SURGERY FOR AORTIC STENOSIS
with special reference to myocardial metabolism, postoperative heart failure and long-term outcome

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“Evolution of science develops by a zigzag course of trial and error….”

Richard J. Bing

To Jane
Kristin, Charlotte and Katarina
ABSTRACT

Postoperative heart failure (PHF) remains a major determinant of the outcome after cardiac surgery. However, characteristics of and risk factors for PHF after valve surgery have received little attention. Post-ischaemic disturbances of myocardial metabolism that may contribute to PHF and are amenable to metabolic treatment have been identified early after coronary surgery (CABG). Knowledge derived from these studies may not be applicable to other patient groups. We therefore studied myocardial energy metabolism in 20 elective patients undergoing aortic valve replacement (AVR) for isolated aortic stenosis (AS). The metabolic studies indicated that myocardial oxidative metabolism had not fully recovered when the procedure was completed. Free fatty acids were the only major substrates taken up by the heart. Signs of preoperative and postoperative metabolic adaptation with substantial uptake of glutamate, previously demonstrated in patients with coronary artery disease, were found. Postoperative infusion of glutamate, (2 mL per kg body weight and hour of 0.125 M solution) based on assessment of myocardial glutamate requirements in CABG patients, resulted in a two-fold increase in myocardial glutamate uptake and a seven-fold increase in AV differences across the leg. This was associated with a significant myocardial uptake of lactate and metabolic changes in the leg suggesting mitigation of net amino acid loss and peripheral tissue lipolysis.

Characteristics of and risk factors for PHF were evaluated in 398 patients undergoing isolated AVR for AS from 1 January 1995 to 31 December 2000. These were compared with 398 patients, matched for age and sex, undergoing on-pump isolated CABG. Forty-five AVR and 47 CABG patients fulfilled criteria for PHF and these were studied in detail. PHF usually presented at weaning from cardiopulmonary bypass. After CABG it was closely associated with preoperative ischaemic events and intraoperatively acquired myocardial infarction. Potential causes and eliciting events of PHF after AVR for AS were obvious only in one-third of the patients. Risk factors for PHF after AVR for AS indicated either pre-existing myocardial dysfunction, increased right or left ventricular after-load, or intraoperatively acquired myocardial injury. PHF was associated with high early mortality after CABG, whereas the consequences of PHF after AVR for AS became evident only with time, resulting in a 42% five-year mortality. Although PHF had a different temporal impact on late mortality after CABG and AVR for AS, it emerged as the statistically most significant risk factor for mortality occurring within 5 years from surgery both after AVR for AS and after CABG. Potential implications of our findings include needs for greater focus on preoperative surveillance of patients with AS for optimal timing of surgery, mitigation of intraoperatively acquired myocardial injury and tailoring of treatment for PHF. Furthermore, the findings have implications for long-term follow up of AS patients after surgery.
LIST OF ORIGINAL ARTICLES

This thesis is based on the following papers, which are referred by their Roman numerals:


[III]: Influence of early postoperative heart failure on five-year survival after surgery for aortic stenosis compared with CABG. Vánky FB, Håkanson E, Svedjeholm R. *Manuscript*


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Abbreviations

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<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tr>
<td>A-Cs</td>
<td>Arterial – coronary sinus difference</td>
</tr>
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<td>AS</td>
<td>Aortic stenosis</td>
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<td>AV</td>
<td>Arterial – venous</td>
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<td>AVR</td>
<td>Aortic valve replacement</td>
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<tr>
<td>BCCA</td>
<td>Branched-chain amino acids</td>
</tr>
<tr>
<td>BMI</td>
<td>Body mass index</td>
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<tr>
<td>BSA</td>
<td>Body surface area</td>
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<tr>
<td>CABG</td>
<td>Coronary artery bypass grafting</td>
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<tr>
<td>CI</td>
<td>Cardiac index</td>
</tr>
<tr>
<td>CPB</td>
<td>Cardiopulmonary bypass</td>
</tr>
<tr>
<td>EOA</td>
<td>Effective orifice area</td>
</tr>
<tr>
<td>FFA</td>
<td>Free fatty acids</td>
</tr>
<tr>
<td>ICU</td>
<td>Intensive care unit</td>
</tr>
<tr>
<td>LOS</td>
<td>Low cardiac output syndrome</td>
</tr>
<tr>
<td>LV</td>
<td>Left ventricle</td>
</tr>
<tr>
<td>LVSWI</td>
<td>Left ventricular stroke work index</td>
</tr>
<tr>
<td>NYHA</td>
<td>New York Heart Association</td>
</tr>
<tr>
<td>OR</td>
<td>Odds ratio</td>
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<tr>
<td>PHF</td>
<td>Postoperative heart failure</td>
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<tr>
<td>SAP</td>
<td>Systolic arterial pressure</td>
</tr>
<tr>
<td>SD</td>
<td>Standard deviation</td>
</tr>
<tr>
<td>SvO₂</td>
<td>Mixed venous oxygen saturation</td>
</tr>
<tr>
<td>SVRI</td>
<td>Systemic vascular resistance</td>
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</table>
Introduction

In the early years of its development cardiac surgery with deep hypothermia or with cardiopulmonary bypass was a fairly traumatic procedure with high mortality and morbidity rates. It was therefore mostly performed on children and young adults suffering from cardiac diseases in which other treatment options had a very poor prognosis. Improvements in diagnostics, anaesthesia, surgical techniques, cardiopulmonary bypass and postoperative care have resulted in an excellent outcome for cardiac surgery patients of today. It is logical that research on patients undergoing aortic valve replacement has focused mainly on the prosthesis. With the continuous improvements in and development of valve prostheses and the concurrent advances in the surgical technique and perioperative care, cardiac surgery is no longer withheld from elderly patients or patients with co-morbidities. Thus, the challenge of today is to improve the good results in a patient population with increasing age and co-morbidities. To succeed, it is necessary to identify and explore variables that have the most pronounced influence on the postoperative outcome. The Ad Hoc Liaison Committee for Standardizing Definitions of Prosthetic Heart Valve Morbidity has acknowledged that patient variables may be more responsible for the outcome than valve-related factors. The Committee has also pointed out the lack of data on this issue and has encouraged investigators to identify relevant patient factors in addition to factors related to operated valves.

Aortic stenosis

Aortic stenosis (AS) is the most common valvular disease among adults in the Western hemisphere. It is characterized by an obstruction of the left ventricular outflow tract, which may be either congenital or acquired. The origin of acquired AS is usually classified into rheumatic and degenerative. The prevalence of AS increases with age and is around 2% in the population older than 65 years and around 4% in that older than 85 years.

Aetiology

Before 1950 rheumatic disease was assumed to be the predominant cause of isolated aortic valve stenosis, but this cause has declined since then in the western countries. Rheumatic valvulitis may produce oedema, lymphocytic infiltration and neovascularization of the leaflets, followed later by leaflet thickening, commissural fusion, rolling of the leaflet edges and later valvular calcification. Today, degenerative calcification is considered to be the
most common cause of clinically evident aortic stenosis. It begins with collagen disruption and small calcific deposits and ends up with heavily calcified immobile valve leaflets and annulus. Recent studies suggest, however, that lipoproteins may play a key role in the development of aortic valve sclerosis. Thus, sclerosis cannot be considered as a simple degenerative process, but on the contrary it is complex and involves multiple pathogenic mechanisms. Experimental, clinical and epidemiological data all support a link between aortic valvulopathy and atherosclerosis: both are caused by inflammation, lipid deposition, and accumulation of extracellular bone matrix protein. The progress of calcification takes place over several years and usually becomes symptomatic after the fifth decade of life, earlier in bicuspid valves (present in up to 1% of the population) and earlier in men than in women.

Pathophysiology
The primary effect of aortic stenosis is an increased left ventricular afterload with secondary impairment of left ventricular emptying in systole. Aortic stenosis may be quantified by measuring the systolic pressure gradient across the aortic valve or by calculating an effective aortic valve orifice area. Normal values for these two variables are around 5 mmHg and 3 to 4 cm² respectively, while an aortic orifice valve area below 0.7 to 1.0 cm² and a mean aortic valve gradient above 50 mmHg correspond to severe aortic stenosis. An increase in the pressure gradient across the aortic valve results in an elevated left ventricular pressure, in order to maintain a normal pressure in the aorta. In turn, increased left ventricular wall stress is thought to be the stimulus for left ventricular hypertrophy. Severe left ventricular hypertrophy may lead histologically to sarcomere disruption, disarray of myocardial filaments and disappearance of organelles. If left ventricular hypertrophy is insufficient to normalize left ventricular wall stress, a chronic increase in wall stress may result in left ventricular failure with decreased left ventricular contractility and progressive left ventricular dilatation. Decreased left ventricular diastolic compliance appears as a consequence of both the left ventricular hypertrophy and dilatation.

The compensated phase of aortic stenosis with progressive left ventricular hypertrophy may leave the patient asymptomatic for some decades. The rate at which mild aortic stenosis progresses to severe stenosis is variable, but different studies have shown a mean decrease in the aortic valve orifice area of about 0.1 cm²/year. However, most patients with moderate to severe aortic stenosis ultimately develop symptoms of congestive heart failure, angina or syncope.
Congestive heart failure generally reflects elevated pulmonary venous pressure as a direct effect of an increase in afterload or resulting from left ventricular diastolic dysfunction. Exertional angina pectoris in patients with AS is related to an impairment of subendocardial blood flow due to increased left ventricular pressure. Syncope also occurs, as a result either of arrhythmia or of exercise-induced vasodilatation due to abnormal baroreceptor activity and sudden changes in left ventricular pressure.

Surgical correction of aortic stenosis immediately improves the left ventricular ejection fraction, left ventricular end-diastolic volume and pulmonary capillary wedge pressure, as a consequence of a reduced left ventricular afterload. Left ventricular hypertrophy from aortic stenosis tends to decrease over a period of 6 to 12 months after aortic valve replacement, but may not become totally normalized.

**Prognosis**

Asymptomatic aortic stenosis has a good prognosis and the life expectancy is close to that in the normal population. Most patients eventually develop symptoms and the favourable prognosis changes markedly when this occurs. The survival rates 1, 2 and 3 years have been found to be roughly 50%, 30% and 20% respectively in patients with symptomatic aortic stenosis managed medically. It is important to remember that the transition from an asymptomatic to a symptomatic stage may be difficult to detect, particularly in elderly patients, because of a gradual decrease in activity and a sedentary life style.

**Treatment**

At present, medical therapy has a limited role in the treatment of aortic stenosis. Diuretics to minimize symptoms of congestive heart failure and antiarrhythmics to control atrial fibrillation may provide some symptomatic relief, but without altering the unfavourable natural history of symptomatic aortic stenosis. Afterload reduction may excessively reduce the coronary perfusion pressure and is relatively contraindicated. The suggestion that high serum lipids may be contributory to aortic valve sclerosis has resulted in recently completed and other, still ongoing studies. However, in the SATIRE trial, lipid-lowering treatment with atorvastatin did not delay the progression of calcific aortic stenosis. Thus, aortic valve replacement is the treatment of choice for the majority of patients with symptomatic aortic stenosis.
History of aortic valve surgery

In 1914 Tuffier described the first successful attempt to correct human aortic stenosis by inserting a finger through the aortic wall to dilate the aortic valve. Smithy and Parker reported on an experimental study of aortic valvulotomy in 1947. Aortic valve dilatation was subsequently performed with a mechanical dilator inserted through the left ventricle or with a finger through a sleeve sewn onto the aorta (Ellis and Kirklin in 1955). The first time prosthesis was used to treat aortic valve disease was when Hufnagel and Harvey inserted a ball valve in the descending aorta in 1953 in a patient with aortic valve regurgitation. However, this method left the patient with aortic insufficiency of the upper body. Treatment of AS by replacement of the aortic valve did not become possible until after the development of cardiopulmonary bypass by Gibbon in 1954. The first successful replacements of aortic valves in 1960 by Bahnson and Harken, were followed by development of numerous different prosthesis models. There is still an ongoing search for the optimal prosthesis that needs no anticoagulation, has lifelong durability even in young patients, does not reduce the aortic orifice area and is easy to implant.

Prognosis after surgery for AS

The age- and gender-corrected survival after surgery for aortic stenosis has been reported to be almost normalized from the first or second postoperative year. However, the surgical procedure still carries an operative mortality of approximately 2 - 5% in spite of the fact that results have improved dramatically over the last decades. Most studies on the long-term outcome are difficult to interpret because of mixed diagnoses and concomitant procedures. Available data from patients operated on for isolated AS suggest that preoperative factors such as high age, advanced functional class, reduced systolic and diastolic LV function, hypertension, impaired renal function and a high left ventricular mass index are associated with shortened long-term survival. The role of patient-prosthesis mismatch, i.e. a small effective orifice area in relation to body size, for the long-term outcome remains equivocal. The impact of periprocedural events on the long-term outcome has not been elucidated.

Postoperative heart failure

As early as in 1967, John Kirklin noted that when death occurs early after cardiac surgery it was often related to low cardiac output. In spite of the progress in cardiac surgery and perioperative management, postoperative heart failure (PHF) remains one of the most important causes of an adverse outcome of cardiac surgery. It is therefore surprising
that although numerous articles have addressed different treatments of PHF, only a few studies have addressed the issue of PHF per se. In 1973 Jarvinen et al reported a high mortality and an increased incidence of extra-cardiac complications in association with low cardiac output syndrome (LOS) after cardiac surgery involving both valve procedures and coronary artery bypass grafting (CABG)53. In 1996 Rao reported a 9.1% incidence of LOS after CABG54. In these patients the operative mortality was 16.9%, compared to 0.9% in those without LOS (Table 1). A recent survey by the Northern New England study group of outcomes in 8,641 patients who underwent CABG revealed that almost two-thirds of all in-hospital deaths could be directly attributed to PHF. Furthermore, fatal heart failure accounted for 80% of the difference between the surgeons with the highest and lowest mortalities. Recently Maganti et al reported a high operative mortality in association with LOS after aortic valve surgery in a heterogenous cohort41.

In spite of the grave consequences of PHF, there is still no generally accepted definition of this condition and this might partly explain the limited number of studies on PHF. Available data regarding PHF from the last two decades mainly derive from studies on CABG patients. Studies addressing causes of and risk factors for PHF are sparse and the treatment of it, in general, appears uniform regardless of the procedure and underlying causes55. Efforts to prevent PHF and to tailor causal treatment require greater knowledge and insight into these issues. Interpretation of available studies on different treatments of PHF is obscured by the varying criteria used. This is demonstrated by the wide range (21-73%) in mortality reported after use of intra-aortic balloon pump treatment56.

Haemodynamic criteria based on cardiac output measurements have been used by some investigators. Such criteria are distinct and easy to comprehend, but it may be questioned whether they actually always represent insufficient supply, as they do not give an account of how well the systemic requirements are met. Heart failure, in physiological terms, reflects a cardiac output insufficient to meet the systemic requirements. Evidences of such mismatch between supply and demand are low mixed venous saturation and inadequate organ function. In fact, the oxygen demand of peripheral tissues is the main determinant of cardiac output in humans57, 58. This was illustrated by metabolic studies performed at our institution on elective low risk CABG patients with well-preserved left ventricular function and uneventful postoperative outcome59, 60. When anaesthetized, several of these patients, in spite of excellent recovery of the myocardial metabolism and high mixed venous oxygen saturation, had a cardiac output that would have been classified as heart failure with the use of haemodynamic criteria alone.
<table>
<thead>
<tr>
<th>Reference</th>
<th>Surgical procedure</th>
<th>Number of patients</th>
<th>Definition</th>
<th>Prevalence (mortality)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kirklin 1967&lt;sup&gt;50&lt;/sup&gt;</td>
<td>Open heart surgery</td>
<td>49</td>
<td>LCO: CI &lt; 2.0 L/min/m&lt;sup&gt;2&lt;/sup&gt; BSA</td>
<td>NA</td>
</tr>
<tr>
<td>Järvinen 1975&lt;sup&gt;53&lt;/sup&gt;</td>
<td>AVR MVR CABG Combination</td>
<td>188 81 106 16</td>
<td>LOS: intraoperative death or requiring postoperative inotropic support to maintain ABPs &gt; 90 mm Hg and diuresis &gt; 30 mL/h</td>
<td>12% (70%) 33% (67%) 16% (77%) 81% (47%)</td>
</tr>
<tr>
<td>Hammermeister 1990&lt;sup&gt;61&lt;/sup&gt;</td>
<td>CABG Non CABG</td>
<td>8569 1912</td>
<td>LCO: definition not given</td>
<td>3.8% (48%) 8.2% (52%)</td>
</tr>
<tr>
<td>Creswell 1992&lt;sup&gt;62&lt;/sup&gt;</td>
<td>Cardiac surgery</td>
<td>7884</td>
<td>LCO treated by IABP: definition not given</td>
<td>4.0% (28.7%)</td>
</tr>
<tr>
<td>Rao 1996&lt;sup&gt;54&lt;/sup&gt;</td>
<td>CABG (all) CABG (low risk patients)</td>
<td>5113 623</td>
<td>LOS: requiring postoperative IABP or inotropic support for &gt; 30 minutes to maintain ABPs &gt; 90 mm Hg and CO &gt; 2.2 L/min</td>
<td>9.1% (16.9%) 5.8% (NA)</td>
</tr>
<tr>
<td>Freeman 1997&lt;sup&gt;64&lt;/sup&gt;</td>
<td>CABG</td>
<td>3014</td>
<td>LCO: CI ≤ 2.0 L/min/m&lt;sup&gt;2&lt;/sup&gt; BSA, ABPm ≤ 60 mm Hg and PCWP ≥ 8 mm Hg</td>
<td>NA</td>
</tr>
<tr>
<td>O’Connor 1998&lt;sup&gt;51&lt;/sup&gt; Surgenor 2001&lt;sup&gt;52&lt;/sup&gt;</td>
<td>CABG</td>
<td>8641</td>
<td>Fatal PHF: recognised from coding of mode of death by a committee</td>
<td>2.9%</td>
</tr>
<tr>
<td>Charlson 1999&lt;sup&gt;65&lt;/sup&gt;</td>
<td>CABG (elective)</td>
<td>248</td>
<td>Cardiogenic shock: urine output &lt; 10 cc/h for &gt; 2 h with ABPs &lt; 90 mmHg or ABPm ≤ 65 mm Hg and PCWP &gt; 18 mm Hg in combination with CI &lt; 2.2 L/min/m&lt;sup&gt;2&lt;/sup&gt; BSA</td>
<td>1.6% (75%)</td>
</tr>
<tr>
<td>Gorman 2000&lt;sup&gt;55&lt;/sup&gt;</td>
<td>All cardiac surgery</td>
<td>NA</td>
<td>LCO: CI &lt; 2.2 L/min/m&lt;sup&gt;2&lt;/sup&gt; BSA</td>
<td>NA</td>
</tr>
<tr>
<td>Hogue 2001&lt;sup&gt;56&lt;/sup&gt;</td>
<td>CABG</td>
<td>5113</td>
<td>LOS: CI &lt; 2.0 L/min/m&lt;sup&gt;2&lt;/sup&gt; BSA for &gt; 8 h</td>
<td>4.3% (18.9%)</td>
</tr>
<tr>
<td>Sherman 2004&lt;sup&gt;67&lt;/sup&gt; (multicenter trial, USA)</td>
<td>CABG +/- valve</td>
<td>914</td>
<td>LV dysfunction: use of ≥ 4 inotropic drugs, LVAD or IABP</td>
<td>4% (NA)</td>
</tr>
<tr>
<td>Maganti 2005&lt;sup&gt;41&lt;/sup&gt;</td>
<td>AVR</td>
<td>2255</td>
<td>LOS: requiring postoperative IABP or inotropic support for &gt; 30 minutes to maintain ABPs &gt; 90 mm Hg and CO &gt; 2.2 L/min</td>
<td>3.9% (38%)</td>
</tr>
</tbody>
</table>

**Table 1.** Definitions and prevalence of low cardiac output (LCO), low cardiac output syndrome (LOS), postoperative heart failure (PHF), cardiogenic shock and left ventricular dysfunction (LV-dysfunction) after cardiac surgery in some previous scientific publications that either focus on postoperative heart failure, evaluate its treatment or use it as a study end-point. *Operative mortality rates in patients with PHF. AVR = aortic valve replacement; MVR = mitral valve replacement; CABG = coronary artery bypass grafting; CI = cardiac index; BSA = body surface area; ABPs = systolic arterial blood pressure; ABPm = mean arterial blood pressure; PCWP = pulmonary capillary wedge pressure; LVAD = left ventricular assist device; IABP = intra-aortic balloon pump; CO = cardiac output; NA = not available.
Myocardial metabolism

Studies of myocardial metabolism have revealed ways in which myocytes adapt to different pathophysiological states. They have also demonstrated metabolic disturbances that may contribute to contractile dysfunction, and hence provide a rationale and guidance for metabolic interventions.

The heart is a continuously working muscle with limited energy storage and it therefore requires a continuous supply of fuel. To cope with this, the heart is able to utilize a variety of energy substrates. The choice of fuel, in the normal state, is primarily determined by the availability of substrates, i.e. their arterial levels. In the fasting state, with elevated arterial levels of free fatty acids (FFA) and low levels of glucose, FFA oxidation predominates. A carbohydrate-rich meal shifts the myocardial metabolism towards glucose oxidation and during vigorous exercise lactate may become the dominating fuel. In conditions such as starvation or diabetic ketosis, ketone bodies may contribute significantly to myocardial energy production. Amino acids have limited importance as fuels, but certain amino acids seem to play an important role for intermediary metabolism of the heart. Under normal conditions cardiac function is not affected by the utilization of specific substrates.

Myocardial metabolism in association with cardiac surgery has been studied in patients with coronary artery disease. Various degrees of metabolic disturbances have been described and these appear to be related to the magnitude of ischaemic insult and subside with time after the release of the aortic cross-clamp. Available data also suggest a relation between degree of metabolic disturbance and myocardial function. FFA are the major source of energy postoperatively, whereas uptake of carbohydrates is restricted by the systemic response to surgical stress. This constitutes a potentially unfavourable metabolic state during recovery from ischaemia. Oxidation of FFA increases myocardial oxygen expenditure and FFA cannot replenish Krebs cycle intermediates that are depleted during ischaemia. These intermediates are essential for normal oxidative metabolism. Studies early after CABG have demonstrated mechanisms to remedy this situation. Certain amino acids, in particular glutamate, which serve as sources of Krebs cycle intermediates and also contribute to clearing of metabolic waste such as lactate and ammonia, are taken up abundantly during reperfusion. However, it is not known to what extent the myocardial capacity to extract glutamate postoperatively is dependent on an adaptation to chronic or repetitive ischaemia preoperatively, since available data derive from patients with
coronary artery disease. Other pathophysiological differences between patients with coronary disease and those with valvular disease could also influence pre- and postoperative metabolic states.
Aims of the study

- to determine the incidence of postoperative heart failure in patients operated on for aortic stenosis compared with an age- and sex-matched cohort undergoing CABG
- to identify characteristics of postoperative heart failure and potentially eliciting events in patients operated on for AS and coronary artery disease, respectively
- to describe the short-term outcome in patients with postoperative heart failure operated on for AS compared with an age- and sex-matched cohort undergoing CABG
- to analyse risk factors for postoperative heart failure in patients undergoing surgery for isolated aortic stenosis
- to investigate the impact of postoperative heart failure on the overall and late mortality after AVR for AS compared with an age- and sex-matched cohort undergoing CABG
- to describe the myocardial energy metabolism before and after surgery in patients operated on for isolated AS
- to investigate the impact of different rates of glutamate infusion on arterial levels of glutamate and their relation to myocardial glutamate uptake after cardiac surgery
- to evaluate the effects of glutamate infusion on myocardial metabolism after surgery for AS
- to describe peripheral tissue (leg) metabolism after surgery for aortic stenosis
- to evaluate the effects of glutamate infusion on peripheral tissue (leg) metabolism after surgery for AS
Material and methods

Patients

Basic preoperative demographics and intraoperative data on patients included in papers I-VI are presented in Table 2.

Papers I-III
The selection of patients in papers I-III is depicted in Figure 1. All patients who underwent isolated AVR because of AS without clinically significant regurgitation from 1 January 1995 to 31 December 2000 (n=398) were studied [II-III]. In paper III one patient was lost to follow-up. A cohort of 398 patients matched to the AVR patients for age and sex, undergoing on-pump isolated first time CABG was identified for comparison [III]. The total number of patients included in papers I – III was thus 796. From these cohorts all AVR patients (n=45) and CABG patients (n=47) that fulfilled our criteria for PHF were studied in detail [I].

Papers IV-V
Twenty-two patients undergoing elective isolated AVR for AS were included prospectively in papers IV - V. Patients with coronary artery disease, significant aortic valve regurgitation, diabetes mellitus, left ventricular ejection fraction < 40%, weight > 100 kg or age > 75 years were not included. Exclusion criteria were surgical difficulties resulting in an aortic cross-clamp time exceeding 120 minutes and postoperative heart failure requiring inotropic or metabolic treatment. Two patients were excluded on these grounds and 20 patients completed the study.

Paper VI
This study comprised ten male patients with stable angina and well-preserved LV-function undergoing elective CABG. Patients with diabetes mellitus or other major metabolic disorders were not included.

Comments: AVR for AS represents the largest homogeneous group of valve procedures in our practice. Our material included all patients operated on during a six-year period for AS without clinically significant regurgitation or associated coronary artery disease, within an
area of one million inhabitants. Thus there should be no referral selection bias. The matching procedure resulted in a CABG cohort with a higher proportion of women and a higher mean age than in the general CABG population in, which should be considered when comparing the CABG results with those of other studies. In papers IV-VI the patients were chosen with regard to metabolic end-points and the numbers of patients were based on the sample sizes in previous metabolic studies.

<table>
<thead>
<tr>
<th>Paper</th>
<th>I</th>
<th>II</th>
<th>III</th>
<th>IV - V</th>
<th>VI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>AVR (PHF)</td>
<td>CABG (PHF)</td>
<td>AVR</td>
<td>CABG</td>
<td>AVR</td>
</tr>
<tr>
<td>Number of patients</td>
<td>45</td>
<td>47</td>
<td>398</td>
<td>397</td>
<td>398</td>
</tr>
<tr>
<td>Age (years)</td>
<td>72 ± 10</td>
<td>73 ± 10</td>
<td>70 ± 10</td>
<td>70 ± 10</td>
<td>69 ± 10</td>
</tr>
<tr>
<td>Female gender</td>
<td>37.8%</td>
<td>53.2%</td>
<td>48.2%</td>
<td>48.4%</td>
<td>48.2%</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>20.0%</td>
<td>19.1%</td>
<td>11.3%</td>
<td>11.3%</td>
<td>19.3%</td>
</tr>
<tr>
<td>COPD</td>
<td>15.6%</td>
<td>10.6%</td>
<td>8.8%</td>
<td>8.8%</td>
<td>7.8%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>42.2%</td>
<td>40.4%</td>
<td>27.9%</td>
<td>27.7%</td>
<td>43.2%</td>
</tr>
<tr>
<td>History of stroke</td>
<td>13.3%</td>
<td>10.6%</td>
<td>8.8%</td>
<td>8.8%</td>
<td>7.8%</td>
</tr>
<tr>
<td>Severe systolic LV dysfunction*</td>
<td>24.4%</td>
<td>20.5%</td>
<td>6.3%</td>
<td>6.3%</td>
<td>5.8%</td>
</tr>
<tr>
<td>Plasma creatinine &gt;140 μmol/L</td>
<td>4.4%</td>
<td>10.6%</td>
<td>3.8%</td>
<td>3.5%</td>
<td>5.1%</td>
</tr>
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<td>NYHA class III</td>
<td>62.8%</td>
<td>19.5%</td>
<td>51.9%</td>
<td>51.8%</td>
<td>37.4%</td>
</tr>
<tr>
<td>NYHA class IV</td>
<td>20.9%</td>
<td>70.7%</td>
<td>6.0%</td>
<td>6.0%</td>
<td>37.4%</td>
</tr>
<tr>
<td>Euroscore</td>
<td>6.7 ± 2.5</td>
<td>7.6 ± 3.5</td>
<td>5.5 ± 2.2</td>
<td>5.5 ± 2.2</td>
<td>5.0 ± 2.9</td>
</tr>
<tr>
<td>CCT (minutes)</td>
<td>95 ± 30</td>
<td>55 ± 21</td>
<td>81 ± 21</td>
<td>81 ± 21</td>
<td>47 ± 19</td>
</tr>
<tr>
<td>CPB (minutes)</td>
<td>134 ± 42</td>
<td>102 ± 32</td>
<td>106 ± 27</td>
<td>106 ± 27</td>
<td>81 ± 26</td>
</tr>
<tr>
<td>Number of distal anastomoses</td>
<td>_</td>
<td>4.0 ± 0.9</td>
<td>_</td>
<td>_</td>
<td>3.8 ± 1.1</td>
</tr>
<tr>
<td>Use of ITA</td>
<td>_</td>
<td>95.7%</td>
<td>_</td>
<td>_</td>
<td>96.5%</td>
</tr>
<tr>
<td>Biological Prosthesis</td>
<td>73.3%</td>
<td>_</td>
<td>61.3%</td>
<td>_</td>
<td>_</td>
</tr>
</tbody>
</table>

**Table 2.** Basic data on patients included in the studies, given as per cent or mean ± SD. *Left ventricular ejection fraction ≤ 0.30. COPD = chronic obstructive pulmonary disease; CCT = aortic cross clamp time; CPB = cardiopulmonary bypass time; ITA = internal thoracic artery.
Clinical management

In all patients standard surgical techniques with cardiopulmonary bypass (CPB) and aortic cross-clamping were used. Ringer's acetate and mannitol were used for priming the extracorporeal circuit. Moderate haemodilution (haematocrit 20 - 25%) and moderate (30-32°C) [VI] or mild hypothermia (33-36 °C) [I-V] were employed. Antegrade or combined ante- and retrograde delivery of a cold crystalloid cardioplegic solution (Plegisol™, Abbot, IL, US) supplemented with procaine hydrochloride was used for myocardial protection [I-III].

In the metabolic studies, only antegrade cardioplegia was used because of the coronary sinus catheter [IV-VI]. Weaning from CPB was started at a rectal temperature of 35-36 °C. Heparin was neutralized with protamine chloride. Ringer's acetate was used for volume substitution postoperatively. Shed mediastinal blood was routinely retransfused in the ICU. Postoperative rewarming was facilitated by radiant heat provided by a thermal ceiling.

Study protocol

Papers I-III

Demographic and periprocedural data including complications were recorded prospectively in a computerized institutional database (Summit Vista for Windows; Summit Medical Systems Inc., Version 1.98.1). All fields were defined in a data dictionary. Data on mortality was retrieved from the Swedish Civil Registry.

The database comprised 4806 patients who had undergone cardiac surgery from 1 January 1995 to 31 December 2000. There were 398 patients operated on with isolated AVR because of AS without clinically significant regurgitation. To account for evident differences regarding age and sex distribution these patients were compared with a cohort of 398 patients matched for age and sex, undergoing on-pump isolated first time CABG. The matching was blinded for all variables except for age, sex, diagnosis, surgery performed, first time or redo surgery and on-pump or off-pump surgery. If no patient of the same age and same sex at surgery were found among the CABG patients, the closest CABG patient in the database was chosen in the following order: one year older, one year younger, two years older, two years younger and so on. This matching procedure resulted in two cohorts, both with a mean age of 70 ± 10 years and 48 % females. Missing data in the prospectively collected clinical database were completed from the patient records.
Cardiac surgery patients 1995-2000
4806
AVR for Aortic stenosis
398
Matched for sex and age
CABG
398
PHF
45
PHF
47

Figure 1. Selection of patients in paper I – III. AVR = aortic valve replacement; CABG = coronary artery bypass surgery; PHF = postoperative heart failure.

Paper I
Two co-workers recognized PHF patients independently, on the basis of the criteria given below in the section Calculations and Definitions. A second opinion was obtained from a third co-worker in doubtful cases. Forty-five patients undergoing AVR (11.3%) and 47 patients undergoing CABG (11.8%) were found to have had PHF. The records of these patients were scrutinized for further details regarding different characteristics such as eliciting events, presentation of heart failure, treatment and outcome.
Paper II
To identify risk factors for PHF in patients undergoing AVR for AS univariate and multivariate logistic regression analysis was performed on all patients operated on for isolated AS.

Paper III
To investigate the impact of PHF, in relation to other risk factors, on the long-term outcome, univariate and multivariate logistic regression analysis with regard to five-year survival was performed on the patients who had undergone surgery for isolated AS and on the matched CABG cohort. The patients were followed up, regarding mortality over an average period of 7.2 ± 1.7 years that ranged from 5.2 to 11.2 years.

Papers IV – V
Twenty low-risk patients undergoing surgery for isolated aortic stenosis were studied pre- and postoperatively with respect to myocardial metabolism [IV,V], peripheral (leg) tissue metabolism [V] and haemodynamic state [IV-V].
**Paper IV**

To assess the myocardial metabolism and haemodynamic state in patients with isolated aortic stenosis before and after surgery, 20 low-risk patients were studied immediately before (preop) and after the procedure (postop) (Fig. 2). Blood samples were taken simultaneously from the radial artery, coronary sinus and pulmonary artery. They were analysed for plasma FFA, plasma amino acids and for the whole blood contents of glucose, lactate, glycerol and oxygen.

The preoperative samples were taken immediately before the skin incision and the postoperative samples were taken after the skin closure. Haemodynamic measurements were also performed at preop and postop.
Paper V
To assess the impact of postoperative glutamate infusion on the myocardial metabolism, peripheral (leg) tissue metabolism and haemodynamic state, the 20 patients from paper IV were randomised to blinded infusion of 2 mL per kg body weight and hour of 0.125 mol/L L-glutamate (glutamate group) or saline (control group). Blood samples were taken simultaneously from the radial artery, the coronary sinus, the femoral vein and the pulmonary artery immediately before (T0) the infusion was started and after 1 hour of infusion (T1). Haemodynamic measurements were also performed at T0 and T1.

Comment: The postoperative state in paper IV and T0 in paper V correspond (Fig. 2). These samples were taken on average 78 ± 16 minutes after release of the aortic cross-clamp.

Paper VI
To assess the relationship between infusion rates, arterial levels and myocardial arterial-coronary sinus differences of glutamate, 10 low risk CABG patients received a postoperative infusion of 0.1 M glutamate solution over a period of one hour. To achieve a wide variation in arterial glutamate levels, the infusion rate was varied between all patients and in addition the infusion rate was changed for the second 30-minute period. Blood samples for whole blood measurements of glutamate were taken simultaneously from the radial artery and the coronary sinus before the start of glutamate infusion (basal state = 0), every 10 minutes during infusion and 30 minutes after its termination. Arterial and coronary sinus plasma glutamate levels were determined in the basal state, after 60 minutes of infusion and 30 minutes after termination of the infusion.

Comment: The average time from release of the aortic cross-clamp to the basal state was 174 ± 24 minutes. The glutamate infusion rates of glutamate varied from 10 to 87 mg per kg body weight and hour.
Catheterization and haemodynamic measurements

Cardiac output: A Swan-Ganz catheter was inserted through the right internal jugular vein into the pulmonary artery. Cardiac output was measured with the thermodilution technique. In papers IV and V it was calculated from the mean value of three observations. Derived haemodynamic variables were calculated from standard formulae.

Coronary sinus flow: A coronary sinus catheter (CCS-7U-90B, Webster Labs., Inc., Altadena, CA) was inserted through the right internal jugular vein. The final mid-coronary position of the coronary sinus catheter was checked by fluoroscopy, measurement of oxygen saturation, pressure recording and trans-oesophageal echocardiography. Coronary sinus blood flow was determined by a retrograde thermodilution technique and the mean value of three measurements was calculated (CF 300A Flowmeter, Webster Labs., Inc., Altadena, CA).
Femoral vein: A 4 Fr (200 mm) catheter (BD Care FlowTM Becton Dickinson Critical Care Systems, Singapore) was introduced into the right femoral vein [V]. The catheter was positioned with the tip at the level of the inferior acetabulum with the aid of fluoroscopy and verified by injection of 5 ml (320 mg I/ml) contrast medium (VisipaqueTM Amersham Health).

Comment: A coronary sinus catheter provides information about the flow at the tip of the catheter and this is dependent on the anatomy of the coronary sinus and the exact position of the catheter tip. Owing to the anatomy of the coronary sinus, differences in position of the catheter will influence the measurements. Thus, direct comparison of flux values between individual patients should be avoided. However, the method is appropriate for assessment of within-group changes and to some extent for inter-group comparisons.

In view of the larger myocardial mass in aortic stenosis patients, a higher coronary sinus blood flow might have been expected in paper IV and V than in paper VI. Contrary to expectation, we found a slightly lower flow in aortic stenosis patients. However, since the catheter was inserted preoperatively in paper IV and V, a stable mid-coronary position was aimed for to avoid intraoperative catheter displacement. This might have resulted in a somewhat deeper tip location compared to that obtained in paper VI, which in turn could explain the lower flow values.

Biochemical analyses [IV - VI]

Whole blood samples were immediately deproteinized with ice-cold perchloric acid as described by Jorfeldt and Juhlin-Dannfelt. After centrifugation, the protein-free extracts were deep-frozen to -70°C. The glutamate concentration in whole blood was determined fluorometrically by an adapted glutamate dehydrogenase method [VI]. Alanine, D-glucose, lactate and glycerol were also determined fluorometrically [IV-V]. Amino acids in plasma were measured with a conventional amino acid analyser, AminoTac JLC-500, JEOL Inc., Tokyo, Japan [IV-V] or Beckman system 6300, Beckman Instruments, Inc., Palo Alto, CA [VI]. FFA were assayed in plasma as described by Ho.
Comment: Because of the documented storage effect on plasma glutamate, all analyses were done batchwise to minimize the effect on arterial-venous differences, care being taken that corresponding arterial and venous samples were analysed simultaneously.

Calculations and Definitions

PHF was defined as a haemodynamic state secondary to pump failure that is unable to meet systemic demands without supportive measures other than correction of volume or vascular resistance. A low cardiac output can be sufficient to supply the body demands in an anaesthetized or sedated patient, and hence reliance on markers for adequate circulation, in particular mixed venous oxygen saturation (SvO2), and echocardiographic evaluation rather than fixed haemodynamic criteria, were employed to diagnose PHF. The following relationship between SvO2 and systolic arterial pressure (SAP) provide our guidelines to recognize inadequate circulation: SvO2<50% and SAP < 130 mmHg; SvO2<55% and SAP<110 mmHg; SvO2<60% and SAP<90 mmHg; SvO2<65% and SAP<70 mmHg, after correction of shivering and hypovolaemia. In the majority of patients PHF was evident at weaning from cardiopulmonary bypass as an inability to wean from CPB or deteriorating circulation and increasing filling pressures after weaning from CPB. In the remaining patients echocardiographic evidence of left ventricular and/or right ventricular dysfunction associated with above mentioned signs of inadequate circulation was used to diagnose PHF. The atrial filling pressure, systemic pressure and Swan-Ganz data were used to aid the interpretations. PHF in this thesis refers to heart failure occurring during the hospitalisation in association with surgery. Supportive measures or treatment consisted of intraaortic balloon pump, inotropic treatment and metabolic support with glucose-insulin-potassium and/or intravenous glutamate.

Inotropic treatment [I] was defined as continuous infusion for more than 30 minutes of catecholamines (adrenaline, dobutamine) or phosphodiesterase inhibitor (milrinone).

Effective orifice areas [II-III] for the different prostheses used are based on in vivo Doppler echocardiographic measurements reported in the literature. 

32
Early or late mortality [III] was defined as mortality occurring within or later than 30 days from surgery.

Myocardial flux of substrates [IV-VI] was calculated as the product of arterial-coronary sinus concentration difference of blood or plasma and coronary sinus blood or plasma flow.

Coronary sinus plasma flow [IV-VI] was calculated as the product of coronary sinus blood flow and 1-haematocrit.

Uptake or release of a substrate [IV-VI] was defined as flux or arterial-venous difference significantly different from zero (p<0.05).

Oxygen consumption of the heart [IV-V] was estimated as the product of the arterial-coronary sinus blood oxygen content difference and the coronary sinus blood flow. In calculations of the O₂ consumption of the whole body, the product of cardiac output and arterial-pulmonary artery blood oxygen content difference was used.

Oxygen content of the blood [IV-V] was calculated according to the following formula:

\[
\text{Oxygen content (mmol/L) = (B-Hb g/L x sO2 % x 0.00062) + (pO2 kPa x 0.01)}
\]

Extraction ratio [IV-V] refers to the quotient of the arterial-venous difference and the arterial level of a substrate.

Substrate oxygen equivalent [IV-V] was defined as the potential contribution of substrates to myocardial oxygen consumption, assuming that the substrates taken up were fully oxidized. According to stoichiometric analysis 3 mol of oxygen per mol of lactate, 6 mol of oxygen per mol of glucose, and 23 mol of oxygen per mol of FFA (palmitate) are consumed\(^7,3\).

**Statistical analysis**

Data are presented as mean ± standard deviation (SD) [I-V] or mean ± standard error of the mean (SEM) [VI]. Statistical significance was defined as p < 0.05. Statistical analyses were performed with computerized statistical packages (Statistica 5.1 - 7, StatSoft Inc., Tulsa, MINITAB 13, Minitab Inc., Pennsylvania and SPSS 14.0 SPSS Inc., Chicago, IL.
Non-parametric tests, the Mann-Whitney U test and the Wilcoxon matched pairs test for continuous variables with independent and dependent samples respectively and Fisher’s exact test for categorical variables were used [I - V]. Correlations were computed with Spearman rank [IV].

In order to evaluate the independent risk factors [II - III], univariate logistic regression was first employed. Variables were then tested in a stepwise forward multivariate logistic regression model if the univariate p value was less than 0.25. Hosmer-Lemeshow goodness-of-fit statistics was calculated for the final models\(^9\). Cumulative long-term survival [III] was assessed by Kaplan-Meier analysis.

In paper [VI] analysis of variance and post hoc comparisons with the LSD test were carried out for evaluation of repeated measurements. For comparison of two sets of observations the t-test was used if appropriate, and for samples lacking a normal distribution the Wilcoxon test for matched pairs was used. Linear regression was used for analysis of correlation.

Comment: Conventionally, relative hazards for the risk of death during long-term follow up are calculated with Cox proportional hazard model. However, the proportionality assumption was not met in paper III and therefore univariate and multivariate logistic regression was chosen to evaluate the impact of risk factors on defined time periods.

**Ethical aspects**

The studies were performed according to the principles of the Helsinki Declaration of Human Rights and were approved by the Ethics Committee for Medical Research at the University Hospital of Linköping. Written informed consent from the patients was obtained in the prospective studies [IV - VI].
Results

Characteristics of PHF after surgery for AS and after CABG [I]

<table>
<thead>
<tr>
<th></th>
<th>AVR (n=45)</th>
<th>CABG (n=47)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>72 ± 10</td>
<td>73 ± 10</td>
<td>n.s.</td>
</tr>
<tr>
<td>Female gender</td>
<td>37.8% (17/45)</td>
<td>53.2% (25/47)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>26.5 ± 4.1</td>
<td>27.2 ± 5.0</td>
<td>n.s.</td>
</tr>
<tr>
<td>Blood haemoglobin (g/L)</td>
<td>135 ± 15</td>
<td>123 ± 18</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Plasma creatinine (μmol/L)</td>
<td>107 ± 20</td>
<td>110 ± 33</td>
<td>n.s.</td>
</tr>
<tr>
<td>Plasma creatinine &gt;167 μmol/L</td>
<td>0.0% (0/45)</td>
<td>10.6% (5/47)</td>
<td>0.06</td>
</tr>
<tr>
<td>DM (insulin or orally treated)</td>
<td>20.0% (9/45)</td>
<td>19.1% (9/47)</td>
<td>n.s.</td>
</tr>
<tr>
<td>COPD</td>
<td>15.6% (7/45)</td>
<td>10.6% (5/47)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>13.3% (6/45)</td>
<td>10.6% (6/47)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Peripheral artery disease</td>
<td>4.7% (2/43)</td>
<td>8.7% (4/46)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Hypertension</td>
<td>42.2% (19/45)</td>
<td>40.4% (19/47)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Atrial fibrillation or flutter</td>
<td>22.2% (10/45)</td>
<td>2.1% (1/47)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>NYHA III</td>
<td>62.8% (27/43)</td>
<td>19.5% (8/41)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>NYHA IV</td>
<td>20.9% (5/43)</td>
<td>70.7% (20/41)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Severe systolic LV dysfunction*</td>
<td>24.4% (11/45)</td>
<td>20.5% (9/44)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Cardiogenic shock</td>
<td>2.2% (1/45)</td>
<td>4.3% (2/47)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Elective operation</td>
<td>73.3% (33)</td>
<td>12.8% (6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Urgent operation</td>
<td>22.2% (10)</td>
<td>61.7% (29)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Emergency operation</td>
<td>4.4% (2)</td>
<td>25.5% (12)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Euroscore</td>
<td>6.7 ± 2.5</td>
<td>7.6 ± 3.5</td>
<td>n.s.</td>
</tr>
<tr>
<td>Cross-clamp time (minutes)</td>
<td>95 ± 30</td>
<td>55 ± 21</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CPB time (minutes)</td>
<td>134 ± 42</td>
<td>102 ± 32</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Table 3. Demographic and clinical data for AVR and CABG patients with postoperative heart failure. Figures within brackets are the number of patients with the characteristics in question, obtained from those with available data. Results are given as percentage or as mean ± SD. *Left ventricular ejection fraction ≤ 0.30. DM = diabetes mellitus; COPD = chronic obstructive pulmonary disease; NYHA = New York Heart Association class; CPB = cardiopulmonary bypass.
**Preoperative data**
Both the AVR group and the CABG group had a high prevalence of severe systolic left ventricular dysfunction preoperatively. In the CABG group 83.0% had unstable coronary artery disease, 25.5% had significant left main stenosis and 91.3% had 3-vessel disease. The AVR group compared favourably with the CABG group regarding NYHA class IV and preoperative the haemoglobin level. However, preoperative atrial fibrillation was more common in the AVR group (Table 3).

**Intraoperative data**
Compared with the AVR group, a higher proportion of the patients in the CABG group underwent urgent or emergency procedures and myocardial ischaemia on induction occurred more frequently. The aortic cross-clamp time and cardiopulmonary bypass (CPB) time were significantly longer in the AVR group than in the CABG group (Table 3).

**Potential causes and eliciting events of PHF**
A potential eliciting event preceding PHF could be identified in 31% (14/45) of the AVR patients and in 60% (28/47) of the CABG patients. Myocardial ischemia during induction was only found in the CABG group (31.9%; p<0.001). Intraoperative myocardial infarction was recorded in 40.4% of the CABG patients and in 13.3% of the AVR patients (p<0.01). Ten of the 19 patients in the CABG group who developed PMI had ongoing ischaemia at the start of the operation. Septicaemia preceded heart failure in 8.9% of the AVR patients but in no patients in the CABG group (p=0.05) (Table 4).

<table>
<thead>
<tr>
<th></th>
<th>AVR (n=45)</th>
<th>CABG (n=47)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ischaemia during induction</td>
<td>0.0% (0/45)</td>
<td>31.9% (15/47)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Perioperative myocardial infarction</td>
<td>13.3% (6/45)</td>
<td>40.4% (19/47)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Air in coronary vessels</td>
<td>6.7% (3/45)</td>
<td>2.1% (1/47)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Tamponade</td>
<td>2.2% (1/45)</td>
<td>6.3% (3/47)</td>
<td>n.s</td>
</tr>
<tr>
<td>Septicaemia preceding heart failure</td>
<td>8.9% (4/45)</td>
<td>0.0% (0/47)</td>
<td>0.05</td>
</tr>
</tbody>
</table>

**Table 4.** Potential causes and eliciting events of PHF. Figures within brackets are the number of patients with the characteristics in question, obtained from those with available data.
Presentation of PHF

Postoperative heart failure was evident at weaning from CPB in the majority of the patients in both groups. PHF that presented later in the postoperative period was usually preceded by tamponade or septicaemia. Seven of the AVR patients (15.6%) were considered to have isolated right ventricular failure, compared to none in the CABG group (p<0.01) (Table 5).

Comment:

In patients that could sustain circulation that was sufficient to permit haemodynamic measurements before treatment, available data showed SvO2 values of 53.7 ± 11.0 % (n=23) and 48.0 ± 9.3 % (n=23) in the AVR and CABG groups respectively. At this stage the systolic blood pressures were 84 ± 16 mmHg (n=30) and 82 ± 16 mmHg (n=31) while the pulmonary arterial diastolic pressures were 22 ± 5 mmHg (n=19) and 18 ± 4 mmHg (n=26) in the respective groups. Left ventricular stroke work indexes were 23.4 ± 10.2 6 gram-metres*m^{-2} (n=8) and 17.1 ± 7.3 6 gram-metres*m^{-2} (n=3) and cardiac indexes were 1.9 ± 0.5 (n=8) and 1.5 ± 0.2 L*min^{-1}*m^{-2} (n=3) in patients with available Swan-Ganz data in the AVR group and CABG groups respectively.

<table>
<thead>
<tr>
<th></th>
<th>AVR (n=45)</th>
<th>CABG (n=47)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isolated left ventricular failure</td>
<td>75.0% (33/44)</td>
<td>79.5% (35/44)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Isolated right ventricular failure</td>
<td>15.6% (7/44)</td>
<td>0.0% (0/44)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Left + right ventricular failure</td>
<td>9.1% (4/44)</td>
<td>20.9% (9/44)</td>
<td>n.s.</td>
</tr>
<tr>
<td>PHF at weaning off CPB</td>
<td>73.3% (33/45)</td>
<td>57.4% (27/47)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Early PHF in the OR</td>
<td>2.2% (1/45)</td>
<td>23.4% (11/47)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>PHF in ICU</td>
<td>20.0% (9/45)</td>
<td>14.9% (7/47)</td>
<td>n.s.</td>
</tr>
</tbody>
</table>

Table 5. Presentation of postoperative heart failure (PHF). Figures within brackets are the number of patients with the characteristics in question, obtained from those with available data. CPB = cardiopulmonary bypass; OR = operating room; ICU = intensive care unit.
### Risk factors for PHF failure after surgery for AS [II]

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>PHF+ (n=45)</th>
<th>PHF- (n=353)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>72 ± 10</td>
<td>69 ± 10</td>
<td>0.01</td>
</tr>
<tr>
<td>Female gender</td>
<td>37.8% (17/45)</td>
<td>49.6% (175/353)</td>
<td>0.2</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>26.5 ± 4.1</td>
<td>26.1 ± 4.2 (351)</td>
<td>0.2</td>
</tr>
<tr>
<td>Blood haemoglobin (g/L)</td>
<td>135 ± 15</td>
<td>134 ± 13</td>
<td>0.5</td>
</tr>
<tr>
<td>Plasma creatinine (μmol/L)</td>
<td>107 ± 20</td>
<td>99 ± 26</td>
<td>0.003</td>
</tr>
<tr>
<td>DM (insulin or orally treated)</td>
<td>20.0% (9/45)</td>
<td>10.2% (36/353)</td>
<td>0.08</td>
</tr>
<tr>
<td>COPD</td>
<td>15.6% (7/45)</td>
<td>7.9% (28/353)</td>
<td>0.1</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>13.3% (6/45)</td>
<td>8.2% (29/353)</td>
<td>0.3</td>
</tr>
<tr>
<td>Peripheral artery disease</td>
<td>4.7% (2/43)</td>
<td>2.3% (8/348)</td>
<td>0.3</td>
</tr>
<tr>
<td>Hypertension</td>
<td>42.2% (19/45)</td>
<td>26.1% (92/353)</td>
<td>0.03</td>
</tr>
<tr>
<td>Atrial fibrillation or flutter</td>
<td>24.4% (11/45)</td>
<td>14.1% (49/347)</td>
<td>0.08</td>
</tr>
<tr>
<td>Previous myocardial infarction</td>
<td>8.9% (4/45)</td>
<td>4.2% (15/353)</td>
<td>0.2</td>
</tr>
<tr>
<td>Angina pectoris</td>
<td>11.1% (5/45)</td>
<td>24.9% (88/353)</td>
<td>0.04</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>68.9% (31/45)</td>
<td>32.6% (115/353)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Severe systolic LV dysfunction*</td>
<td>24.4% (11/45)</td>
<td>4.0% (14/353)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Systolic PAP ≥ 45 mmHg</td>
<td>22.2% (10/45)</td>
<td>6.5% (23/353)</td>
<td>0.002</td>
</tr>
<tr>
<td>Systolic PAP ≥ 60 mmHg</td>
<td>15.6% (7/45)</td>
<td>1.4% (5/353)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Aortic valve orifice area (cm²)</td>
<td>0.55 ± 0.19 (44)</td>
<td>0.62 ± 0.19 (335)</td>
<td>0.03</td>
</tr>
<tr>
<td>NYHA III</td>
<td>62.8% (27/43)</td>
<td>50.5% (164/325)</td>
<td>0.2</td>
</tr>
<tr>
<td>NYHA IV</td>
<td>20.9% (9/43)</td>
<td>4.0% (13/325)</td>
<td>0.0003</td>
</tr>
<tr>
<td>Elective operation</td>
<td>73.3% (33/45)</td>
<td>94.6% (334/353)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Urgent operation</td>
<td>22.2% (10/45)</td>
<td>5.1% (18/353)</td>
<td>0.004</td>
</tr>
<tr>
<td>Emergency operation</td>
<td>4.4% (2/45)</td>
<td>0.3% (1/353)</td>
<td>0.04</td>
</tr>
<tr>
<td>Preoperatively unstable</td>
<td>13.3% (6/45)</td>
<td>0.6% (2/353)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

**haemodynamics**

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>PHF+ (n=45)</th>
<th>PHF- (n=353)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Euroscore</td>
<td>7.0 ± 2.7</td>
<td>5.3 ± 2.0</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Bioprosthetic</td>
<td>73.3% (33/45)</td>
<td>59.8% (211/353)</td>
<td>0.1</td>
</tr>
<tr>
<td>Aortic valve prosthesis size (mm)</td>
<td>22.7 ± 2.3</td>
<td>23.2 ± 2.2</td>
<td>0.2</td>
</tr>
<tr>
<td>Aortic valve prosthesis 19 mm</td>
<td>6.7% (3/45)</td>
<td>12.2% (43/353)</td>
<td>0.4</td>
</tr>
<tr>
<td>Aortic root enlargement</td>
<td>11.1% (5/45)</td>
<td>9.1% (32/353)</td>
<td>0.6</td>
</tr>
<tr>
<td>Cross-clamp time (minutes)</td>
<td>95 ± 30</td>
<td>79 ± 18</td>
<td>0.0006</td>
</tr>
<tr>
<td>CPB time (minutes)</td>
<td>134 ± 42</td>
<td>103 ± 22</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>EOA Index (cm² / BSA m²)</td>
<td>0.87 ± 0.20 (45)</td>
<td>0.88 ± 0.20 (348)</td>
<td>0.92</td>
</tr>
<tr>
<td>EOA Index &lt; 0.75 cm² / BSA m²</td>
<td>44.4% (20/45)</td>
<td>30.5% (106/348)</td>
<td>0.06</td>
</tr>
</tbody>
</table>

**Table 6.** Preoperative and intraoperative data for AVR patients with and without postoperative heart failure (PHF+ and PHF-). Figures within brackets are the number of patients with the characteristics in question, obtained from those with available data. *Left ventricular ejection fraction ≤ 0.30. NYHA = New York Heart Association class; PAP = pulmonary artery pressure; CPB = cardiopulmonary bypass; EOA = effective orifice area; EOA Index = EOA(cm²) / BSA(m²); BSA = body surface area.
Preoperative and intraoperative data for patients with and without PHF operated on for AS are given in Table 6. Univariate associations between different variables and PHF after AVR for AS are presented in paper II, Table 4. With regard to clinical presentation of AS, angina was associated with a reduced risk of PHF, whereas history of congestive heart failure increased this risk.

In the forward stepwise multiple logistic regression analysis five preoperative (hypertension, history of congestive heart failure, severe systolic left ventricular dysfunction, systolic pulmonary artery pressure ≥60 mmHg, preoperative haemodynamic instability) and two intraoperative variables (aortic cross-clamp time, intraoperative myocardial infarction) emerged as independent risk factors for PHF (Table 7).

Comment: In the PHF group, divergences from standard surgical procedures were reported in 7 of the 45 patients. Details are given in paper II. The average aortic cross-clamp time was 133 ± 46 minutes in these patients, compared with 89 ± 23 minutes in PHF patients without reported divergences (p=0.015). However, these divergences did not in itself provide obvious explanations for PHF and hence a prolonged cross-clamp time per se remains to be considered a major risk factor.

<table>
<thead>
<tr>
<th>Variables (1 = yes, 0 = no); n=398</th>
<th>Adjusted OR</th>
<th>CI (95%)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cross-clamp time (minutes)</td>
<td>1.04</td>
<td>1.02-1.06</td>
<td>0.000004</td>
</tr>
<tr>
<td>Systolic PAP ≥60 mmHg</td>
<td>15.38</td>
<td>3.09-76.68</td>
<td>0.0008</td>
</tr>
<tr>
<td>Unstable haemodynamics preoperatively</td>
<td>8.93</td>
<td>1.32-60.18</td>
<td>0.02</td>
</tr>
<tr>
<td>Myocardial infarction intraoperatively</td>
<td>8.15</td>
<td>1.97-39.59</td>
<td>0.004</td>
</tr>
<tr>
<td>Severe systolic LV dysfunction*</td>
<td>6.49</td>
<td>2.12-19.92</td>
<td>0.001</td>
</tr>
<tr>
<td>History of congestive heart failure</td>
<td>3.20</td>
<td>1.42-7.19</td>
<td>0.005</td>
</tr>
<tr>
<td>Hypertension</td>
<td>2.37</td>
<td>1.08-5.23</td>
<td>0.03</td>
</tr>
</tbody>
</table>

**Table 7.** Multivariate forward stepwise logistic regression analysis of risk factors for PHF. Hosmer-Lemeshow goodness-of-fit test-χ2 (df 8) = 4.52, p = 0.81. CI = confidence interval; OR = odds ratio; PAP = pulmonary artery pressure; *Left ventricular ejection fraction ≤ 0.30.
Early postoperative outcome in patients with PHF [I, III]

In both the AVR and CABG group, patients with PHF had substantially longer ventilator treatment, a three times longer ICU stay, higher transfusion requirements and a higher incidence of renal failure compared to patients without PHF. In both groups, PHF was also associated with an increase in 30-day mortality, 6.7% v 1.4% in AVR patients and 21.3% v 1.1% in CABG patients (Table 8).

Comment: Although substantial, the difference in 30-day mortality (6.7% v 21.3%) in patients with PHF between AVR and CABG groups did not reach statistical significance (p=0.07).

<table>
<thead>
<tr>
<th></th>
<th>AVR PHF+ (n=45)</th>
<th>PHF- (n=353)</th>
<th>p value</th>
<th>CABG PHF+ (n=47)</th>
<th>PHF- (n=351)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time on ventilator (hours)</td>
<td>39 ± 76</td>
<td>7 ± 10 (351)</td>
<td>&lt;0.0001</td>
<td>35 ± 51</td>
<td>5 ± 4</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>P-Creatinine, highest (μmol/L)</td>
<td>138 ± 89</td>
<td>100 ± 35</td>
<td>&lt;0.0001</td>
<td>148 ± 78 (46)</td>
<td>104 ± 60 (350)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>P-Creatinine elevation &gt; 50%</td>
<td>20.0%</td>
<td>2.9% (10/346)</td>
<td>0.0001</td>
<td>21.7% (10/46)</td>
<td>1.7% (6/348)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Dialysis</td>
<td>4.5%</td>
<td>0%</td>
<td>0.01</td>
<td>0%</td>
<td>0%</td>
<td>ns</td>
</tr>
<tr>
<td>Myocardial infarction intraoperatively</td>
<td>13.3%</td>
<td>1.7%</td>
<td>0.0008</td>
<td>40.4%</td>
<td>1.7%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Procedure-associated stroke</td>
<td>6.7%</td>
<td>3.7%</td>
<td>ns</td>
<td>8.5%</td>
<td>2.0%</td>
<td>0.03</td>
</tr>
<tr>
<td>Atrial fibrillation or flutter (postoperative onset)</td>
<td>35.6%</td>
<td>33.4% (116/347)</td>
<td>ns</td>
<td>28.3% (13/46)</td>
<td>35.9%</td>
<td>ns</td>
</tr>
<tr>
<td>Reoperation for bleeding/tamponade</td>
<td>11.1%</td>
<td>4.2%</td>
<td>0.06</td>
<td>8.5%</td>
<td>3.4%</td>
<td>ns</td>
</tr>
<tr>
<td>Pericardial effusion requiring drainage</td>
<td>0%</td>
<td>2.0% (7/347)</td>
<td>ns</td>
<td>0%</td>
<td>0%</td>
<td></td>
</tr>
<tr>
<td>Erythrocyte transfusion</td>
<td>60.0%</td>
<td>33.4%</td>
<td>0.0008</td>
<td>72.3%</td>
<td>33.9%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Number of erythrocyte units*</td>
<td>5.4 ± 5.8</td>
<td>3.0 ± 2.4</td>
<td>0.003</td>
<td>5.6 ± 4.3</td>
<td>2.5 ± 1.9</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Thrombocyte transfusion</td>
<td>17.8%</td>
<td>6.8%</td>
<td>0.02</td>
<td>23.4%</td>
<td>5.4%</td>
<td>0.0002</td>
</tr>
<tr>
<td>Number of thrombocyte units*</td>
<td>1.8 ± 1.8</td>
<td>1.5 ± 0.8</td>
<td>ns</td>
<td>1.8 ± 1.1</td>
<td>1.5 ± 0.7</td>
<td>ns</td>
</tr>
<tr>
<td>ICU stay (days)</td>
<td>3.2 ± 3.9</td>
<td>1.2 ± 0.7 (352)</td>
<td>&lt;0.0001</td>
<td>3.2 ± 3.3</td>
<td>1.2 ± 1.0 (349)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>ICU stay &gt;2 days</td>
<td>33.3%</td>
<td>4.8%</td>
<td>&lt;0.0001</td>
<td>40.4%</td>
<td>4.6%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>30-day mortality</td>
<td>6.7%</td>
<td>1.4%</td>
<td>0.05</td>
<td>21.3%</td>
<td>1.1%</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Table 8. Postoperative data for AVR patients with and without postoperative heart failure (PHF+ and PHF-). Results are given as percentage or as mean ± SD. ICU = intensive care unit; SvO₂ = mixed venous oxygen saturation. *Average number of units given to patients who received transfusion.
Risk factors for early mortality [III]

The number of events was too few to permit meaningful analysis in the AVR group. In the CABG group PHF (OR 15.93; CI(95%) 4.53-56.0; p=0.00002) and preoperative haemoglobin (OR 0.96; CI(95%) 0.92-0.99; p=0.03) emerged as independent risk factors for 30-day mortality. The Hosmer-Lemeshow goodness of fit p-value was 0.49.

Late postoperative outcome in patients with PHF [III]

Mortality

The crude mortality rates at 1 and 5 years in patients with and without PHF after AVR were 8.9% v 4.0% (p=0.13) and 42.2% v 14.2% (p<0.0001) respectively. Corresponding figures for patients with and without PHF in the CABG group were 25.5% v 3.1% (p<0.0001) and 36.2% v 11.1% (p=0.0015). The average time to death within the 5-year follow-up period for PHF patients in the AVR and CABG group was 2.5 ± 1.5 and 0.9 ± 1.5 years respectively (p=0.007). Further details are presented in Table 9 and cumulative survival is illustrated in Figure 4.

<table>
<thead>
<tr>
<th>Mortality</th>
<th>AVR</th>
<th>p value</th>
<th>CABG</th>
<th>p value</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PHF</td>
<td>No PHF</td>
<td>PHF</td>
<td>No PHF</td>
<td>AVR PHF v</td>
</tr>
<tr>
<td>30-day (n)</td>
<td>6.7% (3)</td>
<td>1.4% (5)</td>
<td>0.05</td>
<td>21.3% (10)</td>
<td>1.1% (4)</td>
</tr>
<tr>
<td>1-year (n)</td>
<td>8.9% (4)</td>
<td>4.0% (14)</td>
<td>0.13</td>
<td>25.5% (12)</td>
<td>3.1% (11)</td>
</tr>
<tr>
<td>3-year (n)</td>
<td>22.2% (10)</td>
<td>8.0% (28)</td>
<td>0.005</td>
<td>29.8% (14)</td>
<td>6.0% (21)</td>
</tr>
<tr>
<td>4-year (n)</td>
<td>35.6% (16)</td>
<td>10.8% (38)</td>
<td>0.0001</td>
<td>36.2% (17)</td>
<td>8.8% (31)</td>
</tr>
<tr>
<td>5-year (n)</td>
<td>42.2% (19)</td>
<td>14.2% (50)</td>
<td>&lt;0.0001</td>
<td>36.2% (17)</td>
<td>11.1% (39)</td>
</tr>
</tbody>
</table>

Table 9. Crude mortality in patients undergoing AVR for AS and in the matched CABG patients.
Figure 4. Kaplan-Meier survival curves for AVR patients operated on for AS and for the matched CABG patients. PHF+ = patients with postoperative heart failure; PHF- = patients without postoperative heart failure. The p values are given in Table 9.

The role of PHF in relation to other risk factors for late mortality after AVR for AS

Postoperative heart failure emerged as the independent risk factor with the lowest p value for both overall five-year mortality and for late mortality (between 30 days and 5 years). Preoperative renal dysfunction, procedure-associated stroke, BMI<19 kg/m², increasing age, preoperative atrial fibrillation and preoperative anaemia also turned out as independent risk factors for overall five-year mortality and late mortality occurring between 30 days and 5 years. Details regarding risk factors for mortality are presented in Table 10.
Variables (1 = yes, 0 = no) Overall mort (389) Late mort (381)

| Variable                                      | OR (95% CI)    | p value   | OR (95% CI)    | p value   
|-----------------------------------------------|----------------|-----------|----------------|-----------
| PHF                                           | 5.14 (2.36-11.20) | 0.00004   | 5.08 (2.28-11.31) | 0.00006   
| Plasma creatinine >140 μmol/L preoperatively  | 15.97 (3.69-69.11) | 0.0002   | 16.88 (3.95-72.19) | 0.0001   
| Stroke (procedure-associated)                  | 4.36 (1.76-20.63) | 0.004     | 4.80 (1.27-18.12) | 0.02     
| Body mass index <19 kg/m²                       | 7.71 (1.86-32.03) | 0.005     | 9.03 (2.15-37.93) | 0.003    
| Age (per year)                                 | 1.06 (1.02-1.11)  | 0.006     | 1.05 (1.00-1.09)  | 0.03     
| Preoperative atrial fibrillation               | 2.75 (1.31-5.74)  | 0.007     | 2.60 (1.20-5.61)  | 0.01     
| Preoperative anaemia*                          | 2.27 (1.15-4.46)  | 0.02      | 2.33 (1.16-4.69)  | 0.02     

Table 10. Multiple forward stepwise logistic regression analysis of risk factors for overall and late mortality after AVR for AS. Number of events: overall mortality = 69; late mortality = 61. Hosmer-Lemeshow goodness-of-fit test $\chi^2$ (df 8) = 7.3, p=0.50 and (df 8) = 7.0, p=0.53 for the overall mortality and late mortality model, respectively. *Blood haemoglobin < 134 g/L for men and < 117 g/L for women. OR = odds ratio. CI = confidence interval.

The role of PHF in relation to other risk factors for late mortality after CABG

PHF emerged as an independent risk factor for overall five-year mortality but not for mortality later than 30 days after surgery. Independent risk factors for late mortality in the CABG group were in order of statistical significance diabetes, procedure-associated stroke and increasing age. Details regarding risk factors for mortality are presented in Table 11.

Comment: In contrast to conventional risk factor analyses for postoperative mortality, our model was based on variables known at discharge from hospital with the intention to evaluate the impact of PHF and other periprocedural events on long-term outcome.

The same independent risk factors turned out in the overall and late five-year mortality model for the AVR group as only 8 deaths out of a total of 69 deaths during the five-year period occurred within 30 days from surgery.
It may be argued that the event PHF is only a substitute for other risk factors and underlying causes of PHF. To take these risk factors in account, they were also tested in the multivariate model. None of these turned out as an independent risk factor for five-year mortality.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Overall mort (398)</th>
<th>p value</th>
<th>Late mort (383)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR (95% CI)</td>
<td></td>
<td>OR (95% CI)</td>
<td></td>
</tr>
<tr>
<td>PHF</td>
<td>3.86 (1.87-7.95)</td>
<td>0.0003</td>
<td>3.76 (1.34-5.69)</td>
<td>0.006</td>
</tr>
<tr>
<td>Diabetes (insulin or orally treated)</td>
<td>2.65 (1.36-5.19)</td>
<td>0.004</td>
<td>2.76 (1.18-5.69)</td>
<td>0.006</td>
</tr>
<tr>
<td>Age (per year)</td>
<td>1.05 (1.01-1.09)</td>
<td>0.01</td>
<td>1.06 (1.01-1.11)</td>
<td>0.009</td>
</tr>
<tr>
<td>Stroke (procedure-associated)</td>
<td>4.69 (1.26-17.53)</td>
<td>0.02</td>
<td>6.45 (1.69-24.71)</td>
<td>0.006</td>
</tr>
</tbody>
</table>

Table 11. Multiple forward stepwise logistic regression analysis of risk factors for overall and late mortality in the matched CABG patients. Number of events: overall mortality = 56; late mortality = 42. Hosmer-Lemeshow goodness-of-fit test-χ² (df 8)= 11.5, p=0.18 and (df 8)= 11.3, p=0.18 for the overall mortality and late mortality model, respectively. OR = odds ratio. CI = confidence interval.

**Haemodynamics and oxygen delivery before and after surgery for AS [IV]**

Postoperatively a relative decrease in the myocardial oxygen extraction ratio (p=0.0001) and oxygen consumption (p=0.14) by approximately 20% was observed. Coronary sinus oxygen saturation consequently increased from 37 ± 5% to 49 ± 7% (p=0.0001). In contrast, a significant increase in systemic oxygen consumption by 12% (p=0.0004) was observed postoperatively.

Cardiac index increased by 22% from 1.8 ± 0.2 L/min preoperatively to 2.2 ± 0.4 L/min postoperatively (p=0.002). A decrease in the systemic vascular resistance index of a similar magnitude (23%) was found (p=0.009). Further details are given in Table II in paper IV.
Myocardial exchange of substrates and amino acids before surgery for aortic stenosis

Substrates: Significant uptake of FFA (10.4 ± 8.9 μmol/min), lactate (20.7 ± 21.9 μmol/min) and glycerol (0.8 ± 1.2 μmol/min) was found preoperatively. No significant uptake of glucose was detected. Myocardial uptake and arterial level of lactate are shown in Figure 5.

Assuming complete oxidation, FFA and lactate accounted approximately for 86% and 13% of the oxygen consumption respectively (Fig. 6). Furthermore, the arterial – coronary sinus difference (A-Cs) in lactate correlated with the arterial level of lactate (r=0.66; p=0.002) (Fig. 7).
Figure 6. Substrate oxygen equivalents for FFA and lactate preoperatively and postoperatively. Substrate oxygen equivalents (VO$_2$ equivalents) are presented as percentage of the measured myocardial oxygen uptake (VO$_2$a-cs), assuming complete oxidation of substrates taken up by the heart.

Figure 7. Arterial level of lactate versus arterial-coronary sinus (A-Cs) difference in lactate preoperatively and postoperatively. $r =$ Spearman rank correlation coefficient.
**Amino acids:** Significant uptake of glutamate ($3.11 \pm 2.12 \, \mu\text{mol/min}$), branched-chain amino acids (BCCA) ($1.37 \pm 1.50 \, \mu\text{mol/min}$) and aspartate ($0.04 \pm 0.09 \, \mu\text{mol/min}$) was detected preoperatively. Glutamine ($-2.02 \pm 1.21 \, \mu\text{mol/min}$) and alanine ($-0.84 \pm 1.29 \, \mu\text{mol/min}$) were the main amino acids released from the heart preoperatively (Fig. 8).

Further details regarding substrate exchange and individual amino acids are given in paper IV, tables III-IV.

**Figure 8.** Myocardial flux (mean ± SD) of amino acids preoperatively and postoperatively. *Indicates significant uptake/release. No significant differences were found in comparison between preoperative and postoperative values.
Myocardial exchange of substrates and amino acids after surgery for aortic stenosis [IV]

**Substrates:** The arterial level of lactate was significantly higher postoperatively compared to the preoperative level (1.32 ± 0.46 v 0.75 ± 0.31 μmol/L, p<0.001). In spite of this, there was a significant decrease and cessation of myocardial lactate uptake (Fig. 1). Furthermore, the arterial level threshold for lactate uptake increased from approximately 0.25 mmol/L preoperatively to 1.4 mmol/L postoperatively (Fig. 3). No glucose uptake was detected.

The arterial level of FFA decreased from the preoperative value (780 ± 119 μmol/L) to 646 ± 242 μmol/L (p = 0.03), but the myocardial uptake of FFA remained unchanged.

**Amino acids:** Like preoperatively, significant uptake of glutamate (2.80 ± 1.93 μmol/min) and BCAA (1.67 ± 2.87 μmol/min), and a low uptake of aspartate (0.07 ± 0.11 μmol/min) were found postoperatively. A significant correlation between arterial level of glutamate and A-Cs difference was only found postoperatively (r=0.58; p=0.008) (Fig. 9).

![Figure 9. Arterial plasma glutamate versus arterial-coronary sinus (A-Cs) difference in plasma glutamate postoperatively. r = Spearman rank correlation coefficient.](image)

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Glutamine (-1.52 ± 2.66 μmol/min) and alanine (-1.05 ± 2.62 μmol/min) remained the main amino acids released from the heart postoperatively. In addition, a slight net release of tyrosine (-0.07 ± 0.56 μmol/min; p=0.007) was observed in spite of a net uptake of total amino acids (4.29 ± 17.19 μmol/min; p=0.02) (Fig. 4).

Further details regarding substrate exchange and individual amino acids are given in paper IV, Tables III-IV.

Comment: The postoperative blood samples were taken on average 78 ± 16 minutes after release of the aortic-cross clamp.

Effects of glutamate infusion on arterial levels of substrates and amino acids after surgery for aortic stenosis [V]

Glutamate infusion resulted in an approximately by three-fold increase in the arterial plasma level of glutamate (from 166 ± 49 to 555 ± 177 μmol/L; p=0.005). No significant changes in arterial levels of other substrates were observed from the basal state to one hour after the start of the study infusion (from T0 to T1). However, the change in the plasma level of FFA from T0 to T1 differed between the groups, with a decrease in the glutamate group and an increase in the placebo group (p=0.049) (Figs 10-12).
Figure 10. The effect of postoperative glutamate infusion on the arterial plasma level and myocardial flux of glutamate. *Indicates significant uptake. The p values refer to comparison between T0 and T1 within the glutamate group. Glut = Glutamate group. Contr = control group.

Figure 11. The effect of postoperative glutamate infusion on the arterial level and myocardial flux of plasma lactate. *Indicates significant uptake. The p value refers to comparison between T0 and T1 flux within the glutamate group. Glut = Glutamate group. Contr = control group.
Figure 12. The effect of postoperative glutamate infusion on the arterial level and myocardial flux of plasma free fatty acids (FFA). *Indicates significant uptake. No significant differences were found between groups and within groups. The change in the arterial plasma level of FFA from T0 to T1 was significantly different between the glutamate and the control group (p = 0.049). Glut = Glutamate group. Contr = control group.

Effects of glutamate infusion on myocardial exchange of substrates and amino acids after surgery for aortic stenosis [V]

Infusion of glutamate induced an approximate by two-fold increase in myocardial glutamate uptake (from 2.5 ± 2.2 to 5.2 ± 5.4 µmol/min; p=0.013), and was associated with a close significant increase in myocardial lactate uptake from T0 to T1 (p=0.11), resulting in a significant uptake of lactate (12.3 ± 30.3 µmol/min) at T1 (Figs. 6-7). FFA (10.9 ± 3.5 µmol/min), glutamate (2.8 ± 1.4 µmol/min) and branched-chain amino acids (1.5 ± 0.7 µmol/min) were the only substrates or amino acids taken up by the heart in the placebo group at T1 (Figs. 10-12).

The potential contributions of lactate and FFA to myocardial oxygen consumption are illustrated in Figure 13. Further details regarding substrate exchange and individual amino acids postoperatively in the glutamate and placebo groups are given in paper V, Tables 2-3.
Effects of glutamate infusion on arterial-venous differences in substrates and amino acids across the leg after surgery for aortic stenosis [V]

There was a net release of FFA, glycerol, lactate and amino acids from the leg in the glutamate group at the start of the study infusion (T0). Glutamate was the only amino acid taken up by the leg. Glutamate infusion was associated with an approximately seven-fold increase in arterial – venous (AV) differences in glutamate (p=0.005). In the control group the negative AV differences in FFA (p=0.007) and amino acids (p=0.047) increased from T0 to T1. In contrast, AV-differences of FFA and amino acids tended to change in the opposite direction in association with glutamate infusion, leading to significantly smaller negative AV differences in FFA (p=0.04) and amino acids (p=0.01) at T1, compared with the control group (Figs. 14-17). Further details regarding the substrate exchanges and individual amino acids across the leg postoperatively, in the glutamate and placebo groups are given in paper V, Table 4.
Comment: Leg blood flow measurements were not available. The haemodynamic variables were stable in both groups. No significant differences were seen between the glutamate and the control group and no significant changes occurred from T0 to T1. At T0 cardiac index was 2.3 ± 0.5 and 2.1 ± 0.3 L*min⁻¹*m⁻²body surface area (BSA) in the glutamate and control group respectively. At T1 it was 2.3 ± 0.2 and 2.3 ± 0.3 L*min⁻¹*m⁻²BSA in the glutamate and control group respectively. At T0 systemic vascular resistance index was 1873 ± 263 and 2341 ± 683 dyne*s*cm⁻⁵*m⁻²BSA in the glutamate group and control group respectively. At T1 it was 2046 ± 288 and 2184 ± 357 dyne*s*cm⁻⁵*m⁻²BSA in the glutamate group and control group respectively.

**Figure 14.** The effect of postoperative glutamate infusion on arterial-venous (AV) differences in FFA over the leg. *Indicates significant release. Glut = Glutamate group. Contr = control group.
Figure 15. The effect of postoperative glutamate infusion on arterial-venous (AV) differences in glutamate over the leg. *Indicates significant uptake. The p values refer to comparison between T0 and T1 within the glutamate group. Glut = Glutamate group. Contr = control group.

AV differences in total amino acids

Figure 16. The effect of postoperative glutamate infusion on arterial-venous (AV) differences in total amino acids over the leg. *Indicates significant release.
Figure 17. Arterial-venous (AV) differences in amino acids (AA) over the leg after 1 hour of infusion of glutamate/placebo (T1). *Indicates significant uptake/release. The p values refer to comparison between the glutamate and the control groups.
Effects of different infusion rates of glutamate on arterial levels and myocardial uptake of glutamate after CABG [VI]

The rates of glutamate infusion varied from 10 to 87 mg per kg body weight and hour during the 60-minute period of glutamate infusion (Figure 1, paper VI). A dose-dependent linear increase in arterial whole blood glutamate levels was found (r = 0.95; p<0.001; Figure 2, paper VI).

Myocardial glutamate uptake correlated with arterial whole blood levels of glutamate during the first 30-minute period (r = 0.60 p<0.001; Figure 4, paper VI) and uptake of glutamate increased from 0.7 ± 0.2 μmol/min (basal state) to an early peak of 5.7 ± 1.2 μmol/min at 20 minutes. The arterial whole blood glutamate level had by then increased from 101 ± 10 to 186 ± 18 μmol/L.

A further increase in the arterial glutamate level was not associated with an increase in myocardial glutamate uptake. The significant correlation between arterial whole blood levels and A-Cs differences in glutamate disappeared during the second 30-minute period when higher infusion rates were used. Fractional extraction of glutamate by the heart from the plasma decreased from 43.5% in the basal state to 11.0% at 60 minutes (p<0.001).

However, the individual peak uptake occurred during the first 30-minute period in 6 patients and during the second 30-minute period in 4 patients. The mean of the individual peak uptakes was 6.6 ± 1.1 μmol/min and occurred at an increase in arterial whole blood glutamate by 172 ± 34 μmol/L.

Comment: A strong correlation was found between change in arterial plasma level and change in whole blood level of glutamate from the basal state to 60 minutes after the start of glutamate infusion (r= 0.90; p < 0.001; Figure, 3 paper VI). An increase in arterial whole blood glutamate by 84 μmol/L (after 20 minutes when the mean peak uptake was recorded) and 172 μmol/L (individual peak uptakes) corresponded to increases in arterial plasma levels of glutamate by approximately 230 and 480 μmol/L respectively. Notably, the infusion rate 36.8 mg per kg body weight and hour, in paper V, resulted in an increase in plasma glutamate by almost 400 μmol/L.
Discussion

Although postoperative heart failure (PHF) is a major determinant of the outcome after cardiac surgery, the literature on this issue is surprisingly sparse. With the exception of a few early studies, paper I is to our knowledge the first to address PHF per se in non-CABG patients. The results corroborate previous findings suggesting that PHF is a common and serious complication with high early mortality in CABG patients. Aortic valve replacement (AVR) for aortic stenosis (AS) is a surgical procedure that provides immediate relief of left ventricular outflow obstruction. In spite of this, we found that the incidence of PHF in patients operated on for AS was similar to that in an age- and sex-matched cohort of CABG patients. However, different characteristics of PHF after AVR for aortic stenosis and after CABG were identified. PHF after surgery for AS was not as closely associated with preoperative ischaemic events and intraoperative myocardial infarction as PHF after CABG.

Although PHF after surgery for AS was associated with a marked increase in postoperative morbidity and in the length of postoperative ICU stay, it appeared to be a comparatively benign condition compared with PHF after CABG. However, our further studies showed that the serious consequences of PHF after surgery for AS became evident only with time, resulting in a 5-year mortality not less than that in patients with PHF after CABG.

Potentially eliciting causes of PHF in AVR patients were identified in only one-third of the patients. However, risk factor analysis revealed a strong influence of extended aortic cross-clamp times on development of PHF. This is in agreement with studies that have demonstrated some degree of left and right ventricular dysfunction early after release of the aortic cross-clamp in virtually all patients. The term myocardial stunning has been coined to describe post ischaemic myocardial dysfunction that persists after reperfusion despite the absence of irreversible damage and despite restoration of normal flow. The pathogenesis of myocardial stunning has not been definitively established. Generation of oxygen radicals and calcium overload during reperfusion are among the proposed mechanisms that have received the greatest attention. Unfortunately, strategies to address these mechanisms specifically have so far not been clinically successful in preventing or treating postoperative myocardial dysfunction. Impaired energy production by mitochondria has also been suggested as an underlying mechanism of myocardial stunning. In CABG patients an association between metabolic disturbances of the heart and transient contractile dysfunction has been
demonstrated. There are also reports of encouraging clinical results of metabolic interventions to enhance myocardial recovery in patients with severe heart failure after cardiac surgery. Our study is the first to address myocardial exchange of substrates in patients undergoing surgery for AS.

**METABOLIC CONSIDERATIONS IN SURGERY FOR AORTIC STENOSIS**

**Myocardial metabolism before surgery for AS**

The myocardial metabolism in patients with coronary artery disease is characterized by an increased uptake of glutamate and a release of alanine. It has been suggested that this may represent metabolic adaptation to repetitive ischaemic episodes, as glutamate plays a key role in the intermediary metabolism of the cardiomyocytes, particularly in association with ischaemia. When the glycolytic activity exceeds the oxidative capacity, excess pyruvate is mainly converted to lactate. However, the amino transferase reaction involving glutamate and pyruvate results in production of alanine (instead of lactate) and alpha-ketoglutarate, of which the latter enters the Krebs cycle. Alanine formed during this process is released from the myocytes. In our study the arterio-venous differences in both glutamate and alanine in patients with AS were close to those originally reported by Mudge et al in patients with coronary artery disease. None of our patients had coronary artery disease and, hence, it is conceivable that other conditions such as an increased myocardial workload and left ventricular hypertrophy lead to similar adaptation possibly due to mismatch between oxygen supply and demand.

FFA and lactate were taken up by the heart immediately before surgery in patients with aortic stenosis. Assuming that all substrates taken up by the heart were completely oxidized, FFA would account for approximately 85% of the myocardial oxygen consumption before surgery. A predominant reliance on FFA uptake has previously been reported in the fasting state both in normal post-absorptive man and in patients with coronary artery disease. The remaining oxygen consumption can be explained by myocardial uptake of lactate. The high extraction ratio of lactate and the clear correlation between arterial levels and uptake suggest an undisturbed oxidative metabolism.
Myocardial metabolism after surgery for AS

FFA was the only major substrate taken up postoperatively. Lactate is a preferred substrate under normal conditions and its uptake correlates with the arterial level. The fact that myocardial lactate uptake had decreased and disappeared despite increasing arterial lactate levels postoperatively suggests that normal Krebs cycle activity had not been resumed. In view of the oxygen wasting properties of FFA and their inability to replenish Krebs cycle intermediates, the predominant reliance on FFA as an energy source represents a potentially unfavourable metabolic state under these circumstances and could further delay postoperative recovery.

Glutamate, BCAA and aspartate were the only amino acids taken up by the heart. The magnitude of glutamate uptake, in particular, contributed to a total net uptake of amino acids. Nevertheless, mild myocardial protein degradation was indicated by a small but significant net release of tyrosine. The main amino acids released from the heart were alanine and glutamine. These findings imply a metabolic state similar to that described early after CABG. It is suggested that amino acids, particularly glutamate, play an important role. It is conceivable that mitochondria were fed by amino acids both by external uptake and by degradation of cardiac protein, whereas excess amino groups that formed during this process were exported mainly as alanine and glutamine. Evidence for such a role of amino acids after cardiac surgery has been provided by tracer studies in CABG patients.

The significant correlation between arterial levels of plasma glutamate and arterial-coronary sinus differences found postoperatively could have therapeutic implications, as it also suggests that glutamate uptake can be increased postoperatively by exogenous supply in analogy with the observations reported after CABG.

Dosage of glutamate after cardiac surgery

It is not known to what extent myocardial glutamate uptake is determined by myocardial needs or to what extent it may be limited by the amino acid carrier capacity. In an investigation of L-glutamate transport in sarcommaal vesicles from rat heart, Dinkelborg found that acidosis enhanced glutamate transport, and such a mechanism could explain the increased uptake of glutamate observed in ischaemic and post-ischaemic hearts. Patients
with PHF can be expected to have greater requirements of glutamate than the low-risk patients in our studies.

Pisarenko was the first to investigate the effect of intravenous glutamate infusion after cardiac surgery\textsuperscript{70}. He studied patients with postoperative heart failure treated with inotropic support. Glutamate infusion resulted in functional recovery that was associated with a marked improvement of the previously deranged myocardial metabolism, including conversion of release of lactate and ammonia to uptake. The total amount of L-glutamate administrated was approximately the same as in paper VI, but the infusions were given over a 15-minute period. The arterial-coronary sinus plasma differences in glutamate achieved were almost twice as large as those attained in our paper VI. Arterial plasma glutamate rose approximately 15-fold and the fractional uptake decreased to less than 15%.

In CABG patients a strong correlation between arterial levels and myocardial uptake of glutamate with fractional extraction rates of up to 50\% was later reported\textsuperscript{71,80}. In view of the high capacity to extract glutamate we concluded, even though patients with postoperative heart failure appeared to have greater requirements of glutamate, that lower infusion rates would have sufficed in Pisarenkos study. This could be of importance, as glutamate is not considered a completely innocuous substance\textsuperscript{116,117}. Hence, our aim in paper VI was to explore the relationship between infusion rates, arterial levels and myocardial uptake of glutamate in an attempt to roughly estimate the lowest infusion rate sufficient to supply the postoperative needs of glutamate. We found that glutamate infusion early after CABG induced a dose-dependent linear increase in the arterial level of glutamate and that the correlation between arterial glutamate level and glutamate uptake was lost during the second half hour when the infusion rates were increased. Elevation of the arterial whole blood level by more than two- to three-fold did not substantially increase the myocardial glutamate uptake. This implied that glutamate infusion rates of 30-40 mg per kg body weight and hour could suffice to achieve near maximal glutamate uptake in the heart, at least in routine patients.

In clinical practice the lower range has subsequently been used with encouraging results in patients with postoperative heart failure after CABG\textsuperscript{107}. In patients with aortic stenosis in paper V, we assumed that a slightly higher dose might be appropriate in view of their hypertrophied hearts. Therefore, in paper V a dose of 2 ml per kg body weight and hour of a
0.125 M glutamate solution (36.8 mg of glutamate per kg body weight and hour) was infused and this resulted in an increase in arterial plasma glutamate to the desired level. The myocardial glutamate uptake was doubled and the significant correlation between arterial level of glutamate and myocardial uptake, that was seen before the infusion, disappeared suggesting that the dosage was appropriate to match the myocardial uptake capacity after surgery for AS. This is true at least for the group in general, but owing to the large variations between patients it cannot be ruled out that higher doses might be required in occasional patients to optimize myocardial glutamate uptake.

**Impact of glutamate infusion on myocardial metabolism after surgery for AS**

Our study demonstrates that amplified glutamate uptake by the myocardium during glutamate infusion is not restricted to patients with coronary artery disease. Glutamate infusion has previously been reported to improve recovery of the myocardial metabolism and haemodynamic state after CABG. We found similar metabolic effects of postoperative glutamate infusion on the heart after AVR for aortic stenosis, albeit somewhat more discrete. The uptake of glutamate was doubled and associated with a significant uptake of lactate. Since these findings associated with glutamate infusion are consistent with results from previous animal and human studies using glutamate or its metabolite D-ketoglutarate, it is conceivable that they reflect a true effect. On reviewing the literature it seems that the magnitude of the metabolic effect of glutamate on the heart has been related to the magnitude of metabolic disturbance present when the glutamate infusion was started. In our study the change in lactate uptake within and between groups did not quite reach statistical significance. Our sample size was chosen with regard to previous studies but in retrospect we appreciate that a larger sample could have provided more conclusive results.

Assessment of myocardial metabolism with the coronary sinus catheter technique is reproducible and well documented, which makes comparisons with previous studies appropriate. However, the methodology does not provide direct information on the intracellular metabolic pathways of substrates. Available tracer studies from humans in association with coronary surgery have shown that glutamate taken up by the heart is fed into the Krebs cycle and preferentially oxidized via the alanine aminotransferase reaction. Thus, and also in agreement with animal experimental data, glutamate can be expected to stimulate Krebs cycle activity in humans after ischaemia, which would be reflected by enhanced lactate uptake.
Exchange of substrates in the leg (peripheral tissue) after surgery for AS

AV differences in substrates and amino acids across the leg revealed signs of net protein catabolism, peripheral tissue lipolysis and lactate release postoperatively. The only amino acid taken up by the leg was glutamate. This is in accordance with the post-traumatic neuro-endocrine stress response and has been demonstrated previously after coronary surgery80, 123.

Impact of glutamate infusion on exchange of substrates in the leg (peripheral tissue) after surgery for AS

The impact of glutamate on peripheral tissue metabolism has not been studied previously. Glutamate infusion resulted in an approximately seven-fold increase in the AV difference in glutamate and this was associated with significantly smaller negative AV differences in FFA and amino acids compared with the control group.

The peripheral tissue results need to be interpreted with caution, owing to the lack of flow measurements. Assessment of cardiac output, systemic vascular resistance and oxygen extraction ratios across the leg argue against significant changes in leg blood flow in either group. Furthermore, venous occlusion plethysmography measurements early after coronary surgery have revealed stable flow in the leg during this time frame after cardiac surgery80, 123. Thus it is conceivable that glutamate infusion counteracted an increase in peripheral tissue release of FFA, which is consistent with the observed changes in plasma FFA. Decreased plasma levels of FFA have been reported previously in association with glutamate administration89, 124. This does not necessarily imply a direct effect of glutamate on lipolysis, as glutamate has been shown to increase insulin secretion124. In normal subjects a maximal reduction of plasma FFA may be seen at plasma insulin levels as low as 30 mU/L, which correspond to the reported increment in insulin during glutamate infusion124, 125.

Our data also indicate that the marked increase in glutamate uptake in the leg was associated with a mitigation of net amino acid loss. This appears to be explained by net uptake of glutamate per se and is probably not directly connected to protein turnover, as no evident change was observed in the exchange of non-metabolizable amino acids.
Taken together, the findings suggest that glutamate has a potentially favourable effect not only on myocardial metabolism but also on peripheral tissue metabolism in the postoperative phase.

POSTOPERATIVE HEART FAILURE AFTER SURGERY FOR AORTIC STENOSIS

Different characteristics of PHF after CABG and after surgery for AS

The incidence of PHF after surgery for isolated, first time AS was 11.3%, which was similar to the incidence found in an age- and sex-matched cohort of patients undergoing CABG (11.8%). However, the eliciting events and presentation of heart failure differed between the groups. PHF presented at weaning from cardiopulmonary bypass or within the first hours after surgery in the majority of patients both after AVR for AS and after CABG. PHF that had its onset later in the postoperative period was usually preceded by tamponade or septicaemia.

PHF in the CABG group was more clearly related to preoperative ischaemia and perioperative myocardial infarction. Forty per cent of the patients with PHF after CABG had perioperative myocardial infarction. Half of these showed signs of ischaemia at the induction of anaesthesia. This is in agreement with previous studies in which preoperative ischaemia was identified as a major cause of perioperative myocardial infarction in association with CABG126, 127.

The AVR group had longer aortic cross-clamp time and a higher rate of isolated right ventricular heart failure postoperatively. PHF after surgery for AS was not associated with preoperative ischaemic events and perioperative myocardial infarction was only found in 13% of the patients. This could explain the more favourable short-term outcome in patients with PHF after surgery for AS. The few patients in the AVR group with perioperative myocardial infarction had a high postoperative mortality rate. Mechanical circulatory assist was less frequently used in the AVR group, which also suggests less severe heart failure in the AVR patients. However, it could also imply a lower threshold for using mechanical circulatory assistance in association with myocardial ischaemia.

There are data suggesting that right ventricular dysfunction may contribute to low output syndrome in almost half of the cases after CABG128. Isolated right ventricular failure, on the
other hand, was found in only 2 out of 31 patients with low output syndrome after CABG. In contrast it was noted in 2 out of 7 patients with low output syndrome after AVR. In agreement with these findings, isolated right ventricular failure appeared to be a problem mainly associated with heart failure after AVR in our study. Several factors may have contributed to right ventricular dysfunction after AVR for AS. The occurrence of an increased after-load for the right ventricle due to left ventricular hypertrophy and diastolic dysfunction, insufficient protection of the right ventricle during retrograde delivery of cardioplegia, and air embolism into the right coronary artery due to inadequate de-airing procedures can all lead to right ventricular dysfunction128-131.

Events eliciting PHF could be identified in approximately 2/3 of the CABG patients but only 1/3 of the AVR patients. In addition, the surgical procedure per se, especially cardioplegic arrest, contributes to postoperative depression of myocardial function100. In particular, patients with preoperatively compromised left ventricular function are at increased risk of developing clinical evidence of heart failure after surgery54. Hence, it is conceivable that preoperative left ventricular dysfunction, which was common in both groups in our study, was an important contributor to PHF54, 132, 133. To shed further light on the mechanisms behind PHF in these patients, we decided to analyse risk factors for PHF in the total cohort of patients undergoing surgery for isolated AS.

**Risk factors for PHF after surgery for AS**

With regard to the clinical presentation of AS, angina according to univariate analysis was associated with a reduced risk of PHF, whereas history of congestive heart failure increased this risk. Multivariate logistic regression analysis identified seven variables as independent risk factors for PHF after surgery for isolated AS: five preoperative (hypertension, history of congestive heart failure, severe systolic left ventricular function, pulmonary hypertension, haemodynamic instability preoperatively) and two intraoperative (aortic cross-clamp time, intraoperative myocardial infarction).

After submission of paper II we found a recent paper by Maganti et al, on risk factors for low cardiac output syndrome (LOS) after AVR41. Their paper focused on preoperative variables in order to predict operative mortality and LOS in a heterogeneous cohort including all indications for AVR. They identified renal failure, earlier year of operation, left ventricular
dysfunction, shock, female gender and increasing age as risk factors for LOS. Out of these, left ventricular dysfunction and shock agree with our results.

In order to define preventive measures and to improve the therapeutic approach, it can be more useful to establish pathophysiological relationships between risk factors and complications. Thus, our aim was to identify not only predictive variables, but also factors with a mechanistic relationship to PHF. Variables tested in our models were chosen to meet these aims. Those identified in the final model seem to indicate either preoperatively existing or intraoperatively acquired myocardial dysfunction. Furthermore, arterial and pulmonary hypertension indicating increased left and right ventricular after-load, respectively, emerged as independent risk factors.

Pulmonary hypertension, haemodynamic instability before anaesthesia, intraoperative myocardial infarction and severe systolic left ventricular dysfunction preoperatively had the highest odds ratios for PHF. However, the hazards associated with them were not matched by their explanatory role in the final model. In contrast, the statistically most significant risk factor was aortic cross-clamp time, which was also found to have the highest explanatory role. Extensions of aortic-cross clamp times were partly explained by intraoperative surgical problems. However, these surgical problems did not in themselves provide obvious explanations for PHF and hence a prolonged cross-clamp time per se remains to be considered a major risk factor.

The influence of PHF on the early postoperative outcome after AVR for AS
Although PHF after AVR for AS appeared to be a less serious condition than PHF after CABG, it was associated with an almost five-fold increase in 30-day mortality (6.7% v 1.4%), a substantial increase in postoperative morbidity and consequently increased utilization of ICU resources compared with AVR patients without PHF. The average ICU stay was more than doubled and the time on ventilator was increased more than five-fold. Transfusion requirements were approximately doubled.

Different temporal impact of PHF on mortality after AVR for AS compared with CABG
Our study demonstrates differences in the temporal patterns of the mortality after PHF in CABG and AVR patients, which to our knowledge has not previously been described. PHF is a complication that carries a high early mortality after CABG, whereas its influence on late
mortality after this operation is limited. In contrast, to fully recognize the serious consequences of PHF on survival after AVR for AS an extended follow-up is required. After five years, the mortality exceeded that found in the CABG patients with PHF.

**Risk factors for late mortality after AVR for AS**

To clarify the relative importance of PHF for late mortality, multivariate risk factor analyses were performed. In order of statistical significance, PHF, preoperative renal dysfunction, low body mass index, preoperative atrial fibrillation, procedure-associated stroke, preoperative anaemia and increasing age emerged as independent risk factors for mortality occurring between 30 days and five years after AVR for AS.

It may be argued that PHF as an event is only a substitute for other risk factors and underlying causes of PHF. However, the previously identified risk factors for PHF (hypertension, history of congestive heart failure, severe systolic left ventricular dysfunction, pulmonary hypertension, preoperative haemodynamic instability, aortic cross-clamp time, intraoperative myocardial infarction) were also tested in the multivariate model. None of these emerged as an independent risk factor for late mortality. This emphasizes the importance of PHF per se as a prognostic factor for late mortality after surgery for AS.

The reasons for the extended unfavourable impact of PHF after surgery for AS remain to be clarified. A similar sustained negative influence of preoperative left ventricular diastolic dysfunction on long-term survival has recently been demonstrated. The authors speculated that diastolic dysfunction represented irreversible structural myocardial abnormalities, although they acknowledged the lack of direct histopathological evidence. We had no specific data on left ventricular diastolic dysfunction in our database, but pulmonary hypertension, a related variable, emerged as a strong risk factor for PHF and was associated with a high mortality rate.

**Risk factors for early and late mortality after CABG**

In CABG patients, PHF has previously been reported to be the major cause of early postoperative mortality. Our results are consistent with these findings and this is well illustrated by the survival curves (Fig. 4). PHF had the highest significance of the risk factors for early mortality after CABG in our study. Its impact on early mortality was so pronounced that PHF also emerged as the risk factor with the highest significance for mortality occurring
within five years from surgery, although it did not turn out as an independent risk factor for late mortality. The finding in paper I, which indicates that PHF after CABG was closely related to ischaemic events during the early stages of surgery and to intraoperative myocardial infarction, could explain the unfavourable short-term outcome.

Procedure-associated stroke, diabetes and increasing age were the only significant independent risk factors for mortality occurring between 30 days and 5 years after surgery. These results may not be entirely representative for CABG patients, as the cohort was selected, but nevertheless the identified risk factors are in general agreement with previous experience61, 66, 134, 135.

The patient, the procedure, the prosthesis and PHF

Research in valve surgery has mainly focused on the prosthesis. In addition, preoperative risk factors and postoperative echocardiographic characteristics, such as regression of left ventricular mass, early improvement of the left ventricular ejection fraction and diastolic function, have been evaluated as prognostic factors for the long-term outcome after valve surgery.

Several studies have dealt with preoperative risk factors for operative and in-hospital mortality after AVR37-40, 46, 135-137 and a few have also addressed risk factors for long-term mortality42-46. In contrast to most previous studies, our study is characterized by its homogeneous cohort of AS patients, and that the analysis is based on variables known at discharge from hospital, with the intention of evaluating the impact of PHF and other periprocedural events in relation to other risk factors on long-term survival. Interestingly PHF emerged as the risk factor with the highest statistical significance for mortality within 5-years after AVR for AS although virtually all previously documented preoperative and periprocedural risk factors were included in the analysis. However, evaluation of follow-up variables such as echocardiographic data, medication or biochemical markers such as natriuretic peptides were beyond the scope of this thesis.

The other independent risk factors for mortality within 5-years after AVR for AS besides PHF that emerged in our model were procedure-associated stroke, preoperative renal dysfunction, increasing age, preoperative atrial fibrillation, low BMI and anaemia, which all to some extent have been reported being risk factors for mortality after cardiac surgery37-40, 42, 46, 135-141.
The influence of the prosthesis and of patient-prosthesis mismatch on the outcome has been under debate. Patient-prosthesis mismatch plays a role in postoperative haemodynamics and regression of left ventricular mass. However, data regarding its impact on the clinical outcome and survival are conflicting. In our study no significant association between patient-prosthesis mismatch and PHF or long-term outcome was found. It cannot be excluded that such a relationship might have emerged if a larger cohort had been studied. Nevertheless, other risk factors were obviously of greater importance for both PHF and long-term survival in our study.

PHF has been reported to be the major cause of in-hospital mortality after CABG. Our study demonstrates that PHF is a problem of essentially the same magnitude after surgery for aortic stenosis, although its true impact on survival after surgery for AS becomes evident only with time. Our studies have revealed that PHF per se after surgery for AS carries repercussions beyond those of any of its associated risk factors.

**Clinical implications**

There is an ongoing debate regarding the optimal timing of surgery and whether asymptomatic patients with significant AS should be operated on or not. Currently patients are considered for operation when clinical symptoms have occurred. Our data demonstrate that with this policy approximately ten per cent of the patients arrive for surgery with either severe left ventricular dysfunction or severe pulmonary hypertension. Other investigators have found that moderate to severe diastolic dysfunction has severe and sustained implications for the long-term prognosis after surgery for AS, even in patients with well preserved left ventricular ejection fractions. Transition from an asymptomatic to a symptomatic stage may be difficult to detect, particularly in elderly patients. Thus more meticulous surveillance of asymptomatic patients is warranted and it may be advisable to consider surgery in individual patients before symptoms develop.

Although assessment of preoperative risk factors is essential for predicting the outcome, it is evident that periprocedural events also have to be considered with regard to long-term results. The serious consequences of PHF after surgery for AS call for periprocedural efforts to avoid this complication, and for improved treatment of PHF when it occurs. The importance of
addressing myocardial protection and minimizing the cross-clamp time, particularly in patients with preoperatively compromised myocardial function, is highlighted by our results.

It is apparent from our study and from the literature that treatment of PHF seems to be quite standardized, with use of inotropic agents regardless of the cause of PHF or the type of procedure. On the basis of our findings in and available data in the literature we suggest that greater focus on causal aspects of heart failure, tailoring of treatment and prophylactic measures is warranted. In patients with a severe ischaemic insult and a high probability of myocardial infarction, the use of adrenergic agents that increase the myocardial oxygen demand should be avoided or minimized. Instead, early insertion of an intra-aortic balloon pump and after-load reduction that could enhance myocardial recovery and improve cardiac output without an unnecessary increase of the myocardial workload should be favoured. Adrenergic drugs may not be ideal for treatment of PHF after surgery for AS, as they also have a negative influence on diastolic relaxation in hypertrophic myocardium and may contribute to left ventricular outflow obstruction. Predominant right ventricular failure calls for use of drugs that reduce the right ventricular after-load and stimulate right ventricular contractility. Given the potential adverse effects of inotropic drugs used for treatment of PHF, alternative approaches to enhance myocardial recovery deserve to be explored.

Restrictive use of inotropic agents has been found feasible in surgery for ischaemic heart disease by employing a metabolic strategy, which included metabolic treatment with glutamate and GIK (glucose-insulin-potassium) in selected cases. Glutamate has also been shown to improve myocardial performance and enhance metabolic recovery of the heart after ischaemia. Our data on the effects of postoperative glutamate infusion in low-risk patients undergoing surgery for AS suggest that glutamate deserves evaluation in PHF, also after surgery for AS. Given the lack of conclusive evidence for benefits of any type of treatment, it appears that current treatment of PHF is based mainly on opinion and tradition. Thus, it is obvious that evaluations of treatment strategies of PHF are needed and in view of the long-term consequences after AVR for AS, these evaluations require more than haemodynamic assessment and short-term follow-up. One of the reasons for this scientific deficiency is the absence of generally accepted and uniform diagnostic criteria for PHF. Thus, efforts to reach a consensus about diagnostic criteria for PHF that are easily applicable in the routine clinical setting are desirable to facilitate future research on this important issue.
In chronic congestive heart failure active surveillance and treatment has been shown to be associated with improved prognosis. The recognition of PHF as an important long-term prognostic factor after surgery for AS suggests that PHF as an event deserves to be emphasized in the discharge records, as it cannot be ruled out that these patients could benefit from a more active follow-up.
Summary and conclusions

- A comparison between PHF in patients operated on for aortic stenosis and PHF in an age- and sex-matched cohort undergoing CABG revealed the following:
  - the incidence was similar in the two groups (11.3% and 11.8% respectively)
  - PHF usually presented early, in the operating room, in both patient groups
  - later presentation of PHF was usually preceded by tamponade or septicaemia
  - PHF was associated with a marked increase in early morbidity and subsequent increase in ICU stay

- Different characteristics of PHF were found in patients operated on for aortic stenosis and coronary artery disease respectively
  - PHF after CABG was more closely associated with ischaemic events preoperatively and intraoperative myocardial infarction
  - isolated right ventricular failure was more common in patients after surgery for aortic stenosis
  - short term survival appeared more favourable in patients with PHF after surgery for aortic stenosis
  - a potentially eliciting event to PHF was identified in approximately 2/3 of the CABG patients and in only 1/3 of the AVR patients

- Five preoperative variables (hypertension, history of congestive heart failure, severe systolic left ventricular dysfunction, pulmonary hypertension, preoperative hemodynamic instability) and two intraoperative variables (aortic cross clamp time, intraoperative myocardial infarction) were identified as independent risk factors for PHF after surgery for aortic stenosis
  - these variables indicate preexisting myocardial dysfunction, increased right or left ventricular afterload and intraoperatively acquired myocardial dysfunction

- PHF after CABG was associated with high early postoperative mortality. Its impact on early mortality was so pronounced that it emerged as the risk factor with the highest significance for mortality occurring within five years from surgery, even though it did not turn out as an independent risk factor for late mortality.
• PHF after AVR for AS appeared comparatively benign looking at early mortality but was associated with a sustained negative influence on survival resulting in a five-year survival that was at least as poor as after PHF in the CABG group

• PHF emerged as the risk factor with highest statistical significance for mortality within the five years after AVR for AS
  o other independent risk factors for five-year mortality were preoperative renal dysfunction, procedure-associated stroke, BMI < 19 kg/m², increasing age, preoperative atrial fibrillation and preoperative anaemia
  o risk factors for PHF did not emerge as independent risk factors for late mortality emphasizing the significance of the event of PHF per se

• FFA and lactate were the major substrates taken up by the heart in patients with aortic stenosis preoperatively

• Metabolic adaptation with a substantial myocardial uptake of glutamate of a magnitude previously described in patients with coronary artery disease was observed preoperatively

• Postoperatively a potentially unfavorable metabolic state was observed as indicated by the following findings:
  o FFA were the only major substrates taken up by the heart
  o no significant uptake of lactate uptake indicating not fully recovered oxidative metabolism

• Postoperative infusion of glutamate after CABG indicated:
  o a correlation between arterial levels of glutamate and myocardial uptake
  o that elevation of arterial whole blood levels of glutamate by more than 2-3 fold did not lead to a further substantial increase of myocardial uptake in CABG patients
  o such levels were achieved with a glutamate infusion of 30-40 mg per kg body weight and hour
Postoperative infusion of glutamate 36.8 mg per kg body weight and hour after surgery for AS was associated with:
  o an increase of arterial whole blood glutamate by almost three fold
  o a two fold increase of myocardial uptake of glutamate
  o a net uptake of lactate by the heart

Studies of peripheral tissue metabolism as indicated by AV differences across the leg after surgery for aortic stenosis revealed:
  o no significant uptake of major substrates across the leg
  o a net loss of amino acids
  o that glutamate was the only amino acid taken up by the leg
  o that an infusion of glutamate 36.8 mg per kg body weight and hour after surgery for aortic stenosis resulted in a seven fold increase of AV differences of glutamate
  o that glutamate infusion appeared to counteract peripheral tissue release of FFA suggesting an anti-lipolytic effect
  o that glutamate infusion appeared to mitigate net amino acid loss

A beneficial effect of glutamate on myocardial metabolism is suggested by the results and, hence, glutamate deserves further evaluation in patients operated on for aortic stenosis

The potentially beneficial effect of glutamate on peripheral tissue metabolism suggested by this study warrants further exploration in other conditions associated with activated neuroendocrine stress response
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