuresis, vasodilation, anti-hypertrophy, anti-fibrosis, and inhibition of the sympathetic nervous system and the renin-angiotensin-aldosterone system ³¹. BNP and its N-terminal fragment are released from a pre-prohormone in myocytes and exported into the circulation in response to increased left ventricular filling pressure and wall tension (Fig. 1) ^{32, 33}.

Figure 1. Synthesis and secretion of PreproBNP by the cardiomyocytes processed to ProBNP by enzymatic convertases Corin and Furin. The presumed inactive N-terminal fragment is secreted into the circulation alongside the active C-terminal BNP. Reprinted with permission from Jonas Holm.

BNP and its inert N-terminal fragment (NT-proBNP) are released in a 1:1 ratio into the circulation. BNP has a shorter half-life (21 min) than NT-proBNP (60-120 min) ^{32, 34}. Currently, NT-proBNP is an established biomarker for diagnosing and monitoring heart failure ^{35, 36}. Moreover, NT-proBNP is elevated in a variety of cardiovascular disorders ³⁶. NT-proBNP was correlated with the severity of aortic stenosis. In symptomatic patients, it was shown to be predictive of mortality ³⁷⁻³⁹. In cardiac surgery, NT-proBNP was related to the short-term outcome and the length of stay in an Intensive Care Unit (ICU) ⁴⁰⁻⁴². However, studies on its usefulness have produced conflicting results ^{43, 44}. In aortic valve surgery, pre-operative NT-proBNP was found to be predictive of poor postoperative outcome ^{45, 46}, but its predictive power was considered to be moderate ^{47, 48}. NT-proBNP was also correlated to diastolic function ⁴⁹⁻⁵².

Diastolic function

Diastolic relaxation is when the myocardium returns to a relaxed tension and length before systole. Diastole is often described as the period that starts with closure of the aortic valve and ends with closure of the mitral valve. Diastole can be divided into three phases: in phase one, the muscles relax and blood rapidly fills the ventricle; phase two is diastasis, where the passive filling of the ventricle has slowed down; and phase three is end-diastole, which is marked by active atrial contraction ⁵³. Diastolic relaxation is an active, calcium-dependent process, which mainly influences early left ventricular filling. Ventricular compliance, described as the change in volume over pressure (dV/dP), is most important towards the end of diastole. The opposite of compliance is ventricular stiffness (dP/dV).

All these features of diastolic function are negatively affected by a hypertrophic myocardium, which occurs in aortic valve diseases, particularly aortic stenosis. The severity of diastolic dysfunction can be assessed with

the echo-Doppler technique. The process of diastolic dysfunction starts with abnormal relaxation, although filling pressures often remain normal, at least at rest. In severe diastolic dysfunction, compliance is reduced, which results in increased left ventricular filling pressures.

Diastolic function is graded as normal, Grade I (impaired relaxation pattern), Grade II (pseudonormalization), and Grade III (restrictive filling pattern). Grades II and III are thought to be associated with increased LV filling pressure. Diastolic dysfunction often precedes systolic dysfunction in aortic valve disease ^{54, 55}. The prevalence of diastolic dysfunction is reported to be high in patients with aortic valve disease, and it has been associated with outcomes after interventions ⁵⁶⁻⁵⁹. Diastolic dysfunction was also associated with a poor prognosis in patients with AS that had not undergone surgery ⁶⁰. Although diastolic dysfunction was also found to be associated with a poor outcome after an aortic valve intervention, conflicting data exist ^{61, 62}.

Aortic valve intervention

Currently, aortic valves can be replaced with surgery or with a transcatheter aortic valve intervention (TAVI). Before the TAVI era, patients deemed unfit for open heart surgery were predestined for an early death, due to aortic valve disease ⁶³. In 1953, Hufnagel and Harvey performed the first surgical replacement of an aortic valve by inserting a caged ball valve in the descending aorta. They operated on a patient with aortic insufficiency, which caused insufficient blood flow in the upper body ⁶⁴. However, it was not until the early 1960's that the first successful aortic valve replacements were performed, with the aid of the heart-lung machine constructed by Gibbon in 1954⁶⁴. Currently, aortic valve interventions are among the most common cardiac procedures performed around the world ^{3, 65}. The first TAVI procedure in humans was performed in 2002 ⁶⁶. Since then, this procedure has grown enormously popular ⁶⁷.

Aortic valve prostheses for surgical insertions can be either mechanical or biological. Biological prostheses can be made of autologous tissue, from diseased tissue, or more commonly, from a porcine aortic valve or a valve constructed from bovine pericardium. Mechanical valves have the advantage of durability, but on the downside, they increase the risk of thrombus formation and the risk of an embolic event. Therefore, patients with mechanical valves require life-long anticoagulant medication, which increases the risk of serious bleeding. Biological valves do not require anticoagulant medication, but they have limited durability, due to structural deterioration over time. After aortic valve replacement, regardless of the type of valve, there is a risk of a prosthesis-patient mismatch, where the effective orifice area of the implanted valve is too small for the patient's body surface area ^{68, 69}. Other postoperative complications include arrhythmias and atrioventricular blocks, which require a postoperative pacemaker implantation, and other complications related to open-cardiac surgery, per se, such as bleeding, tamponade, and infections. Complications associated with TAVI include access site bleeding and infection, the need for a postoperative pacemaker, stroke ⁷⁰, and periprocedural myocardial infarction ^{71, 72}.

Myocardial dysfunction in aortic valve surgery

Since the early 1980's, it has been recognized that myocardial dysfunctions can occur in the context of aortic valve replacement ⁷³. Indeed, cardiac interventions alone impose an ischemic injury to an already failing heart, due to the underlying pathology ⁷⁴. Preoperatively, there is often an imbalance between oxygen delivery and demand, which can be due to an obstruction in the coronary arteries, a hypertrophied myocardium, or an increase in the cardiac workload. Both anesthesia and surgery impose additional stress, which affects both oxygen delivery and demand. Anemia frequently occurs, due to hemodilution caused by the bypass circuit or

due to bleeding. Tachycardia is not uncommon, because the surgical trauma induces increased levels of circulating catecholamines, amongst many other stressors. During cardiac arrest, the myocardium can be protected from ischemia with a cold cardioplegic solution, which minimizes cardiac metabolic activity. The remaining metabolism is anaerobic, and it depletes myocytes of certain metabolites; this depletion can cause depressed myocardial function in the early postoperative phase ⁷⁵.

Over the decades, mortality in cardiac surgery has decreased, despite an increase in surgical complexity ⁷⁶. However, PHF continues to be among the most important causes of mortality associated with cardiac surgery and aortic valve interventions ^{6, 77}. Among patients undergoing aortic valve surgery, PHF was associated with 38% short-term mortality, compared to 1.5% in the absence of PHF ⁷⁸. Both systolic and diastolic function has been found to impact the outcome of an aortic valve intervention ^{79, 80}. Previous studies have identified both pre- and intraoperative risk factors for PHF ⁸¹⁻⁸³. Studies on patients that have undergone non-cardiac surgery have shown that the best therapeutic approach to heart failure in the surgical setting is to perform proper patient risk stratification ⁸⁴. In the setting of elective cardiac surgery, myocardial dysfunction can be considered its own entity; many patients require inotropes to prevent end-organ dysfunction and tissue hypoperfusion⁸⁵. In our experience, approximately 10% of patients that undergo aortic valve surgery for AS developed PHF ⁷. Other studies have reported that more than 20% of patients undergoing cardiac surgery exhibited perioperative myocardial dysfunction ⁸⁶

AIMS OF THE THESIS

We attempted to understand why, among patients that underwent surgery for aortic valve disease; those that experienced an episode of PHF had much worse survival after a few years compared to those without PHF. We hypothesized that there might be a myocardial factor that has not been identified with typical preoperative risk evaluations.

The specific aims for each study were:

- I. To describe the impact of PHF on long-term survival after surgery for isolated aortic valve stenosis in patients at low and high risk identified with a commonly used cardiac surgery risk score model, the EuroSCORE.
- II. To investigate the underlying role of heart disease, per se, on preoperative NT-proBNP levels in patients admitted for adult cardiac surgery, after adjusting for known confounders, including age, gender, obesity, and renal function. In addition, we investigated the value of NT-proBNP for predicting severe PHF and postoperative mortality.
- III. To describe the levels of preoperative NT-proBNP and changes in these levels from enrollment to the six-month follow-up, in patients undergoing aortic valve interventions, and to evaluate the association between preoperative NT-proBNP and one-year mortality.
- IV. To explore how aortic valve surgery for aortic stenosis impacted LV diastolic function. In addition, we evaluated the impacts of high LV filling pressure, NT-proBNP, and PHF on postoperative outcome.

METHOD

Study design and patients

The patient populations and study designs of the four studies in this project are summarized in Table 1.

Table 1. Methodological overview of included studies.

Study	I	II	III	IV
Design	Retrospective cohort	Retrospective cohort	Prospective, observational, longitudinal	Prospective, observational, longitudinal
Pathophysiology	AS	CAD, AS and MR	AS $\pm$ CAD and AR	AS $\pm$ CAD
Exposure	SAVR	CABG, SAVR and mitral valve repair or MVR	SAVR or TAVI	SAVR
Period	1995-2000	2010-2016	2008-2013	2008-2013
Patients included	397	2978	462	247
Primary outcome	Late mortality	The role of underlying heart disease on NT-proBNP	Describe the dynamics of NT-proBNP	The effect of SAVR on LV diastolic function
Secondary outcomes	Impact of EuroSCORE	Predictive power of NT-proBNP on severe PHF and early mortality	Predictive power of NT-proBNP on 1 year mortality	Relate high LV filling pressure, PHF and NT-proBNP on outcome
Statistics	Descriptive, survival analysis	Descriptive, survival analysis, linear regression, logistic regression and ROC analyses	Descriptive, survival analysis, correlation, linear regression and ROC analyses	Descriptive, survival analysis, Cox regression correlation, linear regression and ROC analyses

AS=aortic stenosis, CAD=coronary artery disease, MR= mitral regurgitation, AR=aortic regurgitation, SAVR=surgical aortic valve replacement, MVR=mitral valve replacement, TAVI=transcatheter aortic valve implantation, NT-proBNP=N-terminal fragment of brain natriuretic peptide, EuroSCORE= European System for Cardiac Operative Risk Evaluation, ROC=Receiver Operating Characteristic

Data collection

We accessed the patient records registry maintained in our institution with Summit Vista for Windows (Summit Medical Systems INC., Version 1.98.1), in study I, and with Carath version 5.4 (Fujitsu Inc.), in studies II – IV. Additional data were retrieved from patient records (studies I – IV) and from Case Report forms (studies III and IV). Mortality data were retrieved from the Swedish Civil Registry. Causes of death were retrieved from medical records and from autopsy records (study II).

Clinical management

All patients were treated at the University Hospital in Linköping, a tertiary referral hospital and the only center for cardiac surgery in the south-east region of Sweden. This hospital served a population of approximately one million. For all patients undergoing surgery, standardized surgical and anesthetic techniques were used. Surgery included a full median sternotomy, heparinization, and a cardiopulmonary bypass with aortic cross-clamping, followed by antegrade or combined ante- and retrograde cardioplegic arrest, repeated every 20 minutes. After surgery, weaning from bypass was instituted at a rectal temperature of 35–36°C. The heparin effect was reversed with protamine chloride. In study I, a cold crystalloid cardioplegia solution was used, and shed postoperative blood was routinely collected and retransfused into the patient in the ICU. In studies II–IV, a diluted blood cardioplegia solution was prepared with four parts crystalloid cardioplegia solution diluted with one part blood. In those studies, no retransfusion of shed postoperative blood was performed.

Patients undergoing TAVI were placed under general anesthesia with endotracheal intubation. Access was achieved through either a transthoracic or transfemoral pathway. For the transthoracic TAVI implantation, a small, left-sided thoracotomy was performed, and the valve was deployed

via the apex of the heart. This access route was chosen when the common femoral artery was small (<7-8 mm diameter) or when the iliofemoral arteries were severely calcific. The procedure was aided with both fluoroscopy and transoesophageal echocardiography. In all TAVI cases, an expandable Edwards Sapien valve bioprosthesis (Edwards Lifesciences Inc., Irvine, CA) was implanted.

Mixed venous oxygen saturation (SvO₂)

A surgically introduced pulmonary catheter was routinely used to collect blood samples of SvO₂ and to monitor pulmonary artery pressures, particularly during weaning from the bypass ⁸⁷. SvO₂ was routinely monitored in the ICU, and it was used to optimize circulation postoperatively. Oxygen saturation was analyzed in an ABL500 (study I), an ABL725, or an ABL825 (studies II – IV; Radiometer Medical ApS, Brønshøj, Denmark).

NT-proBNP

Venous blood samples were collected in lithium heparin tubes and analyzed within 3 hours to determine NT-proBNP levels. NT-proBNP was measured with an electrochemoluminescence immunoassay on a Roche Elecsys 2010 automated platform (Roche Diagnosis, Basel, Switzerland) in studies II - IV. Briefly, NT-proBNP concentrations were measured with a sandwich technique, with polyclonal antibodies that recognized epitopes on the N-terminal part of proBNP. In study II, preoperative NT-proBNP was analyzed. In study III, we analyzed NT-proBNP at preoperative evaluation before decision was made by a multi-disciplinary heart team on intervention, the day before index procedure, postoperatively on the first and third postoperative day and at the 6 months follow-up. In study IV, we analyzed NT-proBNP the day before surgery and at the six-month fol-

low-up. The inter-assay coefficient of variation was 4%, on average. The age-adjusted upper reference limits were: 450 ng/L for patients <50 years old, 900 ng/L for those 50-75 years old, and 1800 ng/L for those >75 years old ^{88, 89}.

Risk score

To assess risk, we employed the additive EuroSCORE, calculated retrospectively, in studies I and II, and we used EuroSCORE II prospectively in studies III and IV. In study I, patients were divided into two groups, based on their preoperative additive EuroSCOREs. Patients with EuroSCOREs >7 were assigned to a high-risk group, and patients with EuroSCOREs ≤7 were assigned to a low-risk group. Patients were then analyzed according to whether they developed PHF. One might argue that dividing the cohort into two groups, based on the EuroSCORE, was insufficient, and that the norm, based on the literature, would be to divide the cohort into quartiles. However, the sample size and number of events were too few to permit an analysis of four groups. The clear difference in outcome between the two groups verified the clinical relevance of this stratification. However, the EuroSCORE has been known to overestimate the operative risk of mortality, particularly in patients with a high-risk preoperative profile ⁹⁰.

Echocardiography

All patients were preoperatively examined and evaluated with standard 2D and Doppler echocardiography to assess myocardial function and the severity of valvular pathology. All measurements were performed according to guidelines ^{91, 92}.

The mean pressure difference (“gradient”) over a stenotic valve is often a good measure of the severity of a stenosis. The pressure difference can be calculated with the simplified Bernoulli equation: $\Delta P = 4 * v^2$, where ΔP is

the pressure fall over the stenosis, and v is the flow velocity in the vena contracta zone on the distal end of the stenosis. We calculated the mean gradient by tracing the flow velocity curve during systole. The pressure fall depends on the flow over the stenosis. In cases with low flow, for example, in depressed myocardial function, the severity of the stenosis might be underestimated. The aortic valve area (AVA) -that is less flow-dependent was calculated with the continuity equation, based on the LV outflow tract (LVOT) and the velocity time integral (VTI), as follows:

$$\text{AVA} = (\text{cross-sectional area of LVOT}) * (\text{VTI of LVOT}) / (\text{VTI of the aortic valve})$$

Systolic function can be evaluated as the EF, based on volumetric measurements, as follows: $\text{EF} (\%) = \text{LVEDV} - \text{LVESV} / \text{LVEDV} * 100$; where LVEDV is the LV end-diastolic volume, and LVESV is the LV end-systolic volume. However, in studies I – IV, we used a four-degree scale to rate systolic function (i.e., normal, mildly abnormal, moderately abnormal, and severely abnormal), which corresponded to the EF categories recommended by Lang et al.⁹¹. At least two experienced observers performed this rating in each patient.

We calculated LV mass according to the Devereux formula, as follows:

$$\text{LV mass} = 0.8 \times \{1.04[(\text{LVEDD} + \text{PWTd} + \text{SWTd})^3 - (\text{LVEDD})^3]\} + 0.6\text{g}$$

⁹¹. Where LVEDD is LV end diastolic dimension and PWTd is posterior wall thickness in end-diastole, SWTd is septal wall thickness in end-diastole.

In study IV, diastolic function was evaluated the day before surgery and at the six-month follow-up. Diastolic function was evaluated by measuring the mitral inflow, the isovolumetric relaxation time (IVRT), the pulmonary venous flow, the diastolic velocities of the myocardium, the systolic function, and left atrial size⁹³. In study IV, we evaluated diastolic function primarily based on the ratio of the early mitral filling velocity (the E-wave) to the late diastolic filling velocity (the A-wave), i.e., the E/A ratio;

the pulmonary venous systolic and diastolic flow velocities; the left atrial size, i.e., the left atrial end-systolic area in a four-chamber view, indexed to the body surface area; and the ratio of the E-wave to the early diastolic annular velocity (E/e'), where e' is the mean of septal and lateral early diastolic annular velocities. For patients with contradictory or unclassifiable measurements, we took into consideration an individualized evaluation of the mitral flow deceleration time, the IVRT, and tricuspid regurgitation.

Diastolic function was graded into four categories: Normal diastolic function, Grade I (disturbed relaxation), Grade II (pseudonormalization), and Grade III (restrictive filling pattern). In the progression of diastolic dysfunction towards diastolic heart failure, elevated LV filling pressure is a late manifestation of diastolic dysfunction,⁹⁴ and disturbed relaxation is an early manifestation. Therefore, we classified the patients in study IV, based on whether they had elevated LV filling pressure. Patients with Grade I diastolic function were assigned to the low LV filling pressure group; patients with Grades II and III diastolic function were assigned to the high LV filling pressure group. The decision to divide the cohort into two groups was supported by the fact that the presence of Grade I diastolic dysfunction (impaired relaxation) did not appear to increase mortality, compared to normal diastolic function, in cardiac surgery⁸⁶. In determination of the grade of diastolic dysfunction, it is emphasized in the most recent guideline to assess whether elevated left ventricular (LV) filling pressure is present or absent⁹².

Those authors also stressed the value of understanding the definition of the term 'LV filling pressure', because different LV and left atrium diastolic pressures are correlated with different Doppler signals⁹³.

In the early manifestation of diastolic dysfunction, which is marked by abnormal relaxation (Grade I), the LV filling pressures measured as mean pulmonary capillary wedge pressure (PCWP) or mean left atrial pressure (LAP) are typically normal, but the left ventricular end-diastolic pressure

(LVEDP) can be elevated during exercise. In later stages of diastolic dysfunction, or upon physical exertion, the PCWP and LAP rise. However, although the guidelines mentioned the fact that many echocardiographic variables assessed in the diastolic function evaluation are age-dependent, age was not included in their algorithms. Therefore, we used a guideline-based automated algorithm (Fig.2) (<https://liu.se/en/research/left-ventricular-diastolic-function-decision-support>), in which we included the age adjusted normal ranges for grading of diastolic function ⁹⁵.

Figure 2. Assessment algorithm for standardized automated evaluation of LVDF. The assessment is based on E/A, PVs/PVd, E/e', LAAi or LAVi. The algorithm first compares these diastolic parameters to age-corrected normal values, and values are sorted into the categories “low”, “normal”, and “high”. Thereafter, the categorized variables are entered into the analysis in hierarchical order for evaluation of LVDF, and the LVDF category is presented automatically. In the case of conflicting values or missing key variables, a request for manual assessment is presented. LVDF, left ventricular diastolic function. Reprinted with permission from Tamás and Nylander.

Clinical endpoints committee

The Clinical Endpoints committee consisted of consultants in cardiothoracic surgery and cardiothoracic anesthesiology. Members reached a consensus decision, based on the prespecified criteria described above. The members were blinded to the results of NT-proBNP analyses, when they reached a consensus on whether a patient had experienced an episode of PHF or severe PHF. The committee reviewed all cases with suspected PHF, based on SvO₂ and systemic blood pressure, pulmonary artery pressure, central venous pressure, use of inotropic drugs or mechanical circulatory support, an extended ICU stay, or circulatory problems, reported by the anesthesiologists or surgeons in the clinical database. The committee decided whether a circulatory problem had occurred that met the prespecified criteria; whether a circulatory problem was severe; and when a circulatory problem was cardiac in origin, whether it was evident at weaning from the cardiopulmonary bypass or it became evident later in the post-operative course. The committee also decided whether any events leading to death were cardiac in origin.

DEFINITIONS

Postoperative heart failure

PHF refers to heart failure during hospitalization in association with surgery. The definition of PHF differed slightly depending on nature of the studies, particularly depending on if they were retrospective or prospective. Details are given in respective paper.

In general PHF was defined as a hemodynamic state when the cardiac output does not meet the systemic demand without supportive measures other than correction of volume or vascular resistance ^{7 96}. This hemodynamic state was defined by mixed venous oxygen saturation (SvO₂), which in contrast to cardiac output is well documented with regard to outcome ^{87, 96 97, 98}. An empirically found approximate relationship between SvO₂ and systolic arterial pressure (SAP) when using nitroprusside provided a guide for assessing the degree of inadequate circulation, as follows ⁹⁹ : SvO₂<50% and SAP<130 mmHg, SvO₂ <55% and SAP<110 mmHg, SvO₂<60% and SAP<90 mmHg and SvO₂ <65% and SAP<70 mmHg, excluding cases explained by shivering, anemia or hypovolemia.

Supportive measures consisted of inotropic treatment, an intra-aortic balloon pump (IAPB) for counter-pulsation, and/or metabolic support with glucose, insulin, potassium, and/or intravenous glutamate. The drugs, dosages (II-IV) or duration (I) required to be classified as inotropic treatment are specified in respective paper.

In most cases, PHF was evident as an inability to wean from the cardio-pulmonary bypass. The decision if PHF had occurred was determined by the consensus of an Endpoints committee, and the decision was based on available medical records and hemodynamic data.

Echocardiography was routinely used and supported pump failure or hypovolemia as cause for the inadequate hemodynamic state. CVP, PA pressures, urinary output and arterial blood gases were also routinely monitored.

Due to sample size in paper II we studied patients with PHF leading to extended ICU stays (≥ 72 hours) or death due to hemodynamic problems requiring inotropes in prespecified dosages. This facilitated screening and identification of patients with heart failure postoperatively in a cohort including 2978 patients.

Statistics

Baseline data are presented as the mean $\pm$ SD or as the median with interquartile range (IQR), for continuous data, and as a proportion for categorical data. The Mann-Whitney U test was used to compare continuous data between two independent groups. The Kruskal-Wallis test was used to compare continuous data among more than two independent groups. To adjust for multiple comparisons of the mean ranks for all groups, we performed post hoc comparisons of the mean ranks of all pairs of groups¹⁰⁰. For dichotomous data, a Chi-square test or Fisher's exact test was used for comparisons, as appropriate. For comparisons of more than two groups, a Bonferroni correction was performed. For repeated measures within groups, we performed a Wilcoxon signed rank test with the Bonferroni correction. A Pearson correlation analysis was performed, when appropriate. Skewed data, such as NT-proBNP levels, were transformed to $\log_{10}$ before performing linear regression analyses. Collinearity diagnostics with variance inflation factors were performed to exclude multicollinearity in multivariable linear regression analyses. To evaluate the prognostic performance of NT-proBNP with regard to mortality, PHF, and severe PHF, we performed ROC analyses. The best cut-off point for the area under the curve (AUC) was determined according to Youden's index. In model building, variables were selected, a priori, based on theoretical and clinical grounds, and they were held parsimoniously and controlled for to ensure that the assumption for each model was met. Multivariable logistic regression analyses were performed to identify pre- and perioperative risk factors for severe PHF and mortality (study II). Linear regression analyses were performed to explore variables associated with the rise in NT-proBNP during an aortic intervention (study III).

Multivariable logistic regressions were used to explore variables associated with high LV filling pressure (study IV). Survival analyses were performed with the Kaplan-Meier method, and a log-rank test was performed

to evaluate differences in survival between groups. Cox regression analyses were performed to explore variables associated with mortality. For study I, all statistical analyses were performed with Statistica 9.0 (StatSoft Inc., Tulsa, USA). For study II, statistical analyses were performed with SPSS version 23 (IBM) for Windows and Statistica 13.2 (Dell Inc.). For study III, analyses were performed with the statistical package, Statistica V.10.0 (StatSoft, Tulsa, Oklahoma, USA). For study IV, statistical analyses were performed with NCSS 12 Statistical Software, 2018 (NCSS, LLC, Kaysville, Utah, USA: ncss.com/software/ncss) and Statistica v. 13.2 (StatSoft, Tulsa, Oklahoma; USA).

Ethics

All studies were performed in accordance with the World Medical Association`s Helsinki declaration on ethical principles for medical research. The regional Ethics Review Board approved all studies. Approval numbers were: Dnr 03-364 for study I; Dnr 2011/ 497-31 for study II; and M 198-07, T 126-08, 2012/ 422-32 for studies III and IV. Patients in the prospective studies, study III and IV, were enrolled after providing written, informed consent.

RESULTS

The main results from all four studies are summarized here. The detailed results can be pursued in the four papers compiled in this dissertation.

Study I

Study I was a retrospective examination of data on a cohort of patients that underwent surgery for isolated AS between January 1st 1995 and December 31st 2000, focusing on PHF. The preoperative data are presented in Table 2.

Table 2. Preoperative data of patients with (+) and without (-) postoperative heart failure (PHF).

	All patients (n=397)	High risk PHF - (n=48)	High risk PHF + (n=21)	p-value	Low risk PHF - (n=304)	Low risk PHF + (n=24)	p-value
EuroSCORE	5.7±2.2	8.7±1.0	9.7±1.5	0.002	5.0±1.7	5.1±1.9	0.74
Log EuroSCORE	5.7±4.8	11.8±4.4	17.1±9.5	<0.001	4.1±1.9	4.5±2.1	0.43
Age (years)	70±10	79±5	78±4	0.12	68±10	68±11	0.83
Female gender	48%	77%	48%	0.02	45%	29%	0.14
Body Mass Index	26±4	25±4	26±4	0.09	26±4	27±4	0.39
Insulin or orally treated DM	11%	13%	29%	0.17	10%	13%	0.72
Hypertension	28%	23%	43%	0.15	27%	42%	0.15
COPD	9%	17%	24%	0.75	7%	8%	0.67
P-Creatinine (µmol/L)	100±26	100±29	105±25	0.21	99±26	108±16	0.002
P-Creatinine>167 (µmol/L)	1%	4%	0%	1.0	1%	0%	1.0
Stroke	9%	19%	19%	1.0	7%	8%	0.67
Peripheral artery disease	3%	9%	5%	1.0	1%	4%	0.32
Atrial fibrillation/flutter	15%	28%	24%	1.0	12%	25%	0.11
Angina pectoris	23%	35%	5%	0.007	23%	17%	0.62
Congestive heart failure	37%	46%	90%	<0.001	30%	50%	0.06
NYHA class 1 or 2	43%	19%	0%	0.05	51%	29%	0.04
NYHA class 3 or 4	57%	81%	100%	0.05	49%	71%	0.04
Pulmonary hypertension	3%	6%	33%	0.007	1%	0%	<0.99
Critical preoperative state	2%	2%	24%	0.009	0%	4%	0.14
Aortic valve orifice area (cm ²)	0.62±0.19	0.56±0.16	0.45±0.12	0.014	0.63±0.19	0.64±0.18	0.68

*Values are mean ± SD. COPD: Chronic obstructive pulmonary disease; DM: Diabetes mellitus (insulin or orally treated).

In study I, we analyzed the relationship between PHF and mortality. In addition, we took into account the preoperative risk score, determined

with the additive EuroSCORE. PHF occurred in 45 out of 397 (11%) patients. The 30-day crude mortality was 6.7% in patients with PHF and 1.4% in patients without PHF ($p=0.05$). The five-year mortality was 42% in patients with PHF and 14% in patients without PHF ($p<0.001$; Table 3).

Table 3. Intraoperative and postoperative data of patients with (+) and without (-) postoperative heart failure (PHF).

	All patients (n=397)	High risk PHF - (n=48)	High risk PHF + (n=21)	p-value	Low risk PHF - (n=304)	Low risk PHF + (n=24)	p-value
Elective operation	92%	85%	52%	0.006	96%	92%	0.3
Urgent operation	7%	13%	38%	0.02	4%	8%	0.3
Emergency operation	1%	2%	10%	0.22	0%	0%	>0.99
Cross-clamp time (minutes)	81 ± 21	74±17	86±25	0.04	80±19	102±33	<0.001
CPB time (minutes)	106±27	98±21	119±30	0.002	103±22	147±47	<0.001
Biological prostheses	61%	92%	95%	>0.99	55%	56%	>0.99
Valve size 19 mm	12%	27%	10%	0.13	10%	4.0%	0.71
EOA Index<0.75	32%	44%	67%	0.12	28%	25%	0.82
Inotropic treatment	3%	0%	95%	0.001	38%	92%	<0.001
Metabolic treatment	7%	7%	52%	0.001	2%	33%	<0.001
IABP	0.3%	0%	5%	0.30	0%	0%	>0.99
Atrial flutter/fibrillation	34%	34%	38%	0.79	33%	33%	>0.99
Erythrocyte transfusion	37%	58%	71%	0.42	30%	50%	0.06
Thrombocyte transfusion	8%	12%	24%	0.52	6%	12%	0.19
P-Creatinine maximum (μmol/L)	105 ±46	105±40	140±81	0.06	100±35	134±97	0.001
P-Creatinine ≥50%	5%	4%	29%	0.01	3%	13%	0.04
Dialysis	1%	0%	0%	>0.99	0%	8%	0.005
Myocardial infarction	3%	2%	14%	0.08	1%	13%	0.01
Stroke	4%	6%	5%	>0.99	3%	8%	0.22
Bleeding/reoperation	5%	10%	14%	0.69	3%	8%	0.22
Deep sternal wound infection	1%	2%	0%	>0.99	1%	0%	>0.99
Time on ventilator (hours)	11±29	8±11	30±40	0.003	7±9	46±99	<0.001
ICU stay (days)	1.4±1.6	1.4±1.1	3.0±3.1	0.08	1.1±0.6	3.5±4.4	<0.001
Hospital stay (days)	8±4	9±6	10±5	0.77	9±3	11±5	0.03
30-day mortality	2.0%	2.1%	9.5%	0.22	1.3%	4.2%	0.32
5-year mortality	17%	36%	43%	0.60	11%	42%	<0.001

*Values are mean ± SD. CPB: Cardiopulmonary bypass; EOA: Effective orifice area; IABP: Intra-aortic balloon pump; ICU: Intensive care unit; P-Creatinine ≥ 50%: Proportion of patients with postoperative P-Creatinine exceeding the preoperative value by 50%.

Patients at high risk (EuroSCORE>7; n= 69) had a 30-day mortality of 4.3%. In comparison, patients at low risk (EuroSCORE≤7; n=328) had a 30-day mortality of 1.5% ($p=0.15$). The crude five-year mortality was 42% in patients at low risk with PHF, compared to 11% in patients at low risk

without PHF ($p < 0.001$). Among patients at high risk, mortality rates were not significantly different between those with and those without PHF ($p = 0.60$; Fig. 3).

Figure 3: Mortality in low-risk (additive EuroSCORE ≤ 7) and high-risk (additive EuroSCORE > 7) groups with (+) and without (-) postoperative heart failure (PHF). Early mortality is 30-day mortality, late mortality is mortality from 30 days to five years postoperatively.

Study II

In study II, we investigated the influence of the underlying heart disease, per se, on preoperative NT-proBNP levels. We evaluated an unselected cohort of patients that underwent a first-time surgery, from April 2010 to August 2016, for coronary artery disease (CAD; n=2226), AS (n=406), or mitral regurgitation (MR; n=346). We also evaluated the relationships between NT-proBNP and severe PHF and short-term postoperative mortality. The patient selection process is presented in Figure 4. The characteristics of all patients and subgroups are presented in Table 4.

Figure 4. Patient flow chart. CAD: patients with coronary artery disease admitted for first time CABG, AS: patients with aortic stenosis without significant aortic regurgitation admitted for first time aortic valve replacement, MR: patients with mitral regurgitation without significant mitral stenosis admitted for first time mitral valve surgery with or without tricuspid valve procedure. A total of 161 patients underwent mitral valve surgery with tricuspid valve procedure, and, 102 patients had concomitant Maze procedure (26 patients undergoing CABG, 12 undergoing isolated aortic valve surgery, and 64 undergoing mitral valve surgery).

Table 4. Demographic data in all patients and subgroups.

	All patients (n=2978)	CAD (n=2226)	AS (n=406)	MR (n=346)	p*	p [†]	p [‡]	p [§]
Age (years)	70 [63-76]	69 [63-75]	73 [66-78]	67 [58-74]	<0.001	<0.001	<0.001	<0.001
Female gender	24% (714)	18% (410)	50% (202)	29% (102)	<0.001	<0.001	<0.001	<0.001
Preop-NT-proBNP (ng/L)	330 [130-970]	290 [120-833]	595 [260-1510]	400 [110-1350]	<0.001	<0.001	0.050	<0.001
BMI kg/m ²	27 [24-30]	27 [25-30]	27 [24-31]	25 [23-28]	<0.001	>0.99	<0.001	<0.001
Obesity (BMI ≥ 30kg/m ²)	26% (782)	27% (606)	32% (130)	13% (46)	<0.001	0.051	<0.001	<0.001
BSA m ²	1.96 [1.83-2.09]	1.98 [1.85-2.10]	1.90 [1.77-2.05]	1.93 [1.80-2.06]	<0.001	<0.001	<0.001	0.58
Preop hemoglobin g/L	141 [132-150]	141 [132-150]	140 [130-148]	142 [133-149]	0.024	0.025	>0.99	0.08
Preop p-creatinine μmol/L	85 [74-101]	86 [74-102]	80 [68-97]	83 [73-98]	<0.001	<0.001	0.07	0.11
Preop-eGFR mL•min ⁻¹ •1.73m ⁻²	73 [60-86]	73 [60-86]	72 [58-86]	75 [62-87]	0.29			
Preop p-albumin g/L	39 [36-42]	39 [36-42]	40 [37-42]	40 [38-43]	<0.001	<0.001	<0.001	>0.99
Smoker	11% (336)	13% (299)	5% (22)	4% (15)	<0.001	<0.001	<0.001	0.50
Diabetes	25% (739)	29% (655)	17% (67)	5% (17)	<0.001	<0.001	<0.001	<0.001
Hypertension	65% (1934)	70% (1558)	59% (240)	39% (136)	<0.001	<0.001	<0.001	<0.001
COPD	7% (219)	8% (173)	6% (23)	7% (23)	0.28			
Cerebrovascular disease	7% (208)	8% (167)	5% (19)	6% (22)	0.28			
Extracardiac arterial disease	7% (208)	8% (187)	4% (15)	2% (6)	<0.001	0.001	<0.001	0.10
Previous vascular surgery	4% (115)	5% (101)	2% (9)	1% (5)	0.004	0.031	0.007	0.44
Preop dialysis	0.8% (25)	0.8% (18)	1.3% (5)	0.6% (2)	0.59			
Angina	74% (2207)	97% (2151)	14% (56)	0	<0.001	<0.001	<0.001	<0.001
Unstable angina	46% (1372)	62% (1372)	0	0	<0.001	<0.001	<0.001	-
CCS IV	9% (271)	12% (271)	0	0	<0.001	<0.001	<0.001	-
Recent myocardial infarction (<3 weeks)	28% (839)	38% (835)	0.7% (3)	0.3% (1)	<0.001	<0.001	<0.001	0.40
Moderate or severe LV dysfunction	17% (501)	19% (415)	12% (49)	11% (37)	<0.001	0.001	<0.001	0.56
Severe LV dysfunction	4% (134)	5% (121)	2% (10)	0.9% (3)	<0.001	0.011	<0.001	0.09
Preop pulmonary hyper- tension	3% (81)	1% (21)	2% (9)	15% (51)	<0.001	0.028	<0.001	<0.001
NYHA III or IV	58% (1718)	62% (1374)	50% (203)	41% (141)	<0.001	<0.001	<0.001	0.011
NYHA IV	8% (239)	9% (209)	1% (4)	8% (26)	<0.001	<0.001	0.26	<0.001
Preop CHF	17% (506)	14% (306)	15% (62)	40% (138)	<0.001	0.42	<0.001	<0.001
Preop atrial fibrillation	6% (187)	3% (76)	8% (31)	23% (80)	<0.001	<0.001	<0.001	<0.001
Additive EuroSCORE	4 [3-6]	4 [2-6]	6 [4-7]	5 [3-7]	<0.001	<0.001	<0.001	0.07

*Data given as medians [interquartile range] or percentages (number). * between three groups, † CAD vs AS, ‡ CAD vs MR, § AS vs MR. AS: aortic stenosis, BMI: body mass index, CAD: coronary artery disease, COPD: chronic obstructive pulmonary disease, eGFR: estimated glomerular filtration rate according to MDRD formula, LV: left ventricular, MR: mitral regurgitation, NYHA: New York Heart Association functional classification, CHF: congestive heart failure, EuroSCORE: European system for cardiac operative risk evaluation.*

Severe PHF occurred in 130 out of 2978 (4%) patients. After adjusting for known confounders of NT-proBNP (i.e., age, female sex, renal function, and obesity), the mean preoperative NT-proBNP levels in patients with

AS and MR, respectively, were 1.7-fold ($p<0.001$) and 1.4-fold ($p<0.001$) higher than in patients with CAD (Table 5).

Table 5. Multivariable linear regression for $\log_{10}$ NT-proBNP

	Adjusted coefficient*	95%CI	p
Age (years)	0.020	0.018 - 0.022	<0.001
Preop eGFR ($\text{mL} \cdot \text{min}^{-1} \cdot 1.73\text{m}^{-2}$)	-0.006	-0.007 - -0.005	<0.001
Male	ref		
Female	0.114	0.064 - 0.164	<0.001
CAD	ref		
MR	0.150	0.085 - 0.215	<0.001
AS	0.223	0.160 - 0.285	<0.001

Adjusted $R^2=0.215$, ANOVA for the model ($df=5$, $F=164.162$, $p<0.0001$) eGFR: estimated glomerular filtration rate according to MDRD formula, CAD: coronary artery disease, AS: aortic valve stenosis, MR: mitral valve regurgitation.

Patients that developed severe PHF had significantly higher preoperative levels of NT-proBNP compared to those without severe PHF (Table 6).

Table 6. Preoperative NT-proBNP in Patients with or without SPHF and postoperative mortality.

SPHF				Postoperative mortality		
	Yes	No	p	Yes	No	p
All	2060[753-4910]	310[120-910]	<0.001	1780[430-3200]	320[130-958]	<0.001
CAD	2345[655-5810]	280[110-750]	<0.001	1810[440-3260]	280[120-800]	<0.001
AS	1290[563-4018]	585[250-1498]	0.047	2835[230-10090]	595[260-1510]	0.53
MR	1650[925-3802]	345[97-1115]	<0.001	1245[430-2640]	395[110-1280]	0.08

Preoperative NT-proBNP (ng/L) given as medians [interquartile range]. SPHF: severe postoperative heart failure, All: all patients, CAD: coronary artery disease, AS: aortic valve stenosis, MR: mitral valve regurgitation.

For patients with CAD and MR, the ROC AUCs showed that preoperative NT-proBNP could discriminate well between patients who did and those who did not develop severe PHF (Fig. 5).

Figure 5. Discrimination of preoperative NT-proBNP with regard to SPHF in patients with CAD, AS, and MR. Preoperative NT-proBNP demonstrated significant discrimination according to ROC analysis with regard to SPHF in patients with CAD (A: AUC = 0.79, 95% CI 0.73–0.85, $p < 0.0001$; best cutoff 855 ng/L with a sensitivity of 73% and a specificity of 77%), AS (B: AUC = 0.66, 95% CI 0.51–0.81, $p = 0.047$; best cutoff 975 ng/L with a sensitivity of 71% and specificity of 65%), and MR (C: AUC = 0.80, 95% CI 0.72–0.87, $p < 0.0001$; best cutoff 800 ng/L with a sensitivity of 82% and specificity of 69%). ROC: receiver operating characteristics, SPHF: severe postoperative heart failure, AUC: area under the curve, CI: confidence interval.

No significant difference in postoperative mortality was found between groups (Table 7).

Table 7. Intra- and postoperative characteristics in all patients and subgroups.

	All patients (n=2978)	CAD (n=2226)	AS (n=406)	MR (n=346)	p*	p [†]	p [‡]	p [§]
Emergency operation	3% (88)	3% (69)	0.2% (1)	5% (18)	<0.001	0.001	0.044	<0.001
Critical preoperative state	1% (30)	1% (19)	0.5% (2)	3% (9)	0.005	0.76	0.004	0.016
CPB time (minutes)	84 [68-104]	78 [64-95]	90 [79-105]	134 [108-166]	<0.001	<0.001	<0.001	<0.001
Aortic cross-clamp time (minutes)	56 [44-70]	51 [40-62]	65 [56-75]	92 [76-116]	<0.001	<0.001	<0.001	<0.001
ICU stay (hours)	21 [18-23]	21 [17-23]	22 [18-23]	21 [20-23]	<0.001	0.048	<0.001	0.44
ICU stay >72 hours	6% (192)	6% (133)	6% (26)	10% (33)	0.043	0.74	0.012	0.11
Ventilation time (hours)	3 [2-5]	3 [2-5]	3 [2-5]	3 [2-6]	0.001	0.21	0.001	0.37
Ventilation time >48 hours	3% (100)	3% (65)	2% (8)	8% (27)	<0.001	0.29	<0.001	<0.001
Severe PHF	4% (130)	4% (88)	3% (14)	8% (28)	0.001	0.63	0.001	0.006
Postoperative stroke	0.7% (22)	0.9% (19)	0.5% (2)	0.3% (1)	0.43			
CK-MB POD1 (µg/L)	16 [10-28]	14 [9-23]	16 [12-23]	40 [26-68]	<0.001	<0.001	<0.001	<0.001
CK-MB POD1 >50 µg/L	12% (345)	9% (202)	5% (22)	35% (121)	<0.001	0.012	<0.001	<0.001
Creatinine elevation ≥ 50%	9% (262)	8% (186)	11% (46)	9% (30)	0.16			
Postoperative mortality	2% (53)	2% (43)	1% (4)	2% (6)	0.41			

*Data given as medians [interquartile range] or percentages (number). * between three groups, [†] CAD vs AS, [‡] CAD vs MR, [§] AS vs MR. AS: aortic stenosis, CAD: coronary artery disease, CPB: cardiopulmonary bypass, CK-MB: creatine kinase-MB isoenzyme, ICU: intensive care unit, MR: mitral regurgitation, POD1: first postoperative day, PHF: postoperative heart failure.*

The ROC curve for patients with CAD indicated that NT-proBNP had good predictive power for 30-day mortality (Fig. 6).

Figure 6. Discrimination of preoperative NT-proBNP with regard to postoperative mortality in patients with CAD. ROC analysis demonstrated an AUC of 0.78 (95% CI 0.71-0.85, $p < 0.001$; best cutoff 905 ng/L with a sensitivity of 67% and specificity of 77%). ROC: receiver operating characteristics, AUC: area under the curve, CI: confidence interval.

Study III

In a prospective, longitudinal, observational study, between June 2008 and January 2013, we investigated the dynamics of NT-proBNP and related them to one-year mortality in patients that underwent either SAVR or TAVI. The preoperative and postoperative characteristics are given in Table 8.

Table 8. Pre- and postoperative characteristics.

Variable	All-SAVR n=336	AS (SAVR) n=199	AS+CABG (SAVR) n=75	AR (SAVR) n=42	P Value*	AS (TAVI) n=126	p Value*	p Value**
Preoperative data								
Age (years)	70 [63-77]	70 [65-76]	75 [68-79]	60 [46-68]	0.08	82 [76-85]	<0.001	<0.001
Female gender	138 (41%)	100 (50%)	27 (36%)	3 (7%)	0.10	66 (52%)	<0.001	<0.001
EuroSCORE II	1.9 [1.2-3.5]	1.6 [1.1-2.7]	3.2 [1.8-5.6]	1.6 [0.8-2.6]	<0.001	5.0 [3.0-7.6]	<0.001	<0.001
Diabetes mellitus	50 (15%)	27 (14%)	19 (25%)	3 (7%)	0.06	24 (19%)	0.56	0.03
COPD	19 (6%)	9 (5%)	4 (5%)	3 (7%)		15 (12%)	0.08	
NYHA class III/IV	178 (53%)	107 (54%)	48 (64%)	11 (26%)	0.38	117 (93%)	<0.001	<0.001
Congestive heart failure	50 (15%)	22 (11%)	16 (21%)	6 (14%)	0.08	53 (42%)	<0.001	<0.001
P-Cystatin C (mg/L)	1.17 [1.1-1.35]	1.15 [0.99-1.30]	1.30 [1.10-1.43]	1.07 [0.95-1.31]	0.01	1.56 [1.26-1.90]	<0.001	<0.001
Previous cardiac surgery	4 (1%)	3 (2%)	1 (1%)	0 (0%)	>0.99	34 (27%)	<0.001	<0.001
LVEF (<45%)	41 (12%)	16 (8%)	10 (13%)	11 (26%)	0.55	21 (17%)	0.05	0.05
Elective	326 (97%)	197 (99%)	69 (92%)	41 (98%)	>0.99	124 (98%)	>0.99	0.03
Dyspnoea/fatigue	248 (74%)	147 (74%)	60 (80%)	25 (60%)	0.88	109 (87%)	0.02	0.005
AP/CHF/Syncope	149 (44%)	87 (44%)	41 (55%)	11 (26%)	0.32	75 (60%)	0.02	<0.001
Waiting time (days)	126 [89-170]	130 [95-177]	105 [54-159]	130 [85-202]		121 [49-232]		0.05
Postoperative outcome								
P-Cystatin C (mg/L)		1.34 [1.13-1.63]	1.45 [1.25-1.87]	1.09 [1.01-1.25]	0.08	1.62 [1.34-1.95]	<0.001	<0.001
AF at discharge	30 (9%)	20 (10%)	4 (5%)	2 (5%)		14 (11%)		0.38
Stroke	3 (1%)	1 (0.5%)	1 (1%)	1 (2%)		3 (2%)		0.49
PMI	13 (4%)	4 (2%)	6 (8%)	1 (2%)		5 (4%)		0.12
30-day mortality	3 (1%)	1 (0.5%)	2 (3%)	0 (0%)	0.37	9 (7%)	>0.99	0.003
1-year mortality	11 (3%)	4 (2%)	6 (8%)	1 (2%)	0.06	16 (13%)	>0.99	<0.001

Values are given as n (%) and median (25th to 75th percentile).

*=Multiple comparisons of mean ranks for all groups p Value (2-tailed), post-hoc comparisons of mean ranks of all pairs of groups and chi-square 2x2 with Bonferroni correction for dichotomous variables. p Values after each variable display comparison with AS (SAVR) group
 **=Kruskal-Wallis test for comparison of the subgroups for continuous data and chi-square test in large contingency table for dichotomous data. SAVR, surgical aortic valve replacement; AS, aortic stenosis; CABG, coronary artery bypass grafting; AR, aortic regurgitation; TAVI, transcatheter aortic valve intervention; COPD, chronic obstructive pulmonary disease; NYHA, New York Heart Association; LVEF, left ventricular ejection fraction; AP, angina pectoris; CHF, congestive heart failure; PMI, perioperative myocardial infarction.

We observed a statistically significant increase in NT-proBNP, which was elicited by the aortic valve intervention (Fig. 7).

Figure 7. The NT-proBNP levels for surgical aortic valve replacement (SAVR) patients (A), transcatheter aortic valve replacement (TAVI) patients (C), and for the three large subgroups of SAVR patient based on cardiac pathology (B, D, and E). Data are shown as median and 25th to 75th percentile. Wilcoxon signed rank test with Bonferroni correction was used for repeated comparisons within groups.

Among patients that underwent SAVR, NT-proBNP levels peaked on the third postoperative day. In comparison, patients that underwent TAVI showed a NT-proBNP peak on the first postoperative day. Despite a median waiting time of four months from the preoperative evaluation to the intervention, we observed no increase in NT-proBNP levels. At the six-month postoperative follow-up, the levels of NT-proBNP had fallen to or below preoperative values in all patients. In patients that underwent SAVR, both the preoperative and early postoperative NT-proBNP values were associated with one-year mortality, but this association was not observed for patients that underwent TAVI (Table 9, 10).

Table 9. NT-proBNP (ng/L) values measured before and after surgery in relation to 1-year mortality.

	All	Dead	Survivors	p Value
All-SAVR n=336		n=11 (3%)	n=325 (97%)	
Preoperative	490 [180-1120]	1250 [960-3580]	460[170-1090]	<0.001
Postoperative day-1	2580 [1540-4000]	4770 [2680-13600]	2550[1540-3840]	0.02
Postoperative day-3	3770 [2540-6310]	9480 [4880-12300]	3730[2460-6130]	<0.001
AS (SAVR) n=199		n=4 (2%)	n=195 (98%)	
Preoperative	430 [170-1030]	2415 [1120-7790]	410 [170-990]	0.01
Postoperative day-1	2545 [1575-3940]	1535 [4410-9450]	2530 [1565-3840]	0.01
Postoperative day-3	3800 [2580-6520]	7820 [6030-10830]	3750 [2580-6210]	0.03
AS+CABG (SAVR) n=75		n=6 (8%)	n=69 (92%)	
Preoperative	730 [260-1770]	1185 [960-2600]	720 [230-1770]	0.04
Postoperative day-1	3245 [1915-4730]	4770 [2680-14000]	3220 [1890-4630]	0.26
Postoperative day-3	4675 [2780-7910]	11700 [10500-12300]	4350 [2760-7110]	0.04
AS (TAVI) n=126		n=16 (13%)	n=110 (87%)	
Preoperative	2030 [1030-4960]	2525 [1465-4260]	1990 [920-5120]	0.87
Postoperative day-1	3440 [1770-5320]	4780 [1950-5750]	3325 [1710-5220]	0.25
Postoperative day-3	3050 [1350-6070]	4840 [3260-10900]	2615 [1345-5595]	0.10

Values are given as median [25th to 75th] percentile. NT-proBNP, N-terminal pro-B-type natriuretic peptide; SAVR, surgical aortic valve replacement; AS, aortic stenosis; CABG, coronary artery bypass grafting; AR, aortic regurgitation; TAVI, transcatheter aortic valve intervention.

Table 10. ROC analysis with AUC for NT-proBNP and 1-year mortality

	Preoperative	Postoperative day 1	Postoperative day 3
All-SAVR			
AUC [95 % CI]	0.79 [0.71-0.88]	0.71 [0.52-0.89]	0.79 [0.61-0.94]
<i>p</i> Value	0.001	0.03	0.002
NT-proBNP cut-off (ng/L)	955	4040	4815
Sensitivity/Specificity	0.82/0.71	0.70/0.76	0.90/0.63
AS (SAVR)			
AUC [95 % CI]	0.86 [0.76-0.96]	0.85 [0.76-0.94]	0.82 [0.70-0.94]
<i>p</i> Value	0.014	0.017	0.03
NT-proBNP cut-off (ng/L)	975	4040	4855
Sensitivity/Specificity	1.0/0.74	1.0/0.78	1/0.73
AS+CABG (SAVR)			
AUC [95 % CI]	0.75 [0.60-0.90]	-	0.78 [0.46-1.0]
<i>p</i> Value	0.045	-	0.042
NT-proBNP cut-off (ng/L)	915	-	10035
Sensitivity/Specificity	0.83/0.64	-	0.80/0.93

ROC, receiver operations characteristics; AUC, area under the curve; NT-proBNP, N-terminal pro-B-type natriuretic peptide; SAVR, surgical aortic valve replacement; AS, aortic stenosis; CABG, coronary artery bypass grafting.

NT-proBNP levels were higher in patients that underwent TAVI than in patients that underwent SAVR, both preoperatively and at the six-month follow-up (Table 11).

Table 11. Comparison of NT-proBNP (ng/L) between groups.

Time point	AS (SAVR) n=199	AS+CABG (SAVR) n=75	p Value*	AR (SAVR) n=42	p Value*	AS (TAVI) n=126	p Value*	p Value between groups**
Enrolment	380 [180-920]	570 [245-1125]	0.83	270 [200-860]	>0.99	1790 [780-4260]	<0.001	<0.001
Index***	0.36 [0.19-0.96]	0.51 [0.18-0.99]	>0.99	0.46 [0.26-0.73]	>0.99	1.13 [0.50-2.83]	<0.001	<0.001
Preoperative	430 [170-1030]	730 [260-1770]	0.47	215 [110-640]	0.26	2030 [1030-4960]	<0.001	<0.001
Index***	0.38 [0.18-0.99]	0.54 [0.18-1.12]	>0.99	0.32 [0.13-0.62]	>0.99	1.33 [0.73-3.02]	<0.001	<0.001
Postoperative day 1	2545 [1575-3940]	3245 [1915-4730]	0.39	1515 [1015-2295]	0.001	3340 [1770-5320]	0.11	<0.001
Index***	2.38 [1.68-3.64]	2.42 [1.69-2.68]	>0.99	1.94 [1.54-2.75]	>0.99	2.13 [1.15-3.44]	0.49	0.17
Postoperative day 3/4	3800 [2580-6520]	4675 [2780-7910]	0.81	2670 [1420-4150]	0.007	3050 [1350-6070]	0.002	<0.001
Index***	3.74 [2.59-5.46]	3.87 [2.23-5.91]	>0.99	3.09 [2.08-5.23]	>0.99	1.82 [0.82-3.18]	<0.001	<0.001
6-months follow-up	300 [170-650]	470 [250-820]	0.47	215 [100-600]	>0.99	1185 [480-2175]	<0.001	<0.001
Index***	0.29 [0.17-0.54]	0.42 [0.17-0.64]	>0.99	0.34 [0.15-0.60]	>0.99	0.80 [0.37-1.37]	<0.001	<0.001

Values are given as median [25th to 75th percentile].

*=Multiple comparisons of mean ranks for all groups p Value (2-tailed), post-hoc comparisons of mean ranks of all pairs of groups, p Values after each variable display comparison with AS (SAVR) group

**=Kruskal-Wallis test for comparison of the subgroups.

*** = The ratio of NT-proBNP to the reference NT-proBNP value for age; 450 ng/L for >50 years, 900 ng/L for 50-75 years, and 1800 ng/L for >75 years. AS, aortic stenosis; SAVR, surgical aortic valve replacement; CABG, coronary artery bypass grafting; AR, aortic regurgitation; TAVI, transcatheter aortic valve intervention.

Study IV

This study included 273 patients scheduled for aortic valve surgery for AS. Pre- and postoperative LV filling pressures were evaluated in 247 of 273 patients. Patient demographics and preoperative data are shown in Table 12.

Table 12. Baseline characteristics^a.

Variable	Preoperative low LV filling pressure (n=193)	Preoperative high LV filling pressure (n=54)	P value
Age (yrs.)	70 [65-76]	75 [67-80]	0.01
Sex female	89 (46%)	24 (44%)	0.82
BMI (kg/m ²)	27 [24-30]	27 [25-30]	0.36
BSA (m ²)	1.9 [1.8-2.1]	1.9 [1.8-2.1]	0.88
Hypertension	99 (51%)	34 (63%)	0.13
Diabetes mellitus (insulin or oral treatment)	28 (15%)	13 (24%)	0.09
Angina pectoris	51 (26%)	23 (43%)	0.02
CHF	12/191 (6%)	15/53 (28%)	<0.001
EuroSCORE II	1.6 [1.1-2.7]	3.1 [1.6-5.4]	<0.001
NYHA III/IV	99(52%)	36 (67%)	0.04
Biochemistry			
P-Cystatin C (mg/L)	1.1 [1.0-1.3] n=184	1.3 [1.0-1.4] n=53	0.003
P-Creatinine clearance (ml/min/m ²)	74 [61-92]	64 [48-81]	0.006
Blood hemoglobin (g/L)	140 [133-148]	132 [123-146]	0.01
NT-proBNP (ng/L)	320 [170-775] n=189	1100 [510-3030] n=53	<0.001
NT-proBNP >960 (ng/L)	32/189 (17%)	30/53 (57%)	<0.001
Echocardiography			
Systolic LVF			
Normal/mild dysfunction	186/191 (97%)	45/53 (85%)	0.002
LV mass index (g/m ²)	125 [101-146] n=158	137 [109-172] n=44	0.05
- >95 (female) ^b	52/72 (72%)	16/18 (89%)	0.22
- >115 (male) ^c	65/86 (76%)	20/26 (77%)	0.89
Diastolic LVF			
E/A	0.8 [0.7-0.9] n=193	1.6 [1.2-2.1] n=54	
E/e ⁺	8 [6-10] n=191	8 [6.5-9.5] n=54	
- >14 ^d	96/193 (50%)	43/54 (80%)	
LAA index (cm ² /m ²)	11.3 [9.8-12.9] n=193	12.9 [11.2-15.1] n=54	
- >13 ^e	45/193 (23%)	26/54 (48%)	
PV s / PV d ^f	1.5 [1.3-1.8] n=192	0.8 [0.5-1] n=54	
Aortic valve			
EOA (cm ²)	0.6 [0.5-0.8] n=192	0.6 [0.5-0.8] n=54	0.10
iEOA (cm ² /m ²)	0.3 [0.3-0.4] n=192	0.3 [0.2-0.4] n=54	0.12
Mean pressure gradient (mmHg)	55 [44-68] n=188	49 [36-69] n=53	0.11

^a Data is given as medians [IQR] or numbers (%).

BMI = body mass index, CHF = Congestive Heart Failure, EuroSCORE II = European system for cardiac operative risk evaluation, NYHA = New York Heart Association functional classification, LVF = Left ventricular function, LV mass index = Left Ventricular mass/BSA, BSA = Body Surface Area, ^b = upper limit values for normal LV mass for females, ^c = upper limit values for normal LV mass for males, E/A = early diastolic mitral flow velocity/late diastolic mitral flow velocity, E/e' = early diastolic mitral flow velocity/early diastolic myocardial velocity, ^d = reference value for E/e' indicating high filling pressure (Nagueh S F et al J Am Soc Echocardiogr 2016), LAA index = Left Atrial Area/BSA, ^e = reference value for enlarged left atrium (Kou s et al Eur Heart J Cardiovasc Imaging 2014;15(6):680-90), ^f = pulmonary vein systolic flow velocity / pulmonary vein diastolic flow velocity, EOA = Effective Orifice Area, iEOA=EOA/BSA

High LV filling pressure was observed in 22% (n=54) of patients. Among those with elevated preoperative LV filling pressure, half (27/54, 50%) had improved at the six-month postoperative evaluation. Among the 193 patients that presented with low LV filling pressure at the time of surgery, 24 (12%) had deteriorated to high LV filling pressures at six months (Fig. 8).

Figure.8 Diastolic function categorized as low or high filling pressure before and 6 months after surgical aortic valve replacement (SAVR) with corresponding levels of NT-proBNP (ng/L).

Peri- and postoperative data and adverse events for patients with low and high preoperative LV filling pressures are presented in Table 13.

Table 13. Perioperative data and adverse events

Variable	Preoperative low LV filling pressure (n=193)	Preoperative high LV filling pressure (n=54)	P value
Concomitant CABG	48 (25%)	21 (39%)	0.04
Elective surgery	189 (98%)	54 (100%)	0.58
Redo surgery	3 (1.6%)	1 (1.8%)	>0.99
Cross-clamp time (min)	70 [61-88]	70 [62-87]	0.87
ECC-time (min)	96 [83-117]	101 [85-126]	0.42
Outcome			
Time on ventilator (hrs.)	3 [2-5]	4 [3-8]	0.04
Time in ICU (hrs.)	21 [17-22]	22 [21-24]	0.02
CK-MB day 1	19 [14-27]	18 [12-27] n=52	0.59
P-Creatinine (μmol/L) maximum	87 [70-106] n=192	106 [83-134]	<0.001
P-Creatinine (μmol/L) at discharge	81 [67-99] n=192	88 [76-119]	0.003
P-Cystatin C (mg/L) Day 3	1.3 [1.1-1.6] n=180	1.6 [1.3-1.9]	0.002
Postoperative AF	84/193 (44%)	24/53 (45%)	0.72
Stroke	2/193 (1.0%)	0	>0.99
PMI	7/193 (3.6%)	2 (3.8%)	>0.99
PHF	14 (7.3%)	12 (22.2%)	0.002
Reoperation valve failure or PVL	0	0	
Reoperation DSWI	0	1 (1.9%)	0.22
30 day mortality	0	1 (1.9%)	>0.22
1 year mortality	4 (2.1%)	2 (3.7%)	>0.61
Long term mortality*	38 (20%)	14 (26%)	0.32

^a Data is given as medians [IQR] or numbers (%).

AF= Atrial Fibrillation, CABG=Coronary artery bypass surgery, ECC=Extra corporeal circulation, ICU=Intensive care unit, PMI=Perioperative myocardial infarction, PHF=Postoperative heart failure, PVL= Paravalvular leakage, DSWI=Deep Sternal Wound infection. *= Median follow-up 7.1 (4.1-9.1) years.

Both the bypass time and the cross-clamp time were longer in the group that experienced a deterioration in low LV filling pressures, compared to those that maintained low LV filling pressures, at the six-month postoperative echocardiographic evaluation (Table 14).

Table 14. Data on patients with preoperative low filling pressure ^a

Variable	Low preoperative LV filling pressure sustained n=153	Low preoperative LV filling pressure deteriorated n=24	P value
Age (yrs.)	70 [65-76]	70 [64-77]	0.98
Female	70/153 (46%)	9/24 (38%)	0.45
BMI (kg/m²)	27 [25-30]	26 [24-29]	0.29
BSA (m²)	1.9 [1.8-2.1]	2.0 [1.8-2.1]	0.38
Hypertension	77/153 (50%)	13/24 (54%)	0.73
Diabetes mellitus (insulin or oral treatment)	23/153 (15%)	2/24 (8%)	0.38
Angina pectoris	40/153 (26%)	9/24 (38%)	0.25
CHF	8/151 (5%)	2/24 (8%)	0.54
EuroSCORE II	1.6 [1.1-2.7]	1.8 [1.2-3.1]	0.45
NYHA III/IV	79/153 (52%)	11/24 (46%)	0.6
Concomitant CABG	35/153 (23%)	10/24 (42%)	0.05
Elective surgery	149/153 (97%)	24/24 (100%)	>0.99
Redo surgery	2/153 (1%)	0/24	>0.99
Biochemistry			
P-Creatinin C (mg/L)	1.4 [1-1.3] n=145	1.1 [1-1.3] n=23	0.71
P-Creatinine clearance (ml/min/m²)	74 [61-91]	74 [52-106]	0.85
Blood hemoglobin (g/L)	140 [133-149]	142 [136-144]	0.73
NT-proBNP (ng/L)	290 [158-723] n=150	570 [240-940] n=23	0.09
NT-proBNP>960 (ng/L)	22/150 (15%)	5/23 (22%)	0.37
Echocardiography			
Normal/mild dysfunction	147/151 (97%)	23/24 (96%)	0.53
LV mass index (g/m²)	126 [103-147] n=125	119 [97-128] n=21	0.27
- >95 (female) ^b	41/55 (75%)	6/9 (67%)	0.69
- >115 (male) ^c	54/70 (77%)	8/12 (67%)	0.47
EOA (cm²)	0.6 [0.5-0.7] n=152	0.7 [0.6-0.8]	0.28
iEOA (cm²/m²)	0.3 [0.3-0.4] n=152	0.3 [0.3-0.4]	0.49
Mean pressure gradient (mmHg)	55 [44-68] n=149	52 [43-62] n=23	0.38
Perioperative data			
Cross-clamp time (min)	68 [60-82]	90 [64-100]	0.02
ECC-time (min)	94 [81-113]	120 [88-133]	0.02
Time on ventilator (hrs.)	3 [2-5]	3 [2-5]	0.12
Time in ICU (hrs.)	21 [17-22]	22 [18-23]	0.22

Postoperative		
P-Cystatin C (mg/L) Day 3	1.3 [1.1-1.5] n=143	1.3 [1.1-1.9] n=21
CK-MB DI	19 [14-26]	31 [14-51]
P-Creatinine (μmol/L) maximum	87 [72-103]	97 [74-130]
P-Creatinine (μmol/L) discharge	81 [68-95]	90 [71-107]
Postoperative AF	70/153 (46%)	9/24 (38%)
Stroke	1/153 (0.7%)	0/24 (0%)
PMI	4/153 (2.6%)	2/24 (8%)
PHF	9/153 (6%)	2/24 (8%)
Long term mortality ^a	26/153 (17%)	7/24 (29%)
Echocardiography 6-months follow up		
Normal/mild dysfunction	148/151 (98%)	22/24 (92%)
VTI (L/VOI) ^b (cm)	22 [19-25] n=152	22 [18-27] n=22
LV mass index (g/m ²)	98 [84-110] n=108	93 [82-109] n=23
- >95 (female)	18/47 (38%)	2/9 (22%)
- >115 (male)	12/61 (20%)	4/14 (29%)
LV mass index regression* (g/m ²)	25 [1-41] n=91	13 [4-37] n=20
E/A	0.9 [0.8-1.1]	1.6 [1.1-2.2]
E/é	11.0 [9.0-12.5]	9.3 [7.6-13.1]
- >14	27/153 (18%)	2/24 (8%)
LAA-index (cm ² /m ²)	11.5 [10.3-12.8]	11.4 [9.8-14.8]
- >13	31/153 (20%)	8/24 (33%)
PV s /PV d ^c	1.3 [1.2-1.6]	0.8 [0.7-1]
Velocity max (m/s)	2.5 [2.2-2.7]	2.5 [2.3-2.7] n=23
FOA (cm ²)	1.4 [1.2-1.6]	1.4 [1.1-1.5] n=20
PPM	119/153 (78%)	18/24 (90%)
Severe PPM	50/153 (33%)	7/24 (35%)
Mean pressure gradient (mmHg)	13 [11-16]	14 [12-17] n=22
NT-proBNP 6-months follow up		
NT-proBNP (ng/L)	260 [143-420] n=144	480 [200-1160] n=23
NT-proBNP>960 (ng/L)**	22/150 (15%)	5/23 (22%)
		0.003
		0.43

BMI = body mass index, CHF = Congestive Heart Failure, EuroSCORE II = European system for cardiac operative risk evaluation, NYHA = New York Heart Association functional classification, LVF = Left ventricular function, LV mass index = Left Ventricular mass/BSA, BSA = Body Surface Area, EAO = Effective Orifice Area.

^a Data is given as medians [IQR] or numbers (%).

^b = upper limit values for normal LV mass for females,

^c = upper limit values for normal LV mass for males, E/A = early diastolic filling velocity/late diastolic filling velocity, E/e' = early diastolic filling velocity/early diastolic myocardial velocity,

^d = reference value for E/e' indicating high filling pressure (Nagueh S F et al J Am Soc Echocardiogr 2016), LAA index = Left Atrial Area/BSA,

^e = reference value for enlarged left atrium (Kou s et al Eur Heart J Cardiovasc Imaging 2014;15(6):680-90),

^f = pulmonary vein systolic flow velocity/ pulmonary vein diastolic flow velocity, ^g = Median follow-up 7.1 (4.1–9.1) years * = Preoperative LV mass index-Postoperative LV mass index, **= best cut off point for preoperative NT-proBNP in regard for discriminating 5 year mortality.

Coronary artery bypass surgery (CABG) was significantly more common in patients that experienced a deterioration in diastolic function (n=10, 42%) compared to those that maintained diastolic function (n=35, 23%; $p=0.049$). At six months after surgery, patients with improved LV filling pressures had higher NT-proBNP levels (1910 [623-4410] ng/L) than patients that retained high LV filling pressures (NT-proBNP: 760 [260-1760] ng/L; $p=0.035$; Table 15).

Table 15. Data on patients with preoperative high filling pressure^a

Variable	High preoperative LV filling pressure improved n=27	High preoperative LV filling pressure sustained n=19	P value
Age (yrs.)	70 [66-78]	78 [68-80]	0.15
Female	10/27 (37%)	11/19 (58%)	0.16
BMI (kg/m ²)	27 [25-31]	27 [25-30]	0.93
BSA (m ²)	1.9 [1.8-2.1]	1.9 [1.8-2.2]	0.79
Hypertension	18/27 (67%)	13/19 (68%)	0.90
Diabetes mellitus (insulin or oral treatment)	5/27 (19%)	7/19 (37%)	<0.001
Angina pectoris	9/27 (33%)	10/19 (53%)	0.19
CHF	7/26 (27%)	4/19 (21%)	0.74
EuroSCORE II	2.7 [1.2-4.3]	3.8 [1.9-5.4]	0.66
NYHA III/IV	20/27 (74%)	11/19 (58%)	0.25
Concomitant CABG	11/27 (41%)	7/19 (37%)	0.79
Elective surgery	27/27 (100%)	19/19 (100%)	-
Redo surgery	1/27 (4 %)	0/19	>0.99
Biochemistry			
P-Cystatin C (mg/L)	1.3 [1.0-1.4] n=26	1.3 [1.2-1.4] n=19	0.53
P-Creatinine clearance (ml/min/m ²)	64 [49-82]	69 [51-81]	0.88
Blood hemoglobin (g/L)	137 [127-150]	131 [117-145]	0.47
NT-proBNP (ng/L)	1910 [623-4410] n=26	760 [260-1760]	0.035
NT-proBNP>960 (ng/L)	18/26 (69%)	7/19 (37%)	0.03
Echocardiography			
Normal/mild dysfunction	23/27 (85%)	17/18 (100%)	0.63
LV mass index (g/m ²)	143 [127-178] n=23	111 [100-151] n=16	0.02
- >95 (female) ^b	5/9 (56%)	4/8 (50%)	>0.99
- >115 (male) ^c	8/14 (57%)	4/8 (50%)	>0.99
EOA (cm ²)	0.5 [0.5-0.8]	0.6 [0.4-0.8]	0.60
iEAO (cm ² /m ²)	0.3 [0.2-0.4]	0.3 [0.2-0.4]	0.60
Mean pressure gradient (mmHg)	49 [36-75] n=26	51 [38-67]	0.94
Perioperative data			
Cross-clamp time (min)	72 [59-86]	68 [62-98]	0.66
ECC-time (min)	103 [88-125]	100 [86-135]	0.91
Time on ventilator (hrs.)	4.5 [2.8-11.7]	3.9 [2.7-7.9]	0.45
Time in ICU (hrs.)	21.8 [20-27]	21.5 [20.8-23.5]	0.92

Postoperative data		
P-Cystatin C (mg/L) Day 3	1.3 [1.2-1.9] n=24	1.7 [1.3-2.0] n=18
CK-MB DI	16 [13-26]	21 [13-29]
P-Creatinine (μmol/L) maximum	109 [78-126]	102 [82-137]
P-Creatinine (μmol/L) discharge	85 [73-114] n=26	90 [72-122]
AF	7/26 (30%)	11/19 (58%)
Stroke	0	0
PMI	1/26 (4%)	0
PHF	7/27 (26%)	1/19 (20%)
Long term mortality ^p	8/27 (30%)	2/19 (11%)
Echocardiography 6-months follow up		
Normal/mild dysfunction	21/26 (81%)	18/19 (95%)
VTI (LVOI) ^a (cm)	23 [18-26] n=26	21 [19-25] n=18
LV mass index (g/m ²)	116 [95-134] n=22	98 [82-125] n=17
- >95 (female)	5/7 (71%)	4/9 (44%)
- >115 (male)	8/15 (53%)	4/8 (50%)
LV mass index regression* (g/m ²)	32 [1-47] n=19	30 [9-44] n=15
E/A	0.9 [0.7-1.1]	1.6 [1.2-2]
E/ε	9.8 [7.5-11.8]	10.0 [9-12.0]
- >14	3/226 (12%)	0/19
LAA-index (cm ² /m ²)	12.8 [11.2-13.8]	13.4 [10.9-14.0]
- >13	12/27 (44%)	12/19 (63%)
PV s /PV d ^b	1.3 [1.2-1.5]	0.7 [0.6-1]
Velocity max (m/s)	2.6 [2.3-2.9]	2.5 [2.1-2.9]
EOA (cm ²)	1.3 [0.9-1.4] n=24	1.3 [1.0-1.6] n=18
PPM	21/27 (88%)	14/19 (74%)
Severe PPM	15/27 (63%)	8/19 (42%)
Mean pressure (mmHg)	15 [11-20]	13 [8-17]
NT-proBNP 6-months follow up		
NT-proBNP (ng/L)	620 [255-950] n=25	800 [495-1090] n=17
NT-proBNP>960 (ng/L)**	18/26 (20%)	7/19 (26%)
		0.21
		0.03

BMI = body mass index, CHF = Congestive Heart Failure, EuroSCORE II = European system for cardiac operative risk evaluation, NYHA = New York Heart Association functional classification, LVF = Left ventricular function, LV mass index = Left Ventricular mass/BSA, BSA = Body Surface Area, EAO = Effective Orifice Area.

^a Data is given as medians [IQR] or numbers (%).

^b = upper limit values for normal LV mass for females,

^c = upper limit values for normal LV mass for males, E/A = early diastolic filling velocity/late diastolic filling velocity, E/e' = early diastolic filling velocity/early diastolic myocardial velocity,

^d = reference value for E/e' indicating high filling pressure (Nagueh S F et al J Am Soc Echocardiogr 2016), LAA-index = Left Atrial Area/BSA,

^e = reference value for enlarged left atrium (Kou s et al Eur Heart J Cardiovasc Imaging 2014;15(6):680-90),

^f = pulmonary vein systolic flow velocity/ pulmonary vein diastolic flow velocity, ^g= Median follow-up 7.1 (4.1–9.1) years * = Preoperative LV mass index-Postoperative LV mass index, **= best cut off point for preoperative NT-proBNP in regard for discriminating 5 year mortality.

Patients with high LV filling pressures had higher NT-proBNP levels, both pre- and postoperatively, compared to patients with low LV filling pressures (Tables 12, 13). However, both groups showed significant reductions in NT-proBNP levels postoperatively (Fig. 8).

Pre- and postoperative NT-proBNP levels in patients with low and high LV filling pressures are presented in Figure 9.

Figure 9. NT-proBNP pre- and postoperatively in patients with Low vs. High LV filling pressure before surgery. NT-proBNP was significantly higher in patients with High LV filling pressure both preoperatively and postoperatively ($p < 0.001$).

The relationships between pre- and postoperative NT-proBNP levels and the pre-operative left atrial area index are presented in Figure 10.

Figure 10. NT-proBNP pre- and postoperatively in patients with Normal vs. preoperative High LAA index before surgery. NT-proBNP was significantly higher in patients with High LAA index both preoperatively and postoperatively ($p<0.001$).

Figure 11 shows the relationship between pre- and postoperative NT-proBNP levels and preoperative E/e values that were below or above 14.

Figure 11. NT-proBNP pre- and postoperatively in patients with E/e <14 vs. E/e >14 before surgery. NT-proBNP was significantly higher in patients with E/e >14 both preoperatively ($p<0.001$) and postoperatively ($p=0.01$).

The proportion of patients with normal LV systolic function was lower in the high LV filling pressure group ($n=34$, 63%) than in the low LV filling pressure group ($n=174$, 90%; $p<0.001$). Postoperatively, LV mass decreased significantly in both groups (Table 13). Although the LV mass decline was similar in both groups, those with high preoperative LV filling pressures had higher postoperative LV-mass indices than those with low preoperative LV filling pressures (Table 13). The median follow-up for this study was 7.1 years (range: 4.1 to 9.1 years). During that period, 63 patients died (23%). Variables associated with long-term mortality, based on a Cox regression analysis, are presented in Table 16.

Table 16. Cox regression mortality, univariable and multivariable.

Variable	Regression Coef- ficient (B)	SE	p-value	RR	95 % CI
Age (Yrs.)	0.07	0.02	<0.001	1.07	1.03-1.10
Male	Ref.				
Female	-0.63	0.27	0.02	0.53	0.31-0.90
BMI	-0.003	0.03	0.92	1.00	0.94-1.06
P-Creatinine clearance (ml/min/m ²)	-0.02	-0.04	<0.001	1.00	0.96-0.99
CCT (min.)	0.01	0.006	0.08	1.01	1.00-1.02
ECC (min.)	0.009	0.003	0.003	1.01	1.00-1.01
NT-proBNP>960 (ng/L)	1.3	0.26	<0.001	3.59	2.15-6.0
DM	0.69	0.28	0.01	2.01	1.15-3.51
HT	0.44	0.27	0.09	1.56	0.93-2.62
Cardiac failure	1.01	0.29	<0.001	2.75	1.55-4.86
Concomitant CABG	0.69	0.26	0.008	1.99	1.20-3.30
Preoperative high filling pressure	0.35	0.31	0.26	1.42	0.77-2.63
Systolic function					
Mild - severe LV dysfunction	0.77	0.32	0.02	2.17	1.15-4.08
PHF	1.23	0.28	<0.001	3.44	1.98-5.95
PMI	1.33	0.43	0.002	3.76	1.62-8.74
Final model					
NT-proBNP>960 (ng/L)*	0.90	0.30	0.002	2.47	1.38-4.41
Age (Yrs.)	0.06	0.02	0.004	1.06	1.02-1.10
DM (insulin or oral treatment)	0.87	0.31	0.005	2.38	1.30-4.32
Female	-0.87	0.32	0.006	0.42	0.22-0.78

BMI=Body mass index, CCT=Cross-clamp time, ECC= Extra corporeal circulation, DM=Diabetes Mellitus, HT=Hypertension, CABG=Coronary artery bypass surgery, PHF=Postoperative heart failure, PMI=Perioperative myocardial infarction (defined as Troponin T ≥ 2000 ng/L on the third postoperative day or later), *= best cut off point for preoperative NT-proBNP in regard for discriminating 5 year mortality.

No significant differences in long term mortality depending on pre- or postoperative high LV filling pressure were found (Fig.12, panel A and B). A ROC analysis showed that a preoperative NT-proBNP level of 960 ng/L was the best cut-off value for predicting all-cause five-year mortality; the AUC was 0.7 (95% CI: 0.6-0.8, p=0.001). Figure 12 (panels C and D) shows cumulative survival curves, constructed according to the Kaplan-Meier method.

Figure 12. Kaplan-Meier survival curves categorized according to preoperative diastolic function (A) and postoperative diastolic function at the 6 months follow up (B). Episode of PHF (C) and preoperative NT-proBNP above or below 960 ng/L (D).

DISCUSSION

Although aortic valve surgery typically provides excellent results, even in older patients with a high burden of comorbidities, PHF remains a considerable cause of postoperative morbidity and mortality ⁶. Currently, we have TAVI in our armament for treating the oldest and sickest patients; nevertheless, these patients also experience cardiac-related complications in association with the intervention ⁷⁰. Some issues have remained unanswered, including; how to select the intervention that will provide the most benefit to each patient; how to optimize the timing of an intervention; and how long can we refrain from an intervention in asymptomatic patients, before causing more harm than good? This dissertation cannot answer all these questions, but hopefully, our findings will add to existing knowledge to provide a better understanding of these matters.

PHF

No definition of PHF or low cardiac output syndrome exists that is universally accepted. Therefore, different definitions are used in literature ^{86, 101}. The difficulty in finding a definition for PHF can be appreciated by considering the editorial published by the journal, Cardiovascular Research, where they endeavoured to find a definition of heart failure by surveying their reviewers ¹⁰². We overcame this issue by devising the definition of PHF described in the Methods section. Bias was addressed by the use of a blinded Clinical Endpoints committee.

A previous study showed that PHF was an independent risk factor for late mortality after SAVR for AS ⁸. In that analysis, the weight of the preoperative risk score (EuroSCORE) was not included. Although the EuroSCORE was created to predict operative mortality after cardiac surgery, it can also predict long-term outcome ⁸¹. The results from our work confirmed the

concept that patients at high risk of operative mortality carried that risk over time. However, we also provided a new finding, which was the serious effect PHF had over time in patients that were assigned to a low-risk group. We found that patients at low risk that were treated for PHF, and otherwise successfully discharged from the hospital, were in danger of a premature death. The European Society of Cardiology and The European Association of Cardiothoracic Surgery, in their latest (2017) guidelines for the management of valvular heart disease, emphasized that heart failure after valve surgery should be treated according to relevant guidelines for heart failure ³⁵. This guideline indicated that surgeons must emphasize in the discharge records that a patient had experienced an episode of PHF, and that increased attention is warranted during follow-up. This guideline is important, because active surveillance and treatment has been shown to improve the prognosis of patients with chronic heart failure ^{103, 104}. A previous report on this particular cohort identified five preoperative risk factors (pulmonary hypertension, severe systolic LV dysfunction, history of congestive heart failure, hypertension, and unstable preoperative hemodynamics) and two intra-operative risk factors (long cross-clamp times and a perioperative myocardial infarction) for PHF ⁸². We could not explain why patients at low risk that developed PHF had such a poor prognosis; neither severe systolic dysfunction nor the other known risk factors for PHF emerged as independent risk factors for late mortality ⁸. Diastolic function was not investigated in our previous works on PHF, although diastolic dysfunction has been reported to have a negative effect on long-term survival after surgery for AS ^{58, 105}. Taking this observation into account, we surmised that diastolic dysfunction could be the missing link in understanding PHF development. Consequently, we hypothesized that a preoperative evaluation of diastolic dysfunction, perhaps with an adjunct of available biomarkers for heart failure, such as NT-proBNP, might shed light on PHF development. In our second study, we showed that NT-proBNP could predict short-term mortality in patients with CAD. This

finding provided prognostic information about patients with CAD and MR, with regard to the development of severe PHF.

NT-proBNP and PHF

The results of the second study showed that valvular pathologies, such as AS and MR, were associated with higher preoperative NT-proBNP levels than CAD, upon admission to surgery. This finding was consistent with previous studies¹⁰⁶⁻¹¹³. The novelty of this finding was that it held true, even after adjusting for known confounders. Several confounding factors that are not directly related to underlying heart disease are known to increase NT-proBNP, including older age, female gender, and renal function¹¹⁴⁻¹¹⁶; in contrast, only one of these confounding factors, obesity, was associated with lower levels of NT-proBNP¹¹⁷.

Our results suggested that the release of NT-proBNP was more dependent on pressure overload (e.g., in AS) or volume overload (e.g., in MR) than on ischemia alone. In valvular pathology, there is evidence that NT-proBNP release is elicited by the hemodynamic effects on the ventricle, rather than by the severity of the valvular lesions^{118, 119}. The mechanism involved in NT-proBNP release in ischemia is not entirely clear¹²⁰, although Xu et al. observed a relationship between NT-proBNP and CAD severity¹²¹. The results of our study supported previous findings that showed that, in cardiac surgery, NT-proBNP levels were associated with morbidity and mortality¹²²⁻¹²⁶. In contrast to other studies, we found that the ability of NT-proBNP to predict severe PHF was less convincing in the context of AS¹⁰⁸. There could be several reasons for this finding. The incidence of severe PHF was low in patients with AS in our cohort, even though we had a rather large sample size. In addition, the discrepancy between our findings and those of other studies could have been due to differences in endpoints, follow-up times, sample sizes, and/or surgery timing. However, the healthcare systems and the availability of cardiothorac-

ic surgery in Sweden allow most patients to be treated in accordance with current guidelines ^{127, 128}.

Although the second study was a rather large study, one limitation was its retrospective nature. Moreover, the follow-up time was relatively short, which was a major reason for the less clear predictive value of NT-proBNP in AS. Further studies on the relationship between NT-proBNP and PHF are needed with longer follow-up times. We addressed this issue in the third and fourth studies.

Timing is of essence in heart treatments; thus, we strive to intervene on patients with AS at an optimal time. If we intervene too early, the risk associated with the intervention might exceed the gain. On the other hand, if we operate too late, the underlying heart disease might have caused irreversible damage, which could prevent the patient from gaining the full benefit of the procedure. In the third study, for the first time, to our knowledge, the levels of NT-proBNP was described from a preoperative assessment to the six-month follow-up in a cohort of unselected patients that underwent an aortic valve intervention. By selecting patients that underwent either SAVR or TAVI, we could compare the two different procedures. Despite a median of four months between the preoperative evaluations to the intervention, none of the groups showed increases in NT-proBNP levels while awaiting the valve intervention. Moreover, none of the patients appeared to deteriorate during the time spent on the waiting list. Interestingly, patients with NT-proBNP levels above the upper reference limit (URL) had shorter waiting times compared to those with NT-proBNP levels below the URL, even though the NT-proBNP results remained blinded. Our results supported associations between NT-proBNP levels and factors that influenced the waiting time ^{47, 129}.

All aortic valve interventions elicit a rise in NT-proBNP. In SAVR, the rise was more pronounced and levels peaked on the third day, compared to TAVI, which displayed a less pronounced rise and a peak on the first postoperative day ^{109, 130-132}. Interestingly, we found no difference in the

change in NT-proBNP (Δ NT-proBNP, calculated as the third-day value subtracted from the preoperative value) between AS (SAVR) and AS+CABG (SAVR). However, we observed a significantly smaller Δ NT-proBNP with aortic insufficiency (SAVR). We believe that this difference was not dependent on the surgical trauma, because the cross-clamp time and extracorporeal circulation time showed no correlation with the Δ NT-proBNP, and the surgical traumas were similar. More likely, the difference was due to patient-related factors and the degree of cardiac dysfunction¹³³⁻¹³⁵.

The postoperative rise in NT-proBNP is undoubtedly related to the surgical intervention. However, it is also influenced by age, preoperative cardiac function, the degree of perioperative ischemia, and the development of PHF, as suggested by the multivariable linear regression model. In TAVI, higher preoperative and postoperative levels of NT-proBNP were observed compared to the surgical cohort. These differences were probably a reflection of the older mean age in the TAVI group and the increased risk profile, with more comorbidity, compared to the SAVR group. The earlier and less pronounced rise in NT-proBNP observed in TAVI was probably due to the reduced trauma associated with this intervention, compared SAVR. The variance in NT-proBNP observed in the postprocedural rise in TAVI could to 20% be explained by systolic LV function and ischemia, which was evidenced as a rise in CK-MB.

As part of the ongoing debate on the optimal timing of aortic interventions, it has been suggested that serial measurements of NT-proBNP should be performed³⁹. Our results showed that high pre- and early postoperative levels of NT-proBNP were associated with mortality, which was consistent with other studies^{41, 136, 137}. We also showed that an aortic valve intervention had a beneficial effect on NT-proBNP levels, even in patients with the highest preoperative levels. However, we could not find an association between high preoperative or early postoperative NT-proBNP levels and mortality in patients that received TAVI. These results contrasted

with results from other studies ^{138, 139}, but they were consistent with results from the study by Seiffert et al. ¹⁴⁰. One explanation for this discrepancy could be that patients treated with TAVI in our cohort were older and had more comorbidity, compared to those deemed fit to undergo SAVR. These factors could have reduced the power of NT-proBNP levels for predicting mortality ¹⁴¹.

Our cohort was one of the largest reported among prospective studies that evaluated NT-proBNP levels in patients that underwent SAVR and TAVI. Nevertheless, the TAVI group was too small and the number of events too low for sufficient statistical power to detect the ability of NT-proBNP to predict mortality. Only the SAVR group had sufficient statistical power to detect the predictive ability of NT-proBNP. On the other hand, we showed that all interventions had a beneficial effect on NT-proBNP, independently of pathophysiology, preoperative levels, and the type of intervention. However, high early postoperative levels should warrant increased surveillance and follow-up, according to the guidelines for chronic heart failure ³⁵.

Diastolic dysfunction, NT-proBNP and PHF

In our fourth study, we found that 22% (54/247) of patients had signs of high preoperative LV filling pressures. This proportion might appear somewhat low, compared to those reported in other studies ^{61, 142, 143}. This discrepancy could be due to differences in cohorts, the types of procedure, referral patterns, and different indices used for classifying diastolic dysfunction ⁵⁶.

One of our main findings was that half of the patients with high preoperative LV filling pressures had normalized LV filling pressures at six months after surgery. In contrast, 12% (n=24) of patients with low LV filling pressures deteriorated and had high LV filling pressures at six months after surgery. Perhaps patients that showed early improvements in diastolic

function represented a subset of patients with reversible hypertrophy. Vilari et al. reported a worsening in diastolic function early after aortic valve replacement, due to a relative increase in fibrosis as the muscular hypertrophy subsided. Improvements in diastolic function typically takes years, due to the slow regression of fibrosis¹⁴⁴. Patients that deteriorated in our study tended to have longer aortic cross-clamping times and longer bypass times. CABG was also more common in that group, which suggested that they experienced profound surgical trauma, such as intraoperative ischemic injury. This possibility was supported by the higher levels of Creatine Kinase-MB (CK-MB) observed in that group. Moreover, this possibility was supported by results from previous studies^{145, 146}.

In the present study, NT-proBNP was found to be the sole predictor of high preoperative LV filling pressure, after adjusting for confounders. Additionally, previous studies have shown an association between NT-proBNP and diastolic function^{37, 147-150}. Our method for the evaluation of high LV filling pressure, starting with E/A taking the age adjusted normal ranges into account for grading of diastolic function, was at least as good as left atrial index and E/é in identifying patients with increased levels of NT-proBNP. In our study, high pre- and postoperative LV filling pressures were associated with elevated NT-proBNP. Nevertheless, there was also a significant decrease in NT-proBNP postoperatively, in both groups, compared to preoperative levels.

A novel finding from this study was that patients with high preoperative LV filling pressures that achieved normalized LV filling pressures postoperatively had significantly higher preoperative levels of NT-proBNP and higher LV-mass indices than patients that experienced no improvement in LV filling pressure. However, patients in the high preoperative LV filling pressure group that did not improve (i.e., they maintained high LV filling pressures at the six-month follow-up) had higher frequencies of diabetes mellitus and atrial fibrillation. These results implied that patients that did not show improvements in LV filling pressure might have

had a more permanent cardiac dysfunction, possibly due to fibrosis ^{151, 152}. Although high preoperative LV filling pressures were associated with PHF and longer ICU stays, we could not find an association between diastolic dysfunction and mortality. In study I, we suggested that diastolic dysfunction might be the underlying myocardial factor responsible for the delayed consequences of PHF ¹⁵³. Indeed, the association between NT-proBNP and a poor long-term outcome supported the assumption that an underlying myocardial factor might play a key role in PHF-related mortality. Although our results clearly discarded elevated LV filling pressure as the culprit involved in long-term mortality, we could not rule out the possibility that diastolic dysfunction due to fibrosis might play a role. The methods used in this study could not differentiate between high LV filling pressures caused by hypertrophy and those caused by fibrosis. It is also possible that the permanence or transience of fibrosis might play different roles in diastolic dysfunction in the presence of aortic valve disease. Indeed, these potentially different roles of fibrosis might explain the conflicting results found on the impact of diastolic dysfunction on prognosis after AVR for AS ^{61, 142}.

The results from the fourth study described in this dissertation confirmed our previous results that both PHF and high preoperative NT-proBNP were associated with poor long-term survival. A limitation in this study was that we did not distinguish between cardiac-related deaths and deaths from other causes. Missing data and the possibility of a type II error could have influenced our results. However, it was apparent that factors other than diastolic dysfunction were of greater importance for the outcome. One of the strengths of the fourth study is that we used several Doppler parameters as recommended in the guidelines in evaluating LV filling pressure as opposed to evaluating, for instance only the E/e' ratio that is widely used ¹⁵⁴. The Euro-filling study demonstrates that assessment of LV filling pressure non-invasively using the current guidelines are both reliable and useful in estimating invasive LV end-diastolic

pressure (LVEDP) ¹⁵⁴. In the future, a potential avenue of exploration could be to quantify and relate fibrosis to diastolic function and prognosis, possibly by evaluating images acquired with different techniques, such as magnetic resonance imaging (MRI).

CONCLUDING REMARKS

In this research project, we showed that patients that developed PHF in the setting of aortic valve replacement for AS had a poor long-term prognosis, regardless of whether they were considered to be at low or high risk preoperatively. We also showed that preoperative NT-proBNP was highest among patients with a pressure overload (like in AS) and next-highest among those with a volume overload (like in MR). In addition, we confirmed that NT-proBNP could predict severe PHF in patients with CAD and MR, but it was less predictive in patients with AS, at least in the short-term. NT-proBNP was also found to be predictive of short-term mortality among patients with CAD. An intervention for AS elicited a rise in NT-proBNP, which was much more pronounced among patients that received SAVR, compared to those that received TAVI. However, after six months, the levels returned to preoperative levels, or below, in most patients. The pre- and early postoperative NT-proBNP levels were also shown to predict the one-year mortality. In the fourth study of this dissertation, we could not establish whether diastolic dysfunction, per se, was associated with long-term mortality; in contrast, both NT-proBNP and PHF had implications for long-term survival.

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