NT-proBNP as a marker of postoperative heart failure in adult cardiac surgery

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To Shujin, Zilin and Xuelin

“Learn avidly. Question it repeatedly. Analyze it carefully. Then put what you have learned into practice intelligently.”

Confucius
# CONTENTS

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABSTRACT</td>
<td>1</td>
</tr>
<tr>
<td>SVENSK SAMMANFATTNING</td>
<td>3</td>
</tr>
<tr>
<td>LIST OF PAPERS</td>
<td>5</td>
</tr>
<tr>
<td>ABBREVIATIONS</td>
<td>7</td>
</tr>
<tr>
<td>ACKNOWLEDGEMENTS</td>
<td>9</td>
</tr>
<tr>
<td>INTRODUCTION</td>
<td>11</td>
</tr>
<tr>
<td>Postoperative heart failure</td>
<td>11</td>
</tr>
<tr>
<td>Natriuretic peptides</td>
<td>13</td>
</tr>
<tr>
<td>BNP and NT-proBNP in cardiology</td>
<td>14</td>
</tr>
<tr>
<td>Preoperative BNP and NT-proBNP in cardiac surgery</td>
<td>15</td>
</tr>
<tr>
<td>Postoperative BNP and NT-proBNP in cardiac surgery</td>
<td>17</td>
</tr>
<tr>
<td>Treatment of postoperative heart failure</td>
<td>18</td>
</tr>
<tr>
<td>Glutamate</td>
<td>19</td>
</tr>
<tr>
<td>AIMS OF THE DISSERTATION</td>
<td>21</td>
</tr>
<tr>
<td>MATERIAL AND METHODS</td>
<td>23</td>
</tr>
<tr>
<td>Patients</td>
<td>23</td>
</tr>
<tr>
<td>Paper I and II</td>
<td>24</td>
</tr>
<tr>
<td>Paper III and IV</td>
<td>25</td>
</tr>
<tr>
<td>Clinical management</td>
<td>26</td>
</tr>
<tr>
<td>Paper I and II</td>
<td>26</td>
</tr>
<tr>
<td>Paper III and IV</td>
<td>27</td>
</tr>
<tr>
<td>Surgical pulmonary artery catheter</td>
<td>28</td>
</tr>
<tr>
<td>Study protocol</td>
<td>28</td>
</tr>
<tr>
<td>Paper I</td>
<td>28</td>
</tr>
<tr>
<td>Paper II</td>
<td>29</td>
</tr>
<tr>
<td>Paper III</td>
<td>30</td>
</tr>
<tr>
<td>Paper IV</td>
<td>30</td>
</tr>
<tr>
<td>Methods</td>
<td>31</td>
</tr>
</tbody>
</table>
NT-proBNP measurement ................................................................. 31
Mixed venous oxygen saturation (SvO₂) measurement ................. 32
EuroSCORE calculations ............................................................... 32
Definitions ....................................................................................... 32
Postoperative heart failure ............................................................. 32
Severe postoperative heart failure .................................................. 33
LV dysfunction ................................................................................ 34
Postoperative mortality ................................................................. 34
Hospital mortality ............................................................................ 34
Statistics .......................................................................................... 34
Ethics ............................................................................................... 35

RESULTS ............................................................................................ 37
Preoperative NT-proBNP and underlying heart disease (Paper I) .... 37
Preoperative NT-proBNP and severe postoperative heart failure (Paper I) .......................................................... 38
Preoperative NT-proBNP and postoperative mortality (Paper I) .... 39
NT-proBNP levels in relation to PHF in surgery for aortic stenosis (Paper II) .......................................................... 41
NT-proBNP and PHF related to long-term survival after surgery for aortic stenosis (Paper II) .......................................................... 43
PHF and severe PHF in isolated CABG for ACS (Paper III) ......... 46
Postoperative NT-proBNP in relation to PHF in isolated CABG for ACS (Paper III) .......................................................... 47
Postoperative changes of NT-proBNP in relation to PHF in isolated CABG for ACS (Paper III) .......................................................... 49
Postoperative NT-proBNP in relation to severe PHF in isolated CABG for ACS (Paper III) .......................................................... 50
Influence of glutamate on postoperative NT-proBNP in patients undergoing CABG for ACS (Paper IV) .......................................................... 52
Influence of glutamate on postoperative NT-proBNP in high risk patients undergoing CABG for ACS (Paper IV) .......................................................... 53

DISCUSSION .......................................................................................... 57
PHF after cardiac surgery ............................................................... 57
NT-proBNP in cardiac surgery .......................................................... 59
The impact of underlying heart disease on preoperative NT-proBNP ... 59
Preoperative NT-proBNP in cardiac surgery .................................... 60
Postoperative NT-proBNP and postoperative heart failure ............ 62
Abstract
ABSTRACT

Postoperative heart failure (PHF) remains the major cause of mortality after cardiac surgery. Unfortunately, generally accepted diagnostic criteria for PHF are lacking. This may explain why the evidence for the efficacy and safety of current treatment of PHF with inotropes is insufficient. In cardiology practice N-terminal pro-B-type natriuretic peptide (NT-proBNP) is an established biomarker for heart failure. However, the association between NT-proBNP and PHF after cardiac surgery needs further clarification. Glutamate is a key intermediate in myocardial metabolism, which may improve myocardial tolerance to ischemia and facilitate post-ischemic recovery. Glutamate was associated with a reduced risk of developing severe PHF in high-risk patients undergoing coronary artery bypass surgery (CABG). The aim of this thesis was to study the role of NT-proBNP for prediction and assessment of PHF in cardiac surgery (Paper I-III) and the impact of intravenous glutamate infusion on postoperative NT-proBNP after CABG (Paper IV).

**Paper I:** We retrospectively studied the role of underlying heart disease for preoperative NT-proBNP in patients admitted for first time CABG (n=2226), aortic valve surgery (AVR) for aortic stenosis (AS) (n=406) and mitral valve surgery for mitral valve regurgitation (MR) (n=346) by adjusting for non-cardiac confounders (age, gender, obesity and renal function). The level of NT-proBNP in AS or MR was 1.67 (p<0.0001) and 1.41 times (p<0.0001) higher respectively than in coronary artery disease (CAD) after adjusting for confounders. Preoperative NT-proBNP was predictive of severe PHF in CAD and MR patients but less so in AS patients. Preoperative NT-proBNP emerged as an independent risk factor for severe PHF and postoperative mortality in CAD patients.

**Paper II-III:** We prospectively studied the association between postoperative NT-proBNP and PHF in two cohorts, patients undergoing AVR for AS
(n=203) and patients undergoing isolated CABG for acute coronary syndrome (ACS) from the GLUTAMICS-trial (n=382). NT-proBNP was measured preoperatively, on the first (POD1) and third postoperative morning (POD3). An end-points committee blinded to NT-proBNP used prespecified criteria to diagnose PHF and its severity. After AVR for AS only NT-proBNP level on POD1 provided good discrimination of PHF. PHF with NT-proBNP POD1 ≥ 5290 ng•L⁻¹ emerged as an independent risk factor for long-term mortality (Paper II). After isolated CABG for ACS both absolute postoperative levels on POD1 and POD3 and postoperative increases of NT-proBNP were associated with PHF and the levels reflected the severity of PHF (Paper III).

**Paper IV:** We prospectively studied the impact of intravenous glutamate infusion on postoperative NT-proBNP in a randomized double-blind study on patients undergoing CABG for ACS from the GLUTAMICS-trial (n=399). Patients were randomly allocated to intravenous infusion of L-glutamate (n=200) or saline (n=199). No effect of glutamate on postoperative NT-proBNP levels was detected in the whole cohort. According to post-hoc analysis glutamate was associated with less increase of NT-proBNP from preoperative level to POD3 and significantly lower absolute levels on POD3 among high risk patients with EuroSCORE II ≥4.15 (upper quartile).

**Conclusion:** Patients with AS or MR have higher preoperative NT-proBNP than CAD patients after adjusting for confounders. The predictive value of NT-proBNP with regard to severe PHF and postoperative mortality was confirmed in CAD patients. Postoperative NT-proBNP may prove a useful tool for assessment of PHF after AVR for AS and isolated CABG. NT-proBNP POD1 identifies patients with PHF at risk of a poor long-term survival after AVR for AS. Intravenous infusion of glutamate may prevent or mitigate PHF in high-risk patients undergoing CABG but these results need to be confirmed.
SVENSK SAMMANFATTNING


NT-proBNP är en etablerad markör för hjärtsvikt inom kardiologin men har inte fått samma genomslag i hjärtkirurgisk verksamhet. Målsättningen med detta avhandlingsarbete var att utvärdera hur NT-proBNP påverkas av bakomliggande hjärnsjukdom och om NT-proBNP kan användas för att värdera hjärtsvikt efter operation. Glutamat är en aminosyra som har en nyckelroll i hjärtnats ämnesomsättning med potential att kunna underlätta hjärtnats återhämtning efter syrebrist. Vi har därför också studerat om intravenös glutaminfusion påverkar nivåerna av NT-proBNP efter operation.

NT-proBNP nivåerna i blod stiger när hjärntat utsätt för tryck eller volymsbelastning men även syrebrist bidrar i oklar omfattning till förhöjda nivåer. Avhandlingsarbeteet visar att patienter som kommer till operation pga förträngning av aortaklaffen och läckage av mitralisklaffen har klart högre nivåer av NT-proBNP före operation jämfört med kranskärlsjuka patienter. Detta gäller även när man justerar för faktorer som ålder, kön, övervikt och njurfunktion som kan påverka NT-proBNP nivåerna. Resultaten talar för att tryck och volymsbelastning är av större betydelse för NT-proBNP nivåerna än syrebrist.

I likhet med tidigare studier fann vi att hjärtsvikt efter kranskärlsoperation var förenad med hög tidig dödlighet medan tillståndet förelöpte ganska lindrigt till en början hos dem som opererades för aortaklaff-förträngning. De allvarliga konsekvenserna i form av en kraftig ökad dödlighet under uppföljningstiden blev uppenbara först efter några år.

NT-proBNP nivåerna efter operation studerades hos patienter som opererades för aortaklaff-förträngning och kranskärlssjukdom. Nivåerna steg
betydligt mer efter operation hos dem som drabbades av hjärtsvikt. I kranskärlsgruppen graderades svårighetsgraden av hjärtsvikt och nivåerna föreföll då reflektera svårighetsgraden. Hos patienter som opererade för aortaklaff-förträngning var det bara proverna den första dagen efter operation som tydligt var kopplade till hjärtsvikt. Dessa prover kunde dock identifiera vilka patienter med hjärtsvikt det var som löpte en kraftigt ökad risk att avlida de närmaste åren och därför var i behov av ökad uppmärksamhet under uppföljningstiden.

I en avslutande studie fann vi att intravenös glutamatinfusion inte påverkade de genomsnittliga nivåerna av NT-proBNP hos merparten av patienter som kranskärlsopererades. Däremot visade en post hoc-analyss att den fjärde del av patienterna som bedömdes ha högst operationsrisk hade signifikant lägre stegring av NT-proBNP och därmed även lägre nivåer av NT-proBNP efter operation.

Sammantaget har studierna bidragit till ökad kunskap om NT-proBNP i de tre största patientgrupperna som behöver hjärtopereras och de har bekräftat värdet av NT-proBNP som riskmarkör före operation.

Studierna talar för att NT-proBNP efter operation kan användas som markör för hjärtsvikt vilket skulle kunna vara av särskild betydelse för framtida studier där man utvärderar ny behandling för hjärtsvikt efter hjärtkirurgi.

Studierna talar för att NT-proBNP kan identifiera vilka patienter som behöver skärpta kontroller för att de löper ökad risk för fortfödda död med anledning av att de haft hjärtsvikt vid operation för aortaklaff-förträngning.

Slutligen talar NT-proBNP analyser för att intravenös glutamatinfusion minskar risken för hjärtsvikt efter kranskärlsoperation hos patienter med ökad operationsrisk. Dessa resultat behöver dock bekräftas i nya studier innan glutamat kan rekommenderas för allmänt kliniskt bruk.
LIST OF PAPERS

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

II. NT-proBNP and postoperative heart failure in surgery for aortic stenosis.
    Jiang H, Vánky F, Hultkvist H, Holm J, Yang Y, Svedjeholm R.
    Open Heart 2019 :e001063.

III. NT-proBNP for assessment of postoperative heart failure after coronary artery bypass surgery.
     Submitted

IV. The impact of glutamate infusion on postoperative NT-proBNP in patients undergoing coronary artery bypass surgery.
    Manuscript
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACS</td>
<td>Acute coronary syndrome</td>
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<tr>
<td>AMI</td>
<td>Acute myocardial infarction</td>
</tr>
<tr>
<td>AS</td>
<td>Aortic stenosis</td>
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<tr>
<td>AUC</td>
<td>Area under the curve</td>
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<tr>
<td>AVR</td>
<td>Aortic valve replacement</td>
</tr>
<tr>
<td>BMI</td>
<td>Body mass index</td>
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<tr>
<td>BNP</td>
<td>B-type natriuretic peptide</td>
</tr>
<tr>
<td>BW</td>
<td>Body weight</td>
</tr>
<tr>
<td>CABG</td>
<td>Coronary artery bypass surgery</td>
</tr>
<tr>
<td>CAD</td>
<td>Coronary artery disease</td>
</tr>
<tr>
<td>CCS</td>
<td>Canadian Cardiovascular Society</td>
</tr>
<tr>
<td>CI</td>
<td>Confidence Interval</td>
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<tr>
<td>CK-MB</td>
<td>Creatine kinase-MB isoenzyme</td>
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<tr>
<td>COPD</td>
<td>Chronic obstructive pulmonary disease</td>
</tr>
<tr>
<td>CPB</td>
<td>Cardiopulmonary bypass</td>
</tr>
<tr>
<td>CV</td>
<td>Coefficient of variation</td>
</tr>
<tr>
<td>ESC</td>
<td>European Society of Cardiology</td>
</tr>
<tr>
<td>EuroSCORE</td>
<td>European system for cardiac operative risk evaluation score</td>
</tr>
<tr>
<td>eGFR</td>
<td>estimated glomerular filtration rate according to MDRD formula</td>
</tr>
<tr>
<td>GCP</td>
<td>Good Clinical Practice</td>
</tr>
<tr>
<td>GIK</td>
<td>glucose-insulin-potassium</td>
</tr>
<tr>
<td>GLUTAMICS</td>
<td>GLUTAmate for Metabolic Intervention in Coronary Surgery trial</td>
</tr>
<tr>
<td>HR</td>
<td>Hazard Ratio</td>
</tr>
<tr>
<td>ICU</td>
<td>Intensive care unit</td>
</tr>
<tr>
<td>LV</td>
<td>Left ventricular</td>
</tr>
<tr>
<td>LVEF</td>
<td>Left ventricular ejection fraction</td>
</tr>
<tr>
<td>MR</td>
<td>Mitral valve regurgitation</td>
</tr>
<tr>
<td>NAD</td>
<td>Nicotinamide adenine dinucleotide</td>
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<tr>
<td>NT-proBNP</td>
<td>N-terminal pro-B-type natriuretic peptide</td>
</tr>
<tr>
<td>NYHA</td>
<td>New York Heart Association</td>
</tr>
<tr>
<td>OR</td>
<td>Odds Ratio</td>
</tr>
<tr>
<td>PHF</td>
<td>Postoperative heart failure</td>
</tr>
<tr>
<td>POD1</td>
<td>Postoperative day 1 (first postoperative morning)</td>
</tr>
<tr>
<td>POD3</td>
<td>Postoperative day 3 (third postoperative morning)</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Description</td>
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<tr>
<td>PREEV</td>
<td>Preoperative evaluation</td>
</tr>
<tr>
<td>PREOP</td>
<td>Preoperative (the day before the index procedure)</td>
</tr>
<tr>
<td>ROC</td>
<td>Receiver Operating Characteristic analysis</td>
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<tr>
<td>SAP</td>
<td>Systolic arterial pressure</td>
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<tr>
<td>SvO₂</td>
<td>Mixed venous oxygen saturation</td>
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<tr>
<td>TAVI</td>
<td>Transcatheter aortic valve implantation</td>
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<tr>
<td>URL</td>
<td>Upper reference limit</td>
</tr>
</tbody>
</table>
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INTRODUCTION

Postoperative heart failure

Postoperative heart failure (PHF) or low cardiac output syndrome remains the major cause of mortality after cardiac surgery. PHF after coronary artery bypass surgery (CABG), which is reported to occur in 3% to 14% of the cases, typically presents at weaning from cardiopulmonary bypass or during the first hours after surgery and is associated with a high early mortality. The Northern New England Cardiovascular Study group found that differences in postoperative mortality after CABG were mainly explained by differences in mortality rates caused by PHF. Indeed, in a retrospective study performed by Algarni and his colleagues, 427 deaths in 25176 consecutive patients undergoing isolated CABG between 1990 and 2009 were investigated with respect to the predictor of PHF after isolated CABG, PHF was associated with a 17 to 29-fold increase in mortality. Similarly, PHF was associated with a 25-fold increase in mortality in patients undergoing isolated aortic valve replacement (AVR).

In contrast to what was found in a mixed high-risk cohort undergoing AVR, our experience is that the serious consequences of PHF after isolated AVR for aortic stenosis (AS) become evident only after a few years. PHF was found to be an independent risk factor for poor long-term survival. We speculated that this could be explained by a previously undetected myocardial factor, possibly associated with myocardial fibrosis and diastolic dysfunction, that was unmasked by an episode of PHF.

In a study by Vanky and his colleagues, PHF after CABG was strongly associated with perioperative myocardial infarction and myocardial ischemia during the early stages of surgery, which could explain the high early mortality associated with PHF in CABG. In patients undergoing AVR for AS
an eliciting factor for PHF could only be identified in one third of the patients and myocardial ischemia played a subordinate role\textsuperscript{10}.

Although PHF usually is easily recognizable in clinical practice, scientific evaluation of prevention and treatment represents a challenge as universally accepted criteria for the diagnosis of PHF are lacking\textsuperscript{11, 12}. Defining heart failure is difficult under any circumstance as was illustrated by a survey amongst reviewers of Cardiovascular research \textsuperscript{13}. In cardiac surgery it may seem straightforward to rely on cardiac output measurements for the definition. However, cardiac output has to be assessed together with other hemodynamic variables since cardiac output can be very low despite a normal postoperative course due to low systemic oxygen demand in anesthetized patients early after surgery \textsuperscript{14, 15}.

Mixed venous oxygen saturation (SvO\textsubscript{2}) reflects the balance between oxygen delivery to the tissues and systemic oxygen demand. Although, there are well-known pitfalls, SvO\textsubscript{2} in the early postoperative course is well documented with regard to outcome \textsuperscript{16-18}. However, SvO\textsubscript{2} measurements require use of pulmonary artery catheters, which are rarely used routinely.

Echocardiography provides invaluable information in cardiac surgical practice about global and regional myocardial dysfunction and often reveals the underlying cause to heart failure \textsuperscript{19}. However, echocardiography is investigator dependent and criteria for PHF may difficult to establish.

Reliance on treatment criteria for PHF, such as inotrope requirements or need for mechanical cardiac assist device are clouded by the large differences between geographical regions, institutions and individuals regarding threshold for institution of treatment or prophylaxis \textsuperscript{12, 20}. 
For study purposes, it would be desirable if currently available biomarkers for heart failure could be used to assess PHF and its severity.

**Natriuretic peptides**

There are three type of natriuretic peptides, brain natriuretic peptide, atrial natriuretic peptide and C-type natriuretic peptide in the natriuretic peptide family\(^2^1\). In 1988, Sudoh *et al.* first isolated BNP from porcine brain tissue\(^2^2\). Several decades have passed since N-terminal pro-B-type natriuretic peptide (NT-proBNP) was first reported in human plasma by Hunt in 1995\(^2^3\).

Synthesis of pre-pro-BNP is initiated by myocyte stretch with increased wall stress response to volume expansion or pressure overload in the atrial and ventricular myocardium\(^2^4\). In cardiomyocytes, 108-amino precursor pro-B-type natriuretic peptide is cleaved and released as two molecules; an inactive 76-amino acid NT-proBNP fragment and a biologically active 32-amino acid C-terminal BNP \(^2^5\). Despite the 1:1 secretion of B-type natriuretic peptide (BNP) and NT-proBNP, BNP and NT-proBNP are not interchangeable \(^2^6\). The BNP has a half-life of approximately 20 min; while NT-proBNP has a half-life ranging from 1 to 2 h, leading to 5- to 10-fold greater circulating levels and slower fluctuations \(^2^7, 2^8\). Natriuretic peptide receptor C and neutral endopeptidases present within renal tubular cells and vascular cells are involved in clearance of the peptides \(^2^1\). The physiologic function of BNP improves myocardial relaxation and counteracts the antidiuretic effects, sodium retention, and vasoconstriction caused by the activated renin-angiotensin-aldosterone system through coordinated actions in the brain, adrenal glands, kidneys, and vasculature\(^2^1, 2^6\).

Ischemia also contributes to the release of natriuretic peptides, though it remains unclear to what extent this is caused by local myocardial stunning or ischemia per se \(^2^9\).
In addition to ventricular wall stress and ischemia, there are some non-cardiac factors that influence natriuretic peptide levels including advanced age, female gender, renal function, and obesity. In a population-based study, natriuretic peptide increased with age and was higher in women without known cardiovascular disease or detectable structural heart disease. Estrogen might be one of possible explanations for women with higher level natriuretic peptide. The level of NT-proBNP increases with 38% for each 10 ml•min⁻¹•1.73m⁻² decline in glomerular filtration rate. This is not only caused by diminished renal clearance but also explained by a true counter-regulatory response from the heart to the kidney. NT-proBNP and BNP are lower in obese people regardless of heart failure.

Inflammation, which was not addressed in this thesis, has also been reported as a stimulus of natriuretic peptides release in patients with septic shock or with endocarditis. There might be several mechanisms responsible for elevated natriuretic peptides in inflammation, including increased ventricular filling pressure caused by septic cardiomyopathy, proinflammatory cytokines like interleukin-1beta or tumor necrosis factor-alpha that mediated myocardial depression.

Acknowledging the influence of these factors might clarify the role of underlying heart disease per se for NT-proBNP levels and the prognostic utility of NT-proBNP in cardiac surgery.

**BNP and NT-proBNP in cardiology**

BNP and NT-proBNP have been established biomarkers for heart failure according to European Society of Cardiology (ESC) guidelines since 2005. In the PRIDE Study, NT-proBNP was found to be valuable for the identification and exclusion of acute congestive heart failure in the emergency
department setting. In a systematic review with a total of 48 studies reporting 15263 test results, BNP and NT-proBNP showed excellent ability to distinguish acute heart failure from non-cardiac causes of dyspnea at the rule out thresholds of 100 ng·L⁻¹ for BNP and 300 ng·L⁻¹ for NT-proBNP. In order to “rule in” heart failure, higher age-dependent cut points are suggested. Patients with NT-proNP levels >450 pg·ml⁻¹ (<50 years), >900 pg·ml⁻¹ (50-70 years), and >1800 pg·ml⁻¹ (>75 years) all have a high likelihood of heart failure diagnosis. Both the best cutoffs of “rule out” and “rule in” for acute heart failure apply to patients with acute dyspnea in the emergency department.

Available studies also show that natriuretic peptides provide important prognostic information by distinguishing responders and non-responders to treatment of congestive heart failure. The most recent international guidelines recommend natriuretic peptides, particularly BNP or NT-proBNP, to be used as first-line biomarkers for the diagnosis, prognosis, and follow-up of patients with heart failure.

Preoperative BNP and NT-proBNP in cardiac surgery

A few studies report that preoperative natriuretic peptide levels differ between patients accepted for AVR, mitral valve surgery or CABG. However, these studies were either small or they did not adjust for non-cardiac confounders, such as preoperative renal function, age, gender, and obesity, which all have been reported to influence natriuretic peptides. The role of underlying heart disease per se on the preoperative plasma levels of NT-proBNP thus has not been fully clarified. Increased knowledge about this influence could improve our interpretation of NT-proBNP in cardiac surgery and identify possible needs for homogenous patient cohorts when conducting studies on NT-proBNP in cardiac surgery.
Preoperative natriuretic peptides are correlated to preoperative left ventricular ejection fraction (LVEF) and New York Heart Association (NYHA) class. A considerable amount of literature has been published on the prognostic value of natriuretic peptide regarding outcome after cardiac surgery. In adult patients undergoing cardiac surgery elevated preoperative natriuretic peptides have been found to be associated with postoperative heart failure, adverse short-term outcome, such as long ventilation time, prolonged intensive care unit (ICU) stay, long hospital stay and postoperative mortality. In 2009, Cuthbertson et al. investigated 1010 patients undergoing non-emergent cardiac surgery and demonstrated that preoperative NT-proBNP levels was an independent predictor for 30-day mortality after cardiac surgery even after adjusting for Parsonnet score and European system for cardiac operative risk evaluation score (EuroSCORE). Four years later, in a large longitudinal study of the same cohort, preoperative NT-proBNP was found to independently predict 3-year mortality after cardiac surgery. Furthermore, increased preoperative natriuretic peptides have been reported to be associated with hospitalization because of heart failure or cardiac death during 5-year follow-up after isolated CABG. In addition, natriuretic peptides may be useful in congenital cardiac surgery. However, it is unclear if the relationship between preoperative NT-proBNP and PHF or postoperative outcome is similar in the patients with coronary artery disease (CAD), aortic stenosis (AS) or mitral valve regurgitation (MR). Further investigation to assess the predictive value of preoperative NT-proBNP in these cohorts with regard to postoperative outcome might therefore be worthwhile.

Although BNP is an independent predictor of cardiac surgical outcome, it was not included in EuroSCORE II due to poor availability of data. However, Holm et al. found combining preoperative NT-proBNP and EuroSCORE II may improve risk prediction with regard to severe PHF after isolated CABG for acute coronary syndrome (ACS). Preoperative BNP
also was comparable and even better than logistic EuroSCORE in predicting long-term mortality in patients undergoing AVR for AS 56.

Postoperative BNP and NT-proBNP in cardiac surgery

In adult patients undergoing cardiac surgery, both NT-proBNP and BNP increase postoperatively. NT-proBNP reached the peak on the fourth to seventh day 71, 72. The postoperative levels of NT-proBNP were similar in off-pump CABG and on-pump CABG 73. In patients without PHF, BNP peaked on POD3 then diminished, whereas BNP remained elevated without significant differences between POD3 and 5 in patients with PHF after CABG 55.

High plasma concentrations of NT-proBNP and BNP postoperatively were associated with increased use of inotropic drugs and/or intra-aortic balloon pump 2, 55, 71, 73–76. High levels of natriuretic peptides were also reported to be associated with adverse short-term outcome, such as prolonged ICU stay, ventilation time, in-hospital mortality and postoperative mortality 72, 73, 77, 78.

A number of studies have reported the predictive value of postoperative natriuretic peptides with regard to long-term outcome (long-term mortality and major adverse cardiac events during follow-up) after cardiac surgery 44, 76, 77, 79–81. However, there are a limited number of studies specifically on postoperative natriuretic peptides and PHF in cardiac surgery (Table 1).
Table 1. Studies on postoperative natriuretic peptides and PHF in cardiac surgery.

<table>
<thead>
<tr>
<th>Paper</th>
<th>Biomarker</th>
<th>Cohort</th>
<th>Sample size*</th>
<th>Design</th>
<th>PHF criteria</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kerbaul 2004</td>
<td>NT-proBNP</td>
<td>Off-pump</td>
<td>21/60</td>
<td>prospective</td>
<td>Partly defined</td>
<td>Early postop levels – postop complications</td>
</tr>
<tr>
<td>Reyes 2005</td>
<td>NT-proBNP</td>
<td>mixed</td>
<td>15/83</td>
<td>prospective</td>
<td>Treatment</td>
<td>Postop levels higher in patients treated with inotropes</td>
</tr>
<tr>
<td>Provonchere 2006</td>
<td>BNP</td>
<td>Mixed</td>
<td>30/92</td>
<td>prospective</td>
<td>Partly defined</td>
<td>Postop day 1 levels independently predict post cardiac dysfunction</td>
</tr>
<tr>
<td>Fox 2008</td>
<td>BNP</td>
<td>CABG</td>
<td>119/1023</td>
<td>prospective</td>
<td>Treatment</td>
<td>Pre- and postop levels higher in patients with PHF</td>
</tr>
<tr>
<td>Suttner 2008</td>
<td>NT-proBNP</td>
<td>CABG</td>
<td>32/98</td>
<td>prospective</td>
<td>Partly defined</td>
<td>Postop day 1 independently associated with cardiac events</td>
</tr>
<tr>
<td>Nozohoor 2009</td>
<td>BNP</td>
<td>AVR</td>
<td>37/161</td>
<td>prospective</td>
<td>Treatment</td>
<td>BNP on arrival to ICU predicted PHF</td>
</tr>
</tbody>
</table>

*Event number/sample size. AVR, aortic valve replacement; BNP, B-type natriuretic peptide; CABG, coronary artery bypass surgery; NT-proBNP, N-terminal pro-B-type natriuretic peptide; PHF, postoperative heart failure; Postop, postoperative.

Treatment of postoperative heart failure

Traditional treatment for PHF after cardiac surgery includes inotropic drugs, vasodilators, and mechanical circulatory support. Inotropes constitute common treatment for PHF but the use of inotropes in cardiac surgery differs markedly between institutions and individual physicians. Inotropic treatment can enhance cardiac output and tissue oxygenation, but it also aggravates myocardial stress directly by a marked increase of myocardial oxygen demand and indirectly by increasing systemic oxygen demand. This fact and the lack of generally accepted diagnostic criteria
for PHF may explain why the evidence for current treatment of PHF with inotropes is poor. In fact, there are reports suggesting a detrimental effect if these drugs are used liberally or instituted early after severe myocardial ischemia 12, 84.

Inotropes may also carry hazards in patients undergoing AVR for AS since these drugs can trigger life-threatening left ventricular outflow tract obstruction in small and hypertrophied left ventricles if given in association with hypovolemia 83.

Unloading of the heart with mechanical circulatory support theoretically provides a more beneficial myocardial oxygen demand / systemic oxygen delivery ratio but is resource demanding and associated with complications 19 86, 87. These treatments are usually reserved for the sickest patients where they can be life saving19.

Metabolic support has received comparatively little attention in cardiac surgery for prevention and treatment of PHF although a large majority of studies show positive effects of glucose-insulin-potassium (GIK) and / or insulin that extend beyond simple metabolic benefits 88.

**Glutamate**

Glutamate, which is one of the amino acids associated with malate-aspartate, plays a key role in myocardial metabolism particularly during myocardial ischemia 89-91. Several biochemical mechanisms have been reported for glutamate's role of increasing myocardial tolerance to ischemia and enhancing myocardial recovery after ischemia.

During ischemia, glutamate improves myocardial tolerance to ischemia through its role in the malate-aspartate shuttle to facilitate anaerobic metabolism. Glutamate enhances glycolysis during ischemia by regulating the
NAD/NADH (nicotinamide adenine dinucleotide and nicotinamide adenine dinucleotide [reduced form]) balance in the cytosol of the cells by transport of reducing equivalents across the mitochondrial membrane. Glutamate contributes to an alternative anaerobic pathway for regeneration of high-energy phosphates by substrate level phosphorylation in the Krebs cycle. Glutamate improves the clearance of lactate and NH₃ excess by taking part in the reactions involving transamination of pyruvate to alanine and of glutamate to glutamine. After ischemia glutamate contributes to replenishment of Krebs cycle intermediates lost during ischemia to enhance post-ischemic myocardial recovery 89, 90, 92.

In humans it has been shown that patients with CAD have increased demands of glutamate 93-97. Infusion of glutamate to patients with ischemic heart disease delayed onset of angina and ST-changes during pacing and exercise testing 98. Glutamate enriched blood cardioplegia improved ATP preservation in human myocardium and provided more effective myocardial protection 99. Infusion of glutamate after coronary surgery has been reported to enhance both metabolic and hemodynamic myocardial recovery 100, 101. In the GLUTAmate for Metabolic Intervention in Coronary Surgery trial (GLUTAMICS)-trial, glutamate infusion was associated with a reduced risk of developing severe heart failure in high-risk groups 102. For the final paper of this thesis our hypothesis was that glutamate facilitates myocardial recovery in post-ischemic heart failure and, therefore, will be accompanied by a mitigated postoperative increase of NT-proBNP.
AIMS OF THE DISSERTATION

- To investigate the impact of underlying heart disease on preoperative NT-proBNP levels in patients admitted for first time surgery because of CAD, AS, and MR after adjusting for known non-cardiac confounders age, gender, obesity and renal function.

- To investigate the predictive value of preoperative NT-proBNP in CAD, AS and MR cohorts with regard to severe PHF.

- To investigate the predictive value of preoperative NT-proBNP in CAD, AS and MR cohorts with regard to postoperative mortality.

- To investigate the predictive value of preoperative NT-proBNP on long-term survival after elective AVR for AS.

- To investigate the association between postoperative NT-proBNP and PHF in patients undergoing elective AVR for AS.

- To investigate the impact of PHF and postoperative NT-proBNP on long-term survival after elective AVR for AS.

- To investigate the association between postoperative NT-proBNP and PHF and its severity after isolated CABG for acute coronary syndrome.

- To investigate the impact of glutamate infusion on postoperative NT-proBNP levels in patients undergoing CABG for acute coronary syndrome.
Aims of the dissertation
MATERIAL AND METHODS

Patients

An overview of the patients in Paper I - IV is presented in Table 2.

Table 2. Basic data on patients included in the study.

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Study design</td>
<td>Retrospective cohort analysis</td>
<td>Prospective cohort analysis</td>
<td>Prospective cohort analysis</td>
<td>Randomized clinical trial</td>
</tr>
<tr>
<td>Procedure</td>
<td>isolated CABG, isolated AVR, mitral valve surgery due to MR</td>
<td>AVR for AS</td>
<td>isolated CABG</td>
<td>CABG+ concomitant procedure</td>
</tr>
<tr>
<td>Indication</td>
<td>CAD, AS without AR, MR without MS</td>
<td>AS</td>
<td>ACS</td>
<td>ACS</td>
</tr>
<tr>
<td>No of patients</td>
<td>2978</td>
<td>203</td>
<td>382</td>
<td>399</td>
</tr>
<tr>
<td>Age(years)</td>
<td>70 [63-76]</td>
<td>70 [65-77]</td>
<td>69 [62-75]</td>
<td>69 [63-75]</td>
</tr>
<tr>
<td>Female</td>
<td>24% (714)</td>
<td>50% (102)</td>
<td>19% (73)</td>
<td>19% (73)</td>
</tr>
<tr>
<td>Severe LV dysfunction</td>
<td>4% (134)</td>
<td>2% (5)</td>
<td>4% (14)</td>
<td>4% (16)</td>
</tr>
<tr>
<td>EuroSCORE II</td>
<td>N/A</td>
<td>1.6 [1.1-2.8]</td>
<td>2.4 [1.6-3.9]</td>
<td>2.4 [1.7-4.2]</td>
</tr>
<tr>
<td>Follow-up time (years)</td>
<td>30 days/hospital stay</td>
<td>8.6±1.1</td>
<td>30 days/hospital stay</td>
<td>30 days/hospital stay</td>
</tr>
<tr>
<td>PHF</td>
<td>N/A</td>
<td>9% (18)</td>
<td>9% (35)</td>
<td>10% (40)</td>
</tr>
<tr>
<td>Severe PHF</td>
<td>4% (130)</td>
<td>1% (3)</td>
<td>2% (7)</td>
<td>3% (10)</td>
</tr>
<tr>
<td>Postoperative mortality*</td>
<td>2% (53)</td>
<td>0.5% (1)</td>
<td>2% (6)</td>
<td>2% (6)</td>
</tr>
<tr>
<td>30-day mortality</td>
<td>1% (39)</td>
<td>0.5% (1)</td>
<td>1% (4)</td>
<td>1% (4)</td>
</tr>
</tbody>
</table>

Data given as medians [interquartile range], mean±standard deviation or percentages (number). ACS, acute coronary syndrome; AS, aortic stenosis; AVR, aortic valve replacement; CAD, coronary artery disease; CABG, coronary artery bypass surgery; eGFR, estimated glomerular filtration rate according to MDRD formula; EuroSCORE, European system for cardiac operative risk evaluation; LV, left ventricular; N/A, not available; NT-proBNP, N-terminal pro-B-type natriuretic peptide; MR, mitral regurgitation; PHF, postoperative heart failure. * Including hospital mortality.
Material and methods

Paper I and II

The University Hospital in Linköping is the only referral center in the southeast region of Sweden, serving a population of approximately 1 million. In Paper I and Paper II the study population consisted of patients belonging to this referral area operated at this cardiothoracic center.

Paper I

From April 30, 2010, to August 31, 2016, 2289 patients underwent first time isolated CABG for CAD, 570 patients underwent isolated aortic valve surgery for aortic valve disease and 446 patients underwent mitral valve surgery for mitral valve disease at this department. Exclusion criteria were: aortic valve regurgitation (n=109), acute endocarditis (n=65), endocarditis after previous surgery (n=11), redo procedures (n=63), mitral valve stenosis (n=33) and missing preoperative NT-proBNP values (n=46). Concomitant tricuspid valve or Maze procedures were not exclusion criteria. From this cohort, we included 2978 consecutive patients admitted for first time isolated CABG for CAD (n=2226), isolated AVR because of AS without significant aortic regurgitation (n=406) or mitral valve surgery due to MR without mitral valve stenosis (n=346).

Paper II

Between June 2008 and January 2013, 203 patients were prospectively included in a prespecified substudy of the original prospective observational study\textsuperscript{103}. Inclusion criteria were consecutive patients who provided written informed consent and were scheduled to undergo AVR for AS. Exclusion criteria were: active endocarditis or emergency procedure (n=86), surgery for aortic regurgitation (n=43) or equally significant AS and aortic regurgitation (n=5), transcatheter aortic valve implantation (TAVI) (n=126), concomitant CABG (n=75), concomitant MAZE procedure (n=5), concomitant mitral valve surgery (n=5), or a lack of informed written consent. Concomitant tricuspid valve procedure (n=5) or replacement of ascending aorta
with a supracoronary graft that did not require circulatory arrest (n=26) were not exclusion criteria.

**Paper III and IV**

The study population consisted of patients who were prospectively enrolled in a substudy of the GLUTAMICS-trial (ClinicalTrials.gov Identifier: NCT00489827) between May 2007 and November 2009, at three Swedish Cardiac Surgery centers (Linköping University Hospital, Örebro University Hospital, and Karlskrona Hospital) \(^{102}\).

Inclusion criteria were CABG for ACS. Patients were eligible for inclusion regardless if the procedure was done on-pump or off-pump. Exclusion criteria were informed consent not possible because of critical condition or other reason, age > 85 years, redo-procedure, preoperative dialysis, preoperative use of inotropic drugs or mechanical circulatory assist, unexpected intraoperative finding or event that increased the magnitude of the procedure to overshadow the originally planned operation, body weight > 125 kg and food allergy known to have caused flush, rash or asthma.

**Paper III**

382 consecutive patients with ACS undergoing urgent isolated first-time CABG in a double-blind randomized clinical trial (GLUTAMICS-trial) were included. 17 patients were excluded because of CABG with concomitant procedure.

**Comment:** Patients having additional procedures have substantially higher levels of natriuretic peptides both preoperatively and postoperatively \(^{77}\). In order to keep a homogeneous cohort in this observational substudy, only patients with isolated CABG were included in contrast to Paper IV where a double-blind randomized design was employed.
Material and methods

Paper IV
399 consecutive patients with parallel assignment to intravenous infusion of glutamate (n=200) or placebo (saline) (n=199) undergoing urgent first-time CABG with or without concomitant procedure for ACS in a double-blind randomized clinical trial (GLUTAMICS-trial) were included.

Clinical management

Paper I and II
After an overnight’s fast drugs were withheld with the exception of beta-blockers and calcium antagonists. Oxycodone 4-10 mg and scopolamine 0.2-0.5 mg intramuscularly were given as premedication. Thiopentone 1mg·kg\(^{-1}\)BW and fentanyl 30 mg·kg\(^{-1}\)BW were used to induce anesthesia. Neuromuscular blockade was achieved with rocuronium, 50mg at induction and 30mg at sternal closure. Fentanyl and isoflurane were used to maintain anesthesia.

Standard surgical techniques were employed with cardiopulmonary bypass (CPB) and aortic cross clamping. Heparin 3mg·kg\(^{-1}\)BW was given intravenously before CPB to obtain an activated clotting time >480s. Priming of the extracorporeal circuit was achieved with Ringer’s acetate and mannitol. Moderate hemodilution (hematocrit 20-25%) and mild hypothermia (33-36℃) were usually employed. Myocardial protection was achieved with antegrade delivery of cold crystalloid cardioplegic solution. Weaning from CPB was started at a rectal temperature of 35-36℃. Protamine chloride 1:1 (weight) was used to neutralize heparin. Ringer’s acetate was used for volume substitution postoperatively. Seventy patients were operated off pump (Paper I).
Paper III and IV

Clinical management was standardized and similar at the three participating centers with minor differences concerning choice of anesthetic drugs. The patients received beta-blockers and calcium antagonists orally after an overnight’s fast whereas antihypertensive and antidiabetic agents were withheld. Standard premedication consisted of orally administered flunitrazepam 0.5-1.0 mg or diazepam 5-10 mg and ketobemidone 0.1-0.2 mg·kg⁻¹ body weight (BW) or morphine 0.1-0.2 mg·kg⁻¹ BW. Thiopentone (2-3 mg·kg⁻¹ BW) or propofol (2 mg·kg⁻¹ BW) supplemented by a bolus dose of fentanyl 3-5 µg·kg⁻¹ BW was used to induce anesthesia. Pancuronium 0.1 mg·kg⁻¹ BW or rocuronium 0.6 mg·kg⁻¹ BW was used for muscle relaxation. Isoflurane, sevoflurane or propofol supplemented with intermittent doses of fentanyl were used to maintain anesthesia.

Standard monitoring consisted of pulse oximetry, continuous arterial blood pressure monitoring, central venous pressure, 5-lead echocardiogram, and transesophageal echocardiography. All patients received a surgical pulmonary artery catheter ¹⁸.

A median sternotomy was performed in all patients. CPB and aortic cross-clamping was employed in most patients with the exception of twelve who were operated off pump. Myocardial protection was achieved with cold blood cardioplegia in the majority of patients operated on pump. One center used cold crystalloid cardioplegia during the first half of the trial.

Propofol was used for postoperative sedation. Intravenous administration of ketobemidone 7-15 µg·kg⁻¹ BW intermittently and acetaminophen 1 g every 6th hour was used for postoperative analgesia.

The patients were extubated when the following conditions were achieved: body temperature > 37°C, stable hemodynamics including SvO₂ > 55 %,
**Material and methods**

\[ \text{PO}_2 > 10 \text{ kPa with } \text{FiO}_2 0.4 \text{ and } \text{PCO}_2 < 6.5 \text{ kPa with a respiratory rate } < 30 \text{ and drainage loss } < 100 \text{ ml per hour and declining.} \]

After discharge from the ICU patients were transferred to a step-down semi-intensive care unit for at least 24 hours before going to the general ward.

**Surgical pulmonary artery catheter**

According to clinical routine the surgeon introduced a pulmonary artery catheter in every patient before weaning from CPB for monitoring of pulmonary artery pressure and intermittent blood sampling for SvO\textsubscript{2} (Paper I to IV). An epidural needle was used to puncture the outflow tract of the right ventricle and then an epidural catheter cut 5 cm from its tip (Perifix-Katheter, B.Braun Melsungen AG, Germany) was introduced approximately 15 cm into the pulmonary artery. A 4-0 prolene purse string suture was gently tightened around the puncture site to minimize risk for bleeding at withdrawal, which was usually done the next morning before the withdrawal of the chest tubes \textsuperscript{18}.

**Study protocol**

**Paper I**

Paper I was designed as retrospective cohort study. NT-proBNP was routinely measured the day before surgery in elective patients and on the day of surgery in emergency patients. Demographic and perioperative data were registered prospectively in a computerized institutional database (Carath version 5.4, Fujitsu Inc.). Mortality data were retrieved from the Swedish Civil registry.
The 2978 consecutive patients undergoing first time surgery for CAD (n=2226), AS (n=406) or MR (n=346) included in the study were followed 90 days. Multivariable linear regression was used to assess the role of underlying heart disease on NT-proBNP levels at admission to surgery. Multivariable logistic regression was used to identify preoperative and intraoperative risk factors for severe PHF and postoperative mortality.

**Comment:** The timing of surgery and referral selection bias might have an impact on the level of natriuretic peptides. However, availability of cardiac surgical resources permitted most patients to be treated according to current guidelines. Referral selection bias was minimized as the study included virtually all patients operated for CAD, AS and MR during a five-year period in southeastern Sweden.

Paper I has been published in a previous thesis (Linköping Medical Dissertations No. 1680) by Henrik Hultkvist who is co-author. The individual contributions of the authors are given in Paper I.

**Paper II**

This was designed as prospective, observational, longitudinal study evaluating the association between NT-proBNP and PHF after elective first-time AVR for AS. Plasma NT-proBNP was assessed at preoperative evaluation, the day before surgery, the first (POD1) and third postoperative morning (POD3), and at the six-month follow-up. A Clinical Endpoints Committee, blinded to NT-proBNP results, used prespecified hemodynamic criteria to diagnose PHF. Demographic and perioperative data were registered prospectively in a computerised institutional database (Carath version 5.4, Fujitsu Inc.). Mortality data were retrieved from the Swedish Civil registry. 203 patients undergoing elective first-time AVR for AS were followed on average 8.6 ± 1.1 years (range 6.5 - 10.5 years). A receiver operating characteristic (ROC) analysis was carried out to evaluate the discrimination of NT-proBNP for PHF. Multivariable logistic regression was used to identify
Material and methods

risk factors and predictors for PHF. Cox proportional hazards regression models were done to identify risk factors for mortality during follow-up.

Paper III

Paper III was designed as prospective observational study investigating if postoperative NT-proBNP can be used for assessment of PHF in patients undergoing CABG for ACS. Plasma NT-proBNP was measured preoperatively, on POD1 and POD3. A Clinical Endpoints Committee, blinded to NT-proBNP, used prespecified criteria relying mainly on mixed venous oxygen saturation to diagnose PHF and severe PHF. 382 consecutive patients from the GLUTAMICS-trial undergoing isolated CABG for acute coronary syndrome were included in the study. Multivariable linear regression was done to assess the role of PHF or severe PHF on postoperative NT-proBNP levels. ROC analysis was carried out to evaluate discrimination of postoperative NT-proBNP and its trends with regard to PHF and severe PHF respectively. Multivariable logistic regression was used to analyze predictors for PHF.

Paper IV

Paper IV was designed as a prespecified substudy of an investigator-initiated, prospective, double-blind randomized clinical trial, the GLUTAMICS-trial to assess the influence of intravenous glutamate infusion on postoperative NT-proBNP levels in patients undergoing CABG for acute coronary syndrome. Plasma NT-proBNP was measured preoperatively, on POD1 and POD3. A Clinical Endpoints Committee, blinded to both intervention and NT-proBNP used prespecified criteria to diagnose PHF. 399 patients with parallel assignment to intravenous infusion of glutamate (n=200) or placebo (saline) (n=199) undergoing CABG with or without concomitant procedure for acute coronary syndrome were included. Multivariable linear regression was used to assess the role of glutamate on postoperative NT-proBNP level.
**Comment:** Paper III – IV constitute prespecified substudies from the GLUTAMICS-trial using NT-proBNP with different objectives.

**Methods**

**NT-proBNP measurement**

Sampling for NT-proBNP was done at preoperative evaluation (Paper II), the day before surgery (Paper I and II), on the day of surgery in emergency patients (Paper I), immediately before induction of anesthesia (Paper III and IV), the first and third postoperative morning (Paper II, III and IV) and at the six-month follow-up (Paper II).

Venous blood samples were collected in lithium heparin tubes and analyzed within 1 hour (emergency) to 3 hours (elective patients). NT-proBNP was measured in plasma by electro-chemoiluminescence immunoassay on a Roche Elecsys 2010 automated platform (Roche Diagnostics, Basel, Switzerland). The assay had an effective measuring range of 5-35000 ng·L⁻¹. The inter-assay coefficient of variation was at 175 ng·L⁻¹ CV=2.7%, 355 ng·L⁻¹ CV=2.4% and 1068 ng·L⁻¹ CV=1.9%. The results of the assays were released from the laboratory when the trial was terminated (Paper II, III and IV). The following upper reference limits (URLs) were applied: 450 ng·L⁻¹ for <50 years, 900 ng·L⁻¹ for 50-75 years, and 1800 ng·L⁻¹ for >75 years. Values < 300 ng·L⁻¹ were considered normal in all age groups and the intervals between 300 ng·L⁻¹ and the URL for the age group were considered a grey zone 26, 37.
Mixed venous oxygen saturation (SvO₂) measurement

Sampling for SvO₂ was done after weaning from cardiopulmonary bypass, on admission to ICU and whenever unstable hemodynamics was suspected (Paper I-IV).

Mixed venous blood was drawn from a surgical pulmonary artery catheter. SvO₂ was measured in ABL 725 (Radiometer Medical Aps, Brønshøj, Denmark) or ABL 825 (Radiometer Medical Aps, Brønshøj, Denmark - Paper I and II); or an ABL 500 (Radiometer Medical Aps, Brønshøj, Denmark - Papers III, IV). Prespecified SvO₂ criteria were used by blinded Clinical Endpoints Committee to diagnose PHF in Paper II, III and IV.

EuroSCORE calculations

Additive EuroSCORE was automatically calculated in all studies by an algorithm in the institutional database (Carath version 5.4, Fujitsu Inc.). EuroSCORE II was calculated retrospectively for each patient with the EuroSCORE II interactive calculator at www.euroscore.org (Paper II, III and IV).

Definitions

Postoperative heart failure

Paper II, III and IV

Postoperative heart failure was considered present if criteria a+b were fulfilled. a) Decision reached by the Endpoints committee that heart failure was evident at weaning from cardiopulmonary bypass or during the early hours after surgery based on criteria below and supported by available clinical records, echocardiography and hemodynamic data. b) SvO₂ criteria in relation to systolic arterial pressure (SAP) that could not be explained by
shivering, anemia or hypovolemia. The criteria were based on extensive studies on SvO₂ with regard to outcome and clinical experience regarding the approximate relationship between SvO₂ and SAP while using fast acting vasodilator nitroprusside. SvO₂ < 50% and SAP < 130 mmHg; SvO₂ < 55% and SAP < 110 mmHg; SvO₂ < 60% and SAP < 90 mmHg.  

**Severe postoperative heart failure**

Due to lack of generally accepted criteria for severe postoperative heart failure, severe postoperative heart failure had to be defined based on available data in the retrospective study (Paper I). In the prospective studies, a blinded Clinical endpoints committee relied on prespecified criteria to diagnose severe postoperative heart failure (Paper II, III and IV).

**Paper I**

Severe postoperative heart failure was defined as clinical diagnosis in the medical records and/or echocardiographic signs of heart failure and an ICU stay ≥ 72 hours or hospital mortality with one of the following: intra-aortic balloon pump or ventricular assist device, or the use of inotropes (adrenaline ≥ 3 μg∙min⁻¹; milrinone ≥ 0.375 μg∙kg⁻¹∙min⁻¹; need for two inotropes at any dosage; or use of levosimendan at any dosage).

**Comment:** Because of the retrospective nature of the study and the large number of patients that had to be reviewed, ICU stay larger than 72 hours (as opposed to 48 hours in the prospective studies) was used to distinguish patients with severe PHF. In retrospect it seems that CABG patients in the prospective studies and the retrospective study with severe PHF were fairly comparable regarding severity.

**Paper II, III and IV**

Severe postoperative heart failure was defined as PHF leading to death or an extended ICU stay (≥48 hours) in patients requiring treatment with an intra-aortic balloon pump or at least one inotropic agent with the following
Material and methods

Dosages ≥24 h after admission to the ICU: epinephrine ≥0.033 μg·kg⁻¹·min⁻¹, milrinone ≥0.375 μg·kg⁻¹·min⁻¹, dopamine ≥4 μg·kg⁻¹·min⁻¹, dobutamine ≥4 μg·kg⁻¹·min⁻¹, or levosimendan regardless of dose.

LV dysfunction

A preoperative LV ejection fraction (LVEF) of 0.30 or less according to echocardiography was classified as severe left ventricular dysfunction whereas a LVEF of 0.31 - 0.45 was classified as moderate LV dysfunction.

Postoperative mortality

Postoperative mortality was defined as the rate of death from any cause within 30 days after cardiac surgery, or death from any cause later during the same hospitalization period, including discharge to the referral hospital. Medical records were scrutinized for all patients dying within 90 days of surgery. Mortality data were retrieved from the Swedish Civil registry. The cause of death was retrieved from medical records and usually supported by autopsy.

Hospital mortality

Hospital mortality was defined as mortality during the first hospitalization period. This included postoperative stay at the referral hospital as a substantial proportion of patients were discharged to their county hospitals.

Statistics

Data are presented as percentages or mean ± standard deviation or median [interquartile range]. Continuous variables not following a normal distribution, were analysed with Mann-Whitney U test (Paper I, II, III and IV).
Material and methods

and Wilcoxon signed ranks test were used (Paper II and III). Kruskal-Wallis test and pairwise comparison test was used for comparison continuous variables among three groups (Paper I). Pearson Chi-square test was used to compare proportions and to account for multiple testing the Bonferroni correction was used (Paper I). Categorical data were compared with Fisher’s exact test (Paper II, III and IV). Statistical significance was defined as p<0.05. All p-values were two-sided.

Multivariable linear regression was used to assess the association between two or more independent variables and a single continuous dependent variable (Paper I, III and IV).

Multivariable logistic regression was done with a backward (conditional) stepwise (Paper I, II and III). Hosmer-Lemeshow goodness-of-fit statistics were calculated for the final model (Paper I, II and III). Predictive value was assessed with ROC analysis (Paper I, II and III). Youden’s index was used for calculation of best cutoff point with regard to sensitivity and specificity (Paper I, II and III).

Survival curves were generated by means of Kaplan-Meier estimates, and differences in survival were compared with the log-rank test (Paper II). Cox proportional hazards regression models were used to identify risk factors for mortality during follow-up (Paper II).

Statistical analyses were performed with SPSS statistics version 23 (IBM) for windows (Paper I, II, III and IV) and Statistica 13.2, Dell Inc (Paper I), Statistica 12.0 (StatSoft Inc., Tulsa, OK) (Paper II and III).

Ethics

All studies were performed according to the Helsinki Declaration of Human Rights and the studies in Paper III-IV were conducted according to
Material and methods

Good Clinical Practice (GCP) standard. All studies were approved by the Regional Ethical Review Board in Linköping, Sweden (Paper I: Dnr 2011/497-31; Paper II: M 198-07, T 126-08, 2012/422-32; Paper III and IV: original protocol no M76-05; addendum 26-07). The patients were enrolled in the studies after written informed consent was obtained (Paper II, III and IV) with the exception of Paper I. Owing to the nature of that study; the ethics committee waived the need for written informed consent.
RESULTS

Preoperative NT-proBNP and underlying heart disease (Paper I)

Paper I was based on retrospective cohort analysis. Among all 2978 patients, the median age was 70 [63-76] years and 24% were female. The median Additive EuroSCORE was 4 [3-6]. Age, hemoglobin, albumin, proportion of moderate or severe LV dysfunction, atrial fibrillation, and obesity were significantly different among patients with CAD, AS, and MR. Details are given in Table 1 of Paper I.

NT-proBNP was higher in patients with AS than in patients with CAD (595 [260-1510] vs 290 [120-833] ng·L⁻¹, p<0.0001) or patients with MR (400 [110-1350] ng·L⁻¹, p<0.0001). After adjusting for age, eGFR, female gender, and obesity, NT-proBNP was 1.67 times higher in patients with AS than in patients with CAD (adjusted coefficient 0.223, 95%CI 0.160-0.285; p<0.0001) and 1.41 times higher in patients with MR than patients with CAD (adjusted coefficient 0.150, 95%CI 0.085-0.215, p<0.0001; Table 3).

Table 3. Multivariable linear regression results for log₁₀NTproBNP Preop in all patients.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Adjusted coefficient</th>
<th>95%CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>0.020</td>
<td>0.018-0.022</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Preop eGFR (mL·min⁻¹·1.73m⁻²)</td>
<td>-0.006</td>
<td>-0.007 -0.005</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Male ref</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>0.114</td>
<td>0.064-0.164</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>CAD ref</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MR ref</td>
<td>0.150</td>
<td>0.085-0.215</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>AS</td>
<td>0.223</td>
<td>0.160-0.285</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Adjusted R²=0.215, ANOVA for the model (df=5, F=164.162, p<0.0001). CI, confidence interval; eGFR, estimated glomerular filtration rate according to MDRD formula; CAD, coronary artery disease; AS, aortic valve stenosis; MR, mitral valve regurgitation.
Preoperative NT-proBNP and severe postoperative heart failure (Paper I)

A total of 130 patients had severe PHF (88 patients with CAD, 14 patients with AS, 28 patients with MR). According to ROC analysis, preoperative NT-proBNP demonstrated significant discriminatory power with regard to severe PHF in patients with CAD (area under the curve (AUC)=0.79, 95%CI 0.73-0.85, p<0.0001), MR (AUC=0.80, 95%CI 0.72-0.87, p<0.0001) and AS (AUC=0.66, 95%CI 0.51-0.81, p=0.047; Figure 1). The best cutoffs according to Youden’s index were 855 ng·L\(^{-1}\) (sensitivity 73%, specificity 77%) in CAD patients, 975 ng·L\(^{-1}\) (sensitivity 71%, specificity 65%) in AS patients and 800 ng·L\(^{-1}\) (sensitivity 82%, specificity 69%) in MR patients.

In the multivariable analysis, NT-proBNP ≥ 855 ng·L\(^{-1}\) emerged as an independent risk factor for severe PHF in patients with CAD (adjusted Odds
ratio (OR) 2.87, 95% CI 1.56-5.30, p=0.001). Age, preoperative dialysis, aortic cross-clamp time in upper quartile (≥ 62min), moderate to severe LV dysfunction, NYHA IV, insulin-treated diabetes, critical preoperative state, and emergency operation were the other variables in the final model (Table 4). The number of events was too few to permit multivariable analysis in patients with AS or MR.

### Table 4. Multivariable analysis* of risk factors for severe PHF in CAD patients.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds ratio</th>
<th>95%CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>1.05</td>
<td>1.01-1.08</td>
<td>0.005</td>
</tr>
<tr>
<td>Preoperative dialysis</td>
<td>23.1</td>
<td>6.47-82.2</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Preop NT-proBNP ≥855 ng·L⁻¹</td>
<td>2.87</td>
<td>1.56-5.30</td>
<td>0.001</td>
</tr>
<tr>
<td>Cross-clamp time upper quartile (≥262 min)</td>
<td>3.04</td>
<td>1.78-5.18</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Moderate to severe LV dysfunction</td>
<td>2.69</td>
<td>1.51-4.79</td>
<td>0.001</td>
</tr>
<tr>
<td>NYHA IV</td>
<td>2.74</td>
<td>1.39-5.37</td>
<td>0.003</td>
</tr>
<tr>
<td>Insulin-treated diabetes</td>
<td>2.65</td>
<td>1.50-4.68</td>
<td>0.001</td>
</tr>
<tr>
<td>Emergency operation</td>
<td>3.39</td>
<td>1.40-8.24</td>
<td>0.007</td>
</tr>
<tr>
<td>Critical condition preoperatively</td>
<td>7.49</td>
<td>2.19-25.7</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Due to a lack of aortic cross clamp time, patients undergoing off-pump CABG are not included in this model. *Multivariable backward stepwise logistic regression model. Nagelkerke R²=0.322; Hosmer-Lemeshow goodness-of-fit test χ² (df=8) =7.280, p=0.507. Severe PHF, severe postoperative heart failure; CAD, coronary artery disease; CI, confidence interval; LV, left ventricular; NYHA, New York Heart Association.

### Preoperative NT-proBNP and postoperative mortality  
(Paper I)

Fifty-three (2%) patients died postoperatively within 30 days or in-hospital; 40 due to PHF, 2 due to cardiac arrest and 9 due to non-cardiac causes (postoperative stroke n=3, infection n=3, primary renal failure n=1, respiratory cause n=1, intestinal ischemia n=1) whereas cause of death was unknown in 2 patients (Supplemental Table S3 of Paper I). Patients with postoperative mortality had significantly higher preoperative NT-proBNP than
patients without postoperative mortality (1780 [430-3200] vs 320 [130-958] ng·L⁻¹, p<0.0001).

In CAD patients, preoperative NT-proBNP demonstrated significant discrimination with regard to postoperative mortality (AUC=0.78, 95%CI 0.71-0.85, p<0.0001; best cutoff 905 ng·L⁻¹ with a sensitivity of 67% and specificity of 77%; Figure 2). The number of events was too few to permit ROC analysis in patients with AS (n=4) or MR (n=6).

Figure 2. 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<0.0001; best cutoff 905 ng·L⁻¹ with a sensitivity of 67% and specificity of 77%). AUC, area under the curve; CAD, coronary artery disease; CI, confidence interval; ROC, receiver operating characteristics.

NT-proBNP ≥905 ng·L⁻¹ emerged as an independent risk factor for postoperative mortality in patients with CAD (adjusted OR 2.56, 95% CI 1.21-5.40, p=0.014). Age, NYHA IV, preoperative albumin, preoperative dialysis, and emergency operation also remained in the final model for postoperative mortality (Table 5).
Table 5. Multivariable analysis* of risk factors of postoperative mortality in CAD patients.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds ratio</th>
<th>95% CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>1.09</td>
<td>1.04-1.15</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>NYHA IV</td>
<td>2.84</td>
<td>1.23-6.56</td>
<td>0.015</td>
</tr>
<tr>
<td>Emergency operation</td>
<td>3.54</td>
<td>1.29-9.68</td>
<td>0.014</td>
</tr>
<tr>
<td>Preop dialysis</td>
<td>24.2</td>
<td>6.33-92.3</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Preop NT-proBNP ≥ 905 ng·L⁻¹</td>
<td>2.56</td>
<td>1.21-5.40</td>
<td>0.014</td>
</tr>
<tr>
<td>Preop p-albumin, g·L⁻¹</td>
<td>0.93</td>
<td>0.86-0.99</td>
<td>0.025</td>
</tr>
</tbody>
</table>

*Multivariable backward stepwise logistic regression model. Nagelkerke $R^2 = 0.254$; Hosmer-Lemeshow goodness-of-fit test $\chi^2 (df=8) = 6.560$, p = 0.535. CAD, coronary artery disease; CI, confidence interval; NYHA, New York Heart Association functional classification.

NT-proBNP levels in relation to PHF in surgery for aortic stenosis (Paper II)

Paper II was based on a cohort of 203 patients undergoing elective first-time AVR for AS. NT-proBNP was sampled at the following time points: preoperative evaluation (PREEV) (n=195), the day before the index procedure (PREOP) (n=199), POD1 (n=192), POD3 (n=186), and at the six-month follow-up (n=181).

Among all 203 patients, the median age was 70 [65-77] years and 50% were female. The median EuroSCORE II was 1.6 [1.1-2.8]. More details are given in Table 1 Paper II.

Of the 18 patients who fulfilled study criteria for PHF, two had mild transient PHF that resolved without inotropes. Three patients developed severe PHF. No patient with PHF died within 30 days after surgery, but PHF was associated with a significantly longer ICU stay and ventilation time, more signs of myocardial injury, and renal dysfunction (Table 2 Paper II).

NT-proBNP level increased postoperatively in all patients, but this was significantly more pronounced on POD1 in patients with PHF vs. those with...
Results

out PHF (6415 [3145-11220] vs 2445 [1540-3855] ng·L⁻¹, p<0.0001) (Figure 3). The average peak level was recorded on POD1 in the PHF cohort and on POD3 in the cohort without PHF. The NT-proBNP level on POD1 demonstrated good discrimination for PHF (AUC=0.82; 95% CI 0.72-0.91; p<0.0001). The best cutoff value of 5290 ng·L⁻¹ had a sensitivity of 63% and a specificity of 85% (Figure 4). Poor discrimination was found preoperatively and later in the postoperative course (Figure 4).

NT-proBNP POD1 level ≥5290 ng·L⁻¹ emerged as a significant predictor of PHF together with p-CK-MB POD1 > 50 µg·L⁻¹ in the multivariable logistic regression model (Supplemental Table 2 of Paper II). Variables significantly associated with PHF in the univariable analysis are given in Supplemental Table 3 of Paper II.

Figure 3. NT-proBNP levels before and after surgery in patients with PHF (black bars) and without PHF (white bars). PHF, postoperative heart failure; PREEV, preoperative evaluation; PREOP, the day before the index procedure; POD1, first postoperative day; POD3, third postoperative day; Six months postop, at the six-month follow-up. Data are expressed as medians with interquartile ranges; * p<0.05.
Results

Patients with a NT-proBNP level ≥5290 ng·L⁻¹ on POD1 had a significantly longer ICU stay and more signs of myocardial and renal injury. None of these patients died within 30 days (Supplemental Table 4 of Paper II).

NT-proBNP and PHF related to long-term survival after surgery for aortic stenosis (Paper II)

The mean follow-up from the entry into the study was 8.9 ±1.1 years (range 6.5-10.5 years). During this period, there were 48 deaths. Cumulative survival was significantly impaired in patients with PHF (Figure 5) and a NT-proBNP level ≥5290 ng·L⁻¹ on POD1 (Figure 4 in Paper II). The cumulative survival in patients with PHF was impaired if the NT-proBNP level was ≥5290 ng·L⁻¹ on POD1 (Figure 6). The unadjusted hazard ratio (HR) for
Results

PHF for long-term mortality was 3.01 (95% CI 1.45-6.21, p=0.003). The unadjusted HR for patients with a NT-proBNP level ≥5290 ng·L⁻¹ on POD1 for long-term mortality was 3.25 (95% CI 1.77-5.97, p<0.0001).

![Cumulative survival (Kaplan-Meier) for patients with (dashed line) or without postoperative heart failure (PHF) (solid line).](image)

<table>
<thead>
<tr>
<th>Patients at risk</th>
<th>Year</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Without PHF</td>
<td></td>
<td>185</td>
<td>183</td>
<td>180</td>
<td>178</td>
<td>173</td>
<td>166</td>
<td>159</td>
<td>123</td>
<td>89</td>
<td>43</td>
<td>3</td>
</tr>
<tr>
<td>PHF</td>
<td></td>
<td>18</td>
<td>16</td>
<td>14</td>
<td>14</td>
<td>14</td>
<td>13</td>
<td>13</td>
<td>9</td>
<td>5</td>
<td>4</td>
<td></td>
</tr>
</tbody>
</table>

**Figure 5.** Cumulative survival (Kaplan-Meier) for patients with (dashed line) or without postoperative heart failure (PHF) (solid line).

In the multivariable Cox regression model PHF with a NT-proBNP level ≥5290 ng·L⁻¹ on POD1 emerged as a predictor of long-term mortality (HR 6.20, 95% CI 2.72-14.12, p<0.0001) together with preoperative NT-proBNP, age and diabetes mellitus (Table 6). The univariate hazard ratios of variables tested in the multivariable Cox regression are shown in Supplemental Table 5 of Paper II.
Results

Figure 6. Cumulative survival (Kaplan-Meier) in the subgroup with PHF for patients with a NT-proBNP level ≥5290 ng·L⁻¹ (dashed line) or < 5290 ng·L⁻¹ (solid line) on POD1. The NT-proBNP level on POD1 was missing in two patients (one died 6 years after surgery, the other one was alive 7 years after surgery). PHF, postoperative heart failure; POD1, the first postoperative day.

Table 6. Hazard Ratios for long-term mortality in patient undergoing AVR for AS in the multivariable regression model

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hazard Ratio</th>
<th>95%CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>PHF and POD1 NT-proBNP &lt; 5290 ng·L⁻¹</td>
<td>6.20</td>
<td>2.72-14.1</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>NT-proBNP PREOP ≥ 825 ng·L⁻¹*</td>
<td>2.80</td>
<td>1.48-5.29</td>
<td>0.002</td>
</tr>
<tr>
<td>Age (years)</td>
<td>1.07</td>
<td>1.02-1.11</td>
<td>0.002</td>
</tr>
<tr>
<td>Diabetes mellitus†</td>
<td>2.42</td>
<td>1.22-4.80</td>
<td>0.011</td>
</tr>
</tbody>
</table>

* The best cutoff of preoperative NT-proBNP with regard to long-term mortality was 825 ng·L⁻¹ (AUC=0.73, p<0.0001, with a sensitivity of 64% and specificity of 76%). †Diabetes mellitus regardless of treatment. CI, confidence interval; POD1, first postoperative day; PREOP, the day before index procedure.
Results

PHF and severe PHF in isolated CABG for ACS (Paper III)

Paper III was based on a cohort of 382 patients with ACS undergoing urgent isolated first-time CABG. NT-proBNP was available as follows: preoperative (n=366), postoperative day 1 (n=320) and postoperative day 3 (n=325) and data from all three time points available in 267 patients. Among all 382 patients, the median age was 69 [62-75] years and 19% were female. The median EuroSCORE II was 2.4 [1.6-3.9]. More details showed in Table 1 in Paper III.

Overall 88 patients (23%) were treated with inotropes at some stage intraoperatively or postoperatively (Supplemental Table S1 of Paper III). Only 33 of these patients fulfilled criteria for PHF and these patients had significantly worse outcome and more pronounced increase of NT-proBNP postoperatively (Supplemental Table S1 of Paper III).

Overall 35 patients (9%) from the whole cohort fulfilled criteria for PHF. Seven of these patients were also classified to have severe PHF. Two patients had mild transient PHF that resolved without inotropes.

Patients with PHF had a more pronounced risk profile preoperatively and extended cross-clamp and CPB times intraoperatively. Postoperatively they had more signs of myocardial injury, higher incidence of acute kidney injury, extended ventilation time, prolonged ICU stay and a higher hospital mortality compared to those without PHF. Clinical outcomes were further aggravated in patients with severe PHF (Table 2 in Paper II).
Postoperative NT-proBNP in relation to PHF in isolated CABG for ACS (Paper III)

Overall NT-proBNP increased from 420 [150-970] ng·L⁻¹ preoperatively to 2065 [1324-3650] ng·L⁻¹ (p<0.001) POD1 and to 3610 [2167-6010] ng·L⁻¹ (p<0.001) POD3. Patients with PHF had higher pre- and postoperative levels of NT-proBNP compared to those without PHF (Figure 7).

![Graph showing perioperative NT-proBNP levels in patients without PHF, with PHF and severe PHF. Data given as medians with interquartile range. Mann-Whitney U test was performed and p<0.05 was considered significant, indicated by*. PHF, postoperative heart failure.](image)

Figure 7. Perioperative NT-proBNP levels in patients without PHF, with PHF and severe PHF. Data given as medians with interquartile range. Mann-Whitney U test was performed and p<0.05 was considered significant, indicated by*. PHF, postoperative heart failure.

After adjusting for glutamate treatment and known preoperative non-cardiac confounders age, eGFR, female and obesity, NT-proBNP POD1 was 1.46 times higher in patients with PHF than in patients without PHF (ad-
adjusted coefficient 0.164, 95%CI 0.064-0.265, p=0.001; Table 7). Interaction of glutamate was not statistically significant and would have changed the adjusted coefficient for PHF by 3% if kept in the final model.

**Table 7.** Multivariable linear regression results for log10 NT-proBNP POD1 in all patients adjusted for PHF, glutamate treatment and known preoperative non-cardiac confounders*.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Adjusted coefficient</th>
<th>95%CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>PHF</td>
<td>0.164</td>
<td>0.064-0.265</td>
<td>0.001</td>
</tr>
<tr>
<td>eGFR(mL·min⁻¹·1.73m⁻²)</td>
<td>-0.005</td>
<td>-0.006-0.003</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Female</td>
<td>0.176</td>
<td>0.098-0.255</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

*age, eGFR, female gender, obesity. Adjusted $R^2=0.31$, ANOVA for the model (df=3, F=46.48, p<0.0001). CI, confidence interval; eGFR, estimated glomerular filtration rate according to MDRD formula; PHF, postoperative heart failure.

After similar adjustment for glutamate treatment and known preoperative non-cardiac confounders, NT-proBNP POD3 was 1.54 times higher in patients with PHF than in patients without PHF (adjusted coefficient 0.188, 95%CI 0.188-0.289, p<0.0001; Table 8). Interaction of glutamate was not statistically significant and would not have changed the adjusted coefficient for PHF if kept in the final model.

**Table 8.** Multivariable linear regression results for log10 NT-proBNP POD3 in all patients adjusted for PHF, glutamate treatment and known preoperative non-cardiac confounders*.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Adjusted coefficient</th>
<th>95%CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>PHF</td>
<td>0.188</td>
<td>0.088-0.289</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Age (years)</td>
<td>0.011</td>
<td>0.007-0.016</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>eGFR(mL·min⁻¹·1.73m⁻²)</td>
<td>-0.003</td>
<td>-0.005-0.002</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Female</td>
<td>0.104</td>
<td>0.029-0.178</td>
<td>0.006</td>
</tr>
</tbody>
</table>

*age, eGFR, female gender, obesity. Adjusted $R^2=0.39$, ANOVA for the model (df=4, F=50.26, p<0.0001). CI, confidence interval; eGFR, estimated glomerular filtration rate according to MDRD formula; PHF, postoperative heart failure.

NT-proBNP on POD1 demonstrated significant discrimination for PHF (AUC=0.70; 95%CI 0.61-0.79; p<0.0001). The best cutoff value of 1836
ng·L⁻¹ had a sensitivity of 90% and a specificity of 46% (Figure 8A). A similar discrimination was found for NT-proBNP on POD3 (AUC=0.70; 95% CI 0.60-0.81; p<0.0001). The best cutoff value 6065 ng·L⁻¹ had a sensitivity of 57% and a specificity of 79% (Figure 8B).

Figure 8. Receiver operating characteristics (ROC) to evaluate discrimination of postoperative NT-proBNP for PHF. Left panel (A) demonstrates discrimination of NT-proBNP on POD1 for PHF (AUC=0.70; 95% CI 0.61-0.79; p<0.0001, best cutoff 1836 ng·L⁻¹ with a sensitivity of 90% and a specificity of 46%). Right panel (B) demonstrates discrimination of NT-proBNP on POD3 for PHF (AUC=0.70; 95% CI 0.60-0.81; p<0.0001, best cutoff 6065 ng·L⁻¹ with a sensitivity of 57% and a specificity of 79%). AUC, area under curve; CI, confidence interval; POD1, postoperative day 1; POD3, postoperative day 3.

Postoperative changes of NT-proBNP in relation to PHF in isolated CABG for ACS (Paper III)

NT-proBNP increased postoperatively in all patients with the highest values recorded on POD3. The postoperative increase of NT-proBNP was significantly more pronounced in patients with PHF and the postoperative changes of NT-proBNP were associated with PHF.

Postoperative increase of NT-proBNP from preoperative level to POD3 demonstrated significant discrimination for PHF (AUC=0.68, 95% CI
Results

0.56-0.79, p=0.002, best cutoff 7639 ng·L⁻¹ with a sensitivity of 40% and a specificity of 92%). Similar discrimination was found for postoperative change of NT-proBNP from preoperative level to POD1 (AUC=0.66, 95% CI 0.56-0.76, p=0.004, best cutoff 1372 ng·L⁻¹ with a sensitivity of 87% and a specificity of 46%) and for postoperative change of NT-proBNP from POD1 to POD3 (AUC=0.63; 95% CI 0.50-0.76, p=0.028, best cutoff 4299 ng·L⁻¹ with a sensitivity of 38% and a specificity of 90%).

In the multivariable logistic regression analysis, delta Troponin T POD3-Pre, delta NT-proBNP POD3-POD1 ≥ 4299 ng·L⁻¹ and severe LV dysfunction emerged as independent risk factors for PHF (Table 9). The univariable Odds ratios for variables tested in are shown in Supplemental Table S4 of Paper III.

**Table 9** Multivariable analysis* of risk factors for PHF

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds ratio</th>
<th>95%CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delta Troponin T POD3-Pre (ng·L⁻¹)</td>
<td>1.001</td>
<td>1.000-1.002</td>
<td>0.002</td>
</tr>
<tr>
<td>Delta NT-proBNP POD3-POD1 ≥ 4299 ng·L⁻¹</td>
<td>5.12</td>
<td>1.86-14.10</td>
<td>0.002</td>
</tr>
<tr>
<td>Severe LV dysfunction</td>
<td>12.77</td>
<td>2.76-58.99</td>
<td>0.001</td>
</tr>
</tbody>
</table>

*Multivariable backward stepwise logistic regression model. Nagelkerke R² =0.28; Hosmer-Lemeshow goodness-of-fit test x² (df= 8) =5.74, p=0.68. CI: confidence interval.

Postoperative NT-proBNP in relation to severe PHF in isolated CABG for ACS (Paper III)

The highest pre- and postoperative NT-proBNP values were recorded in patients with severe PHF (Figure 7).

Patients with severe PHF had significantly higher NT-proBNP preoperatively (1920 [1030-4202] v 750 [300-1265] ng·L⁻¹, p=0.022) and on POD1
Results

(5040 [3060-10200] v 2740 [1875-4600] ng·L⁻¹, p=0.028) compared to patients with PHF that was not classified as severe.

After adjusting for glutamate treatment and known preoperative non-cardiac confounders age, eGFR, female and obesity, NT-proBNP POD1 was 2.18 times higher in patients with severe PHF than in patients without PHF (adjusted coefficient 0.339, 95%CI 0.134-0.543, p=0.001; Table 10). Interaction of glutamate was not statistically significant and would have changed the adjusted coefficient for severe PHF by 6% if kept in the final model.

Table 10. Multivariable linear regression results for log₁₀ NT-proBNP POD1 adjusted for severe PHF*, glutamate treatment and known preoperative non-cardiac confounders†.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Adjusted coefficient</th>
<th>95%CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe PHF*</td>
<td>0.339</td>
<td>0.134-0.543</td>
<td>0.001</td>
</tr>
<tr>
<td>eGFR (mL·min⁻¹·1.73m⁻²)</td>
<td>-0.005</td>
<td>-0.006- -0.003</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Female</td>
<td>0.166</td>
<td>0.083-0.249</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

*Patients with PHF that were not classified as severe excluded. † age, eGFR, female gender, obesity. Adjusted R² =0.29, ANOVA for the model (df =3, F =41.90, p<0.0001). CI: confidence interval; eGFR: estimated glomerular filtration rate according to MDRD formula; PHF: postoperative heart failure.

After similar adjustment for glutamate treatment and known preoperative non-cardiac confounders, NT-proBNP POD3 was 1.81 times higher in patients with severe PHF than in patients without PHF (adjusted coefficient 0.258, 95%CI 0.042-0.474, p=0.019; Table 11). Interaction of glutamate was not statistically significant would have changed the adjusted coefficient for severe PHF by 0.3% if kept in the final model.

NT-proBNP on POD1 demonstrated significant discrimination for severe PHF (AUC=0.86; 95% CI 0.76-0.95; P=0.001). The best cutoff value of 4575 ng·L⁻¹ had a sensitivity of 71% and a specificity of 84%. A similar discrimination was found for NT-proBNP on POD3 (AUC=0.79; 95% CI 0.55
Results

52
-1.00; P=0.015). The best cutoff value of 6065 ng·L⁻¹ had a sensitivity of 83% and a specificity of 77%.

Table 11. Multivariable linear regression results for log₁₀ NT-proBNP POD3 adjusted for severe PHF*, glutamate treatment and known preoperative non-cardiac confounders†.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Adjusted coefficient</th>
<th>95%CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe PHF*</td>
<td>0.258</td>
<td>0.042-0.474</td>
<td>0.019</td>
</tr>
<tr>
<td>Age (years)</td>
<td>0.012</td>
<td>0.007-0.016</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>eGFR(mL·min⁻¹·1.73m⁻²)</td>
<td>-0.003</td>
<td>-0.004- -0.002</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Female</td>
<td>0.103</td>
<td>0.026-0.180</td>
<td>0.009</td>
</tr>
</tbody>
</table>

*Patients with PHF that were not classified as severe were excluded †age, eGFR, female gender, obesity. Adjusted R² = 0.35, ANOVA for the model (df = 4, F = 41.84, p<0.0001)
CI, confidence interval; eGFR, estimated glomerular filtration rate according to MDRD formula; PHF, postoperative heart failure.

Patients with NT-proBNP above the cutoffs had more pronounced Troponin T elevations, higher incidence of acute kidney injury, extended ventilation time, prolonged ICU stay and higher hospital mortality (Details are given in Supplemental Table S7 and S8 of Paper III).

Influence of glutamate on postoperative NT-proBNP in patients undergoing CABG for ACS (Paper IV)

Paper IV was based on a cohort of 399 patients (glutamate group n=199, control group n=200) patients undergoing CABG for acute coronary syndrome. NT-proBNP measurements were available as follows: preoperative (n=383), postoperative day 1 (n=334) and postoperative day 3 (n=339). A complete set of NT-proBNP data was available in 280 patients. In 17 patients CABG with a concomitant procedure was done (mitral valve surgery n=8, aortic valve surgery n=7, and ablation for atrial fibrillation n=2). The median age was 69 [63-75] years and 19% were female. The median EuroSCORE II was 2.44 [1.65-4.15]. PHF developed in 40 patients and 10 of
these developed severe PHF. Preoperative, intraoperative and postoperative data did not differ significantly between the glutamate group and the control group (Details showed in Table 1 and 2 in Paper IV).

In the whole cohort, postoperative NT-proBNP levels did not differ significantly between the glutamate group and the control group (POD1: 2220 [1484-4040] vs 2041 [1236-3429] ng·L⁻¹, p=0.18; POD3: 3640 [2335-6155] vs 3781 [2081-6020] ng·L⁻¹, p=0.95).

**Influence of glutamate on postoperative NT-proBNP in high risk patients undergoing CABG for ACS (Paper IV)**

Post hoc analysis was done on 101 patients in the upper quartile of risk according to preoperative EuroSCORE II ≥ 4.15 (glutamate group n=56; control group n=45). The groups were evenly distributed, with the exception of higher preoperative Troponin T (40 [0-390] vs 0 [0-30] ng·L⁻¹, p<0.0001) and more patients with angina at rest less than 48 hours before surgery (36% vs 13%, p=0.007) in the control group (Table 12).

In the glutamate group patients had significantly lower postoperative increase of NT-proBNP (POD3-Pre: 3900 [2995-6260] vs 6745 [3455-12687] ng·L⁻¹, p=0.012,) and lower absolute levels of NT-proBNP POD3 compared to the control group (POD3: 4845 [3426-7423] vs 8430 [5370-14100] ng·L⁻¹, p=0.001) (Figure 9). After adjusting for preoperative Troponin T and incidence of angina at rest less than 48 hours before surgery, only glutamate remained in the final multivariable linear regression model with regard to log₁₀NT-proBNP POD3. NT-proBNP POD3 in the glutamate group was 0.62 times of that in the control group (adjusted coefficient -0.208, 95%CI -0.336--0.080; p=0.002).
Table 12. Preoperative characteristics in patients with EuroSCORE II ≥ 4.15.

<table>
<thead>
<tr>
<th>Variables</th>
<th>EuroSCORE II ≥4.15 (n=101)</th>
<th>Glutamate (n=56)</th>
<th>Control (n=45)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>76 [71-79]</td>
<td>76 [70-79]</td>
<td>76 [72-79]</td>
<td>0.85</td>
</tr>
<tr>
<td>Female gender</td>
<td>38% (38)</td>
<td>32% (18)</td>
<td>44% (20)</td>
<td>0.22</td>
</tr>
<tr>
<td>BMI (kg·m⁻²)</td>
<td>25 [22-28]</td>
<td>25 [22-28]</td>
<td>26 [23-28]</td>
<td>0.64</td>
</tr>
<tr>
<td>EuroSCORE II</td>
<td>5.83 [4.89-7.85]</td>
<td>5.86 [5.00-7.54]</td>
<td>5.83 [4.54-8.97]</td>
<td>0.82</td>
</tr>
<tr>
<td>Diabetes</td>
<td>29% (29)</td>
<td>27% (14)</td>
<td>33% (15)</td>
<td>0.38</td>
</tr>
<tr>
<td>Hypertension</td>
<td>72% (72)</td>
<td>68% (38)</td>
<td>76% (34)</td>
<td>0.50</td>
</tr>
<tr>
<td>COPD</td>
<td>18% (18)</td>
<td>21% (12)</td>
<td>13% (6)</td>
<td>0.31</td>
</tr>
<tr>
<td>NT-proBNP (ng·L⁻¹)</td>
<td>1010 [450-2345]</td>
<td>790 [425-1895]</td>
<td>1265 [465-2915]</td>
<td>0.15</td>
</tr>
<tr>
<td>Hemoglobin (g·L⁻¹)</td>
<td>132 [121-142]</td>
<td>133 [125-143]</td>
<td>130 [115-139]</td>
<td>0.08</td>
</tr>
<tr>
<td>Troponin T (ng·L⁻¹)</td>
<td>10 [0-90]</td>
<td>0 [0-30]</td>
<td>40 [0-390]</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>p-Creatinine (umol·L⁻¹)</td>
<td>97 [88-122]</td>
<td>97 [87-115]</td>
<td>97 [90-123]</td>
<td>0.51</td>
</tr>
<tr>
<td>eGFR (mL·min⁻¹·1.73m⁻²)</td>
<td>50 [41 - 68]</td>
<td>50 [44-72]</td>
<td>51 [38–66]</td>
<td>0.38</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>21% (21)</td>
<td>20% (11)</td>
<td>23% (10)</td>
<td>0.81</td>
</tr>
<tr>
<td>Three-vessel disease</td>
<td>83% (83)</td>
<td>82% (46)</td>
<td>82% (37)</td>
<td>1.00</td>
</tr>
<tr>
<td>Left main stenosis</td>
<td>48% (48)</td>
<td>45% (25)</td>
<td>51% (23)</td>
<td>0.55</td>
</tr>
<tr>
<td>AMI&lt;3 weeks</td>
<td>73% (73)</td>
<td>73% (41)</td>
<td>71% (32)</td>
<td>0.83</td>
</tr>
<tr>
<td>History of AMI</td>
<td>82% (82)</td>
<td>82% (46)</td>
<td>80% (36)</td>
<td>0.80</td>
</tr>
<tr>
<td>CCS IV</td>
<td>80% (80)</td>
<td>82% (46)</td>
<td>76% (34)</td>
<td>0.47</td>
</tr>
<tr>
<td>Angina at rest&lt;48h</td>
<td>23% (23)</td>
<td>13% (7)</td>
<td>36% (16)</td>
<td>0.007</td>
</tr>
<tr>
<td>Moderate LV dysfunction</td>
<td>21% (21)</td>
<td>23% (13)</td>
<td>18% (8)</td>
<td>0.62</td>
</tr>
<tr>
<td>Severe LV dysfunction</td>
<td>14% (14)</td>
<td>9% (5)</td>
<td>20% (9)</td>
<td>0.15</td>
</tr>
</tbody>
</table>

Data given as medians [interquartile range] or percentages (number).
AMI < 3 weeks, acute myocardial infarction within 3 weeks of surgery; Angina at rest < 48h, angina at rest within 48 hours before surgery; BMI, body mass index; CCS, Canadian cardiovascular society; COPD, chronic obstructive pulmonary disease; EuroSCORE II, European system for cardiac operative risk evaluation II; LV, left ventricular; eGFR, estimated glomerular filtration rate according to MDRD formula.
Figure 9. Perioperative NT-proBNP levels in patients with EuroSCORE II $\geq 4.15$ (upper quartile). White bars, glutamate group; grey bars, control group. Data expressed as medians with interquartile range. $^* p<0.05$. POD, postoperative day; Preop, preoperative.

Postoperatively patients in the glutamate group had less signs of myocardial injury (Troponin T POD3: 290 [160-480] vs 550 [210-860] ng·L$^{-1}$, p=0.015), shorter ICU stay (21 [19-26] vs 25 [22-45] hours, p=0.022) and a trend towards lower incidence of PHF (14%, n=8 vs 31%, n=14, p=0.053) and severe PHF (4%, n=2 vs 16%, n=7, p=0.074) (Table 4 in Paper IV).
Results
PHF remains the major cause of mortality after cardiac surgery. Given the profound prognostic implications of PHF, it is unfortunate that universally accepted diagnostic criteria of PHF are lacking. NT-proBNP is an established biomarker for heart failure in cardiology practice. However, the literature on the association between postoperative NT-proBNP and PHF after cardiac surgery provides little evidence.

Infusion of glutamate after coronary surgery has been reported to enhance both metabolic and hemodynamic myocardial recovery. The aim of this dissertation has been to study the role of NT-proBNP for prediction and assessment of PHF in cardiac surgery and the impact of intravenous glutamate infusion on postoperative NT-proBNP after CABG.

**PHF after cardiac surgery**

As mentioned in the introduction PHF is associated with increased postoperative morbidity and mortality after cardiac surgery. Our current studies found that hospital mortality of patients with PHF was 9-fold higher than in those without PHF after isolated CABG (Paper III). In contrast, none of the patients with PHF died early after AVR for AS but this was followed by poor long-term survival (Paper II). These results corroborate our previous observations, which showed that postoperative mortality associated with PHF after AVR for AS is low compared with PHF after CABG. Accordingly they also show that the serious consequences of PHF after AVR for AS become evident with time. A plausible explanation for the high early mortality associated with PHF in CABG is the strong association between PHF and myocardial ischemia during the early stages of surgery and perioperative myocardial infarction. In AVR for AS only a small
proportion of PHF cases are explained by perioperative myocardial infarction. Although other potential causes such as preoperative left ventricular dysfunction, long aortic cross clamp time and septicemia can be identified a large proportion remains unexplained. A myocardial factor not yet evident at preoperative evaluation, unmasked by PHF, possibly associated with myocardial fibrosis and diastolic function has been suggested to be responsible for the poor long-term outcome in these patients after AVR for AS.

In contrast to our findings, Maganti et al reported that low cardiac output syndrome after AVR was associated with a high early mortality. However, they studied all aortic valve procedures including a high proportion of reoperations, emergency procedures, and endocarditis with shock and renal dysfunction preoperatively presenting as important risk factors, which could explain the differences in early outcome.

Given the profound consequences of PHF it is a concern that generally accepted criteria for PHF are lacking. Consequently, it is unavoidably questionable whether the criteria used for the diagnosis of PHF in our studies were accurate.

PHF can be regarded as a hemodynamic state when cardiac output fails to meet the systemic demand without supportive measures other than correction of volume or vascular resistance. However, a low cardiac output does not necessarily imply PHF since the need for oxygen delivery can low in anesthetized patients early after cardiac surgery. We defined PHF by use of SvO₂, which can detect a mismatch of oxygen delivery and systemic oxygen demand. SvO₂ is well documented with regard to outcome after cardiac surgery. Furthermore, well-known pitfalls such as hypovolemia, anemia and shivering were taken into account by the Clinical endpoints committee.
Reliance on treatment criteria for diagnosis of PHF, such as inotrope requirements or need for mechanical cardiac assist device are clouded by the large differences between geographical regions, institutions and individuals regarding threshold for institution of treatment or prophylaxis. The attending anesthesiologist, independently of the patient, has been shown to be a strong predictor for instituting inotropic treatment.

Our studies revealed that patients classified as PHF had more adverse outcome than those treated with inotropes who did not fulfil criteria for PHF (Paper II and III). These results suggest that the sickest patients were identified by the blinded endpoints committee using our prespecified criteria (Supplemental Table 3 of Paper II).

**NT-proBNP in cardiac surgery**

The impact of underlying heart disease on preoperative NT-proBNP

The role of underlying heart disease was studied in Paper I. Among patients with CAD, AS and MR, the cohort with AS had the highest level of preoperative NT-proBNP, whereas patients with CAD had the lowest values. These findings are consistent with previous studies.

In the setting of volume expansion, pressure overload or ischemia, the resulting ventricular wall stress causes release of natriuretic peptides from the myocardium. However, renal dysfunction, advanced age and female gender are associated with increased natriuretic peptide levels, regardless of left ventricular systolic function, whereas obesity has an inverse relationship with natriuretic peptide levels. As all of these demographics with the exception of eGFR differed between the studied co-
horts we believe it was important to adjust for these non-cardiac confounders to evaluate the role of underlying heart disease per se. After adjusting for these non-cardiac confounders, we found that AS and MR patients still had higher NT-proBNP levels than CAD patients.

The results suggest that stimuli for release of natriuretic peptides by ventricular wall stress caused by pressure overload or volume overload are more important than ischemia per se. However, ischemia is a well-recognized stimulus for the release of natriuretic peptides, though it is unclear to what extent this is caused by myocardial stunning or ischemia per se. Increasing clinical severity and extent of CAD is associated with higher levels of natriuretic peptides even in the absence of LV dysfunction. Even within the “normal range of NT-proBNP” patients with CAD have higher levels than those without CAD. The association between valvular heart disease and natriuretic peptides has received more attention, as echocardiographic findings are easier to link with natriuretic peptide levels. In MR patients, BNP reflects the hemodynamic consequences of MR, and preserved LVEF, left atrial volume and longitudinal myocardial function are the main determinants of BNP levels. Similarly in AS patients with preserved LVEF, BNP levels reflect the clinical and echocardiographic consequences of the afterload burden on the left ventricle rather than the severity of aortic stenosis per se.

**Preoperative NT-proBNP in cardiac surgery**

Regarding the prognostic value of natriuretic peptides, high levels of these biomarkers have been reported to be associated with postoperative mortality, in-hospital cardiac events, need for inotropic support, and PHF after cardiac surgery. The prognostic value of NT-proBNP with regard to PHF and short-term or long-term mortality in different patient cohort will be discussed in the forthcoming sections.
**Preoperative NT-proBNP and postoperative heart failure**

In Paper I, the discrimination of preoperative NT-proBNP with regard to severe PHF was good in CAD and MR patients. In CAD patients, NT-proBNP also emerged an independent risk factor for severe PHF.

The predictive value of preoperative NT-proBNP with regard to severe PHF was less convincing in patients operated for AS. Similar results in AS patients were found in the prospective study (Paper II) relying on prespecified criteria for PHF. A plausible explanation is that a sizeable proportion of PHF after AVR for AS occurs unexpectedly because of intraoperatively acquired myocardial dysfunction in patients preoperatively considered to carry a low risk.

Weber et al. reported similar results evaluating the prognostic value of baseline NT-proBNP with regard to adverse outcome consisting of cardiac death and or rehospitalization for heart failure during follow-up in patients with AS being treated conservatively or undergoing AVR. Preoperative NT-proBNP independently predicted adverse outcome in conservatively treated patients but not in patients undergoing AVR.

These findings differ from a study, which reports preoperative BNP to accurately predict MACEs after AVR but not after CABG. However, in that study MACEs were defined as one of following: cardiac dysfunction, Q-wave infarction, malignant ventricular arrhythmias, and repeat revascularization, during the first 12 months after surgery.

**Preoperative NT-proBNP and mortality after cardiac surgery**

Paper I showed a best cutoff preoperative NT-proBNP of 905 ng·L−1 with regard to postoperative mortality in patients with CAD. This finding corroborates the results of a prospective study by Holm et al. from our institu-
Discussion on a smaller sample (n=366) undergoing isolated CABG for acute coronary syndrome. They reported preoperative NT-proBNP ≥ 1028 ng·L⁻¹ to be a strong predictor for in-hospital mortality.

There were too few events in AS and MR patients to conduct meaningful analyses with regard to postoperative mortality.

In a multivariable regression model regarding long-term mortality in patients undergoing AVR for AS, preoperative NT-proBNP ≥ 825 ng·L⁻¹ emerged as an independent risk factor (Paper II). This result supports the theory about an underlying myocardial factor as a cause of the increased late mortality, but the proposed role of diastolic dysfunction for long-term outcome after AVR for AS remains disputable and requires further investigation.

Postoperative NT-proBNP and postoperative heart failure

Although previous studies suggest an association between postoperative levels of natriuretic peptides and PHF only half a dozen studies have evaluated postoperative natriuretic peptides with regard to what could be considered PHF. Only two of them included more than one hundred patients but both used treatment criteria for PHF. Three studies used prespecified criteria but they were small and PHF accounted only for a proportion of postoperative complications that constituted the endpoint.

We found that postoperative NT-proBNP displayed good discrimination for PHF in patients undergoing AVR for AS and isolated CABG respectively. Patients with postoperative NT-proBNP above the best cutoff had adverse short-term outcome. To our knowledge this is the first time when a blinded assessment of postoperative NT-proBNP with regard to PHF was done in
prospective studies relying on prespecified hemodynamic criteria. Our results agree with the finding of other studies, in which high postoperative levels of natriuretic peptides have been reported to be linked with adverse outcome, need for inotropic and mechanical circulatory support and one-year mortality 2, 51, 55, 71, 73-76, 119.

In patients undergoing isolated CABG, postoperative NT-proBNP demonstrated significant discrimination for PHF and particularly severe PHF (Paper III). Given that the group with PHF included some mild cases of heart failure it is not surprising that the discrimination of NT-proBNP was more evident with regard to severe PHF. NT-proBNP levels were higher in patients with severe PHF, which is expected given that the release of B-type natriuretic peptide into the circulation is proportional to the ventricular expansion and volume overload 24, 27.

Multivariable analysis identified preoperative left ventricular dysfunction, intraoperative myocardial injury and postoperative increase of NT-proBNP to be associated with PHF. The elevated postoperative levels of NT-proBNP were caused by higher plasma concentrations preoperatively and more pronounced increases postoperatively. Postoperative NT-proBNP, thus, reflected the preoperative condition of the heart as well as myocardial dysfunction sustained during and after surgery. This agrees with the literature, which reports preoperative left ventricular dysfunction and perioperative myocardial infarction to be important causes for PHF in patients undergoing CABG 8, 10.

The cutoff levels of NT-proBNP for PHF and severe PHF in particular after CABG should be interpreted with caution because of the low number of events.
In contrast to what was found in CABG, only NT-proBNP level on POD1 provided good discrimination for PHF in patients undergoing AVR for AS (Paper II). Nozohoor et al. reported that high BNP level on admission to the ICU was an independent predictor of PHF after AVR. The early post-operative natriuretic peptides thus appear to reflect the preoperative cardiac function and myocardial dysfunction sustained during the operation. However, we have no certain explanation to the indecisive results on POD3, but this could be related to the low number of events.

The current results also show that a NT-proBNP level ≥5290 ng•L⁻¹ on POD1 can help identify which PHF patients after AVR for AS carry a markedly increased risk of poor long-term survival and, hence, may require increased postoperative surveillance.

The impact of glutamate on postoperative NT-proBNP

In high-risk patients post hoc analyses, even after adjustment for significant differences in preoperative demographics, demonstrated that intravenous glutamate infusion was associated with mitigated postoperative increase of NT-proBNP resulting in substantially lower NT-proBNP levels on POD3 compared to controls. Based on available knowledge about myocardial metabolism it is conceivable that glutamate influenced postoperative NT-proBNP levels by promoting post-ischemic recovery of myocardial oxidative metabolism. Further studies are necessary to confirm these findings.

As explained in the introduction, the biochemical properties of glutamate could increase myocardial tolerance to ischemia and enhance myocardial recovery after ischemia. Glutamate’s effect is dependent on whether there is a metabolic derangement which glutamate can facilitate the recovery of myocardial oxidative metabolism. As might be expected such an effect could not be detected...
in low-risk patients with no or minimal metabolic derangement\textsuperscript{121}. In the GLUTAMICS-trial, a high proportion of low-risk patients were included\textsuperscript{102}. Glutamate administration contributes little to these patients as the high myocardial extraction rate of glutamate from blood seen normally early after CABG is sufficient for recovery of myocardial metabolism in most of these patients\textsuperscript{95}. This might explain why we were unable to detect an impact of glutamate on postoperative NT-proBNP in the whole cohort.

**Clinical implications**

Our studies confirm the value of preoperative NT-proBNP for predicting operative risk in patients admitted for cardiac surgery. The underlying heart disease has to be taken into account as patients with AS or MR have higher preoperative NT-proBNP than CAD patients undergoing first time cardiac surgery.

Neither echocardiography nor pulmonary artery catheters may be appropriate for diagnosis of PHF in large clinical trials due to the investigator dependence of transesophageal echocardiography and rare routine use of pulmonary artery catheters, although these methods undoubtedly provide important information in the diagnosis of PHF and its treatment. In contrast, a readily accessible and inexpensive option for objective assessment of PHF is provided by natriuretic peptides in clinical trials.

In coronary surgery our results suggest that postoperative NT-proBNP adds an unbiased dimension to the evaluation of PHF and its severity and, hence, can be used as marker of PHF after CABG. This is important since the lack of generally accepted criteria for PHF may partly explain the limited number of trials and the poor evidence for current treatment of the condition responsible for the majority of postoperative deaths.
In AVR for AS our results and a previous study suggest that postoperative natriuretic peptides obtained on POD1 or earlier in the postoperative course can be used as markers of PHF. This is particularly important as assessment of the efficacy of treatment and prophylaxis may require several years of follow-up due to the delayed prognostic consequences of PHF after AVR for AS.

In clinical practice NT-proBNP level ≥5290 ng•L⁻¹ on POD1 can be useful for recognizing patients with an episode of PHF after AVR for AS who are at risk of poor long-term survival and therefore require increased postoperative surveillance. This is advisable since the delayed consequences of PHF after AVR for AS have been reported to be equally profound in patients considered to be low-risk preoperatively.

The finding that glutamate might have an impact on postoperative NT-proBNP levels in high-risk patients undergoing CABG is encouraging and in line with previous metabolic and hemodynamic studies after CABG. The post hoc results, however, need to be confirmed in future prospective clinical trials on high-risk patients before this treatment can be recommended for general use.

**Future Research**

We suggest that future studies on preoperative natriuretic peptides should address if they can be incorporated into available risk scores to improve the prognostic value of risk scores such as EuroSCORE II. Also, it could be worthwhile to study if preoperative natriuretic peptides can be used as a tool for preoperative optimization of high-risk patients.

Increase of postoperative natriuretic peptides can be used to evaluate treatment of PHF in future studies. As we found that postoperative trends of
Discussion

NT-proBNP were of prognostic importance we also suggest that future studies should address if natriuretic peptides can be used for design of goal directed therapy. Furthermore, the role of natriuretic peptides for postoperative surveillance during follow-up after surgery deserves further attention.

The encouraging results regarding the effect of intravenous glutamate infusion on postoperative NT-proBNP levels in association with CABG on high-risk patients has already stimulated the initiation of the ongoing GLUTAMICSII trial (ClinicalTrials.gov Identifier: NCT02592824).
Discussion
CONCLUSIONS

• Patients with AS or MR admitted for first time cardiac surgery had higher preoperative NT-proBNP than CAD patients, even after adjusting for non-cardiac confounders.

• The predictive value of preoperative NT-proBNP with regard to severe PHF was good in CAD and MR patients admitted for surgery, but less convincing in AS patients.

• The predictive value of preoperative NT-proBNP with regard to postoperative mortality was confirmed in patients operated for CAD. The number of events was too few to permit analysis in patients operated for AS or MR.

• The predictive value of preoperative NT-proBNP with regard to long-term survival was confirmed in patients undergoing elective AVR for AS.

• NT-proBNP on POD1 provided good discrimination of PHF in patients undergoing elective AVR for AS.

• PHF after elective AVR for AS was associated with a poor long-term survival, although it initially appeared benign. NT-proBNP $\geq 5290$ ng•L$^{-1}$ on POD1 identified which patients with PHF had an increased risk of poor long-term survival.

• The absolute postoperative levels and postoperative changes of NT-proBNP were associated with PHF after isolated CABG for acute coronary syndrome. The postoperative levels levels reflected the severity of PHF.

• Intravenous infusion of glutamate in patients undergoing CABG for acute coronary syndrome:
  - in the majority of patients glutamate did not affect the postoperative NT-proBNP levels
Conclusions

- in high-risk patients glutamate (EuroSCOREII ≥ 4.15) was associated with reduced increase of NT-proBNP and lower postoperative levels of NT-proBNP

- further studies are necessary to confirm these post-hoc findings
REFERENCES

References


References


References

References


Papers

The papers associated with this thesis have been removed for copyright reasons. For more details about these see:

http://urn.kb.se/resolve?urn=urn:nbn:se:liu:diva-161324
NT-proBNP as a marker of postoperative heart failure in adult cardiac surgery

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