Bone cement implantation syndrome – epidemiology, pathophysiology and prevention

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Abstract

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Bone cementation implantation syndrome (BCIS) has significant morbidity and mortality for patients who are undergoing cemented hip hemiarthroplasty or arthroplasty. The aim of this thesis is to contribute with information of the epidemiological parameters of BCIS and identify risk factors. In addition, the pathophysiological ramifications of BCIS and possible interventions to prevent or reduce the risk of severe cardiopulmonary impairment due to BCIS are investigated.

A retrospective investigation of 1,016 patients who underwent cemented hip hemiarthroplasty due to displaced femoral neck fracture revealed a total incidence of BCIS of 28% (283/1,016 patients), regardless of the severity score. The peri-operative mortality rate was 2%, and 95% of the patients suffered from BCIS grade 3. According to the severity scores, the differences in mortality were not significant ($p=0.15$) when comparing BCIS grade 0 with BCIS grade 1. However, the mortality rates for patients with BCIS grades 2 and 3 were significantly higher than for those with BCIS grade 0 ($p<0.001$ and $p<0.001$, respectively) or grade 1 ($p<0.009$ and $p<0.001$, respectively). An ASA-score >2, chronic obstructive pulmonary disease (COPD), the use of diuretics, and treatment with anti-coagulants (warfarin) were all independent risk factors for the development of BCIS. BCIS grade 2 or 3 was associated with a 16-fold increase in the 30-day post-operative mortality.

We observed a 45% increase in the pulmonary vascular resistance index (PVRI) for patients who were undergoing cemented hemiarthroplasty for femoral neck fracture, and this was accompanied by significant decreases in the right ventricle ejection fraction (RVEF), cardiac index (CI), and stroke volume index (SVI), with the reductions often being sustained throughout the surgical procedure. Gas exchange abnormalities were regularly observed in the

forms of decreasing arterial pO_2 and pO_2/FiO_2 ratio and increasing V_D/V_T ratio. Therefore, cemented hemiarthroplasty in patients with femoral neck fracture results in pronounced pulmonary vasoconstriction and impairment of right ventricle (RV) function, accompanied by pulmonary ventilation/perfusion abnormalities.

Comparing cemented and un-cemented hip arthroplasty, the PVRI increased during and after prosthesis insertion by 45% and 20% in the cemented and un-cemented group, respectively ($p<0.005$). The systolic and mean pulmonary arterial pressure (PAP) increased by 18% and 17% after prosthesis insertion in the cemented group, which was not seen in the un-cemented group ($p<0.001$). There was a trend for a more pronounced fall in RVEF in the cemented group, while there were no differences in cardiac output or stroke volume between the groups. Therefore, the use of bone cement in total hip arthroplasty increases the pulmonary vascular resistance (PVR) and the after-load of the RV, with potentially negative effects on RV performance.

Comparing inhaled aerosolised prostacyclin with inhaled saline, the PVRI increased in both the saline (44%, $p<0.001$) and prostacyclin (36%, $p=0.019$) groups, with a less-pronounced increase in the prostacyclin group ($p=0.031$). The RVEF decreased significantly in both groups, with no difference between the groups. Inhalation of prostacyclin attenuates the increase of PVR in patients who are undergoing cemented hip hemiarthroplasty and could attenuate/prevent the haemodynamic instability induced by the increase in right ventricular after-load seen in this procedure.

Keywords: bone cement implantation syndrome; femoral neck fracture; cemented hip hemiarthroplasty; pulmonary haemodynamic; right ventricle ejection fraction; pulmonary vascular resistance: hemiarthroplasty

Sammanfattning på svenska

I början av 1970-talet ökade rapporterna om allvarliga dödliga intraoperativa komplikationer vid operationer där bencement använts. Ofta observerade symtom var syrebrist, lågt blodtryck och låg puls. Att symtomen uppkom omedelbart efter implantation av cementförankrade proteser i ben väckte tidigt misstankarna att bencement, en polymer (polymetylakrylat), är orsaken till de observerade förändringarna. Termen ben cement implantation syndrom (BCIS) präglades och definierades som plötsligt förkommande minskning av syremättnad och/eller blodtryck samt störningar i hjärtrytmen under eller strax efter cementeringen och införandet av protesen. I allvarliga fall är medvetandet sänkt och/eller hjärtstopp uppstår. BCIS kan förekomma vid alla kirurgiska ingrepp som använder bencement, men mest vanligt är det hos patienter som får en höftprotes. En särskild riskgrupp är äldre patienter med lårbenhalsfraktur som genomgår cementerad halvprotes. Å ena sidan är BCIS en väl känd och fruktat komplikation för narkosläkare och ortopeder världen over, men å andra sidan kan bencement inte tänkas bort från modern ortopedisk kirurgi på grund av sina egenskaper att utjämna inkongruensen mellan ben och protes och ge den nödvändiga stabiliteten.

Syftet med detta arbete var att belysa epidemiologiska faktorer som förekomst av BCIS, dödlighet och riskfaktorer och bidra till bättre förståelse om den bakomliggande patofysiologin. Andra delar av arbetet undersökte möjliga alternativ att förebygga eller behandla BCIS.

Bland våra patienter kunde vi observera BCIS med en förekomst av 28% (283/1016). Den peri-operativa dödligheten (död inom 48) var 2%. Förutom hög ålder (>85), manlig kön, hjärtsvikt, demens och medicinering med diuretika, hade BCIS den högsta effekten (16-faldig) på 30-dagars dödligheten. Hög ASA-poäng, KOL och medicinering med diuretika och warfarin, kunde identifieras som oberoende faktorer som medför ökad risk att drabbas av BCIS.

Emboliskt material som innehåller bland annat rester av benmärg, fett, luft och aktiverade trombocyter hamna i det venösa blodsystemet vid cementeringen och fastna i lungkärlen. Där induceras en serie av patofysiologiska reaktioner. Ändringar av den lung-vaskulära motståndet (PVRI) måste betraktas som nyckeln till den patofysiologiska reaktionen. En signifikant ökning av det lung-vaskulära motståndet med cirka 45% kunde vi observera hos alla våra patienter

som genomgick cementerad höft- eller halvprotes. Höger kammarens funktion påverkades negativt med en signifikant reduktion av höger kammarens utpumpade blodfraktion (RVEF). Ventilationen av det alveolära dead space ökade och syreupptagningen minskade omedelbart efter cementeringen, vilket är en indikation på en bakomliggande embolisk orsak. En försämring av vänstra kammarens funktion med en betydande reduktion av hjärtminutvolymen och slagvolymen kunde observeras regelbunden hos äldre patienter med ASA≥3.

Ett delarbete bestod i en jämförelse av cementerade höftproteser med icke-cementerade höftproteser och effekten på lungcirkulationen och höger kammarens funktion. Det lung-vaskulära motståndet ökade i den cementerade gruppen med 45% och i den icke-cementerade gruppen med 20%. Den observerade skillnaden var signifikant. Det systoliska och medeltrycket i lungartärerna var 18% och 17% i den cementerade gruppen. Lungartärtrycken var inte lika påverkad i den icke-cementerade gruppen. Cementerade höftproteser leder i motsats till icke-cementerade proteser till betydande förändringar i lungcirkulationen.

Prostacyklin, ett prostaglandin, bildas i endotelceller i alla blodkärl och har förutom en trombocytaggregationshämmande effekt, även en betydande kärlvidgande effekt. Inhalation av prostacyklin leder till selektiv kärlvidgning av lungkärl utan kännbar påverkan av den stora cirkulationen. Vi undersökte effekterna av peri-operativ inhalerad prostacyklin på lungcirkulationen och högra kammarens funktion jämfört med inhalation av koksaltlösning. Inhalation av prostacyklin kunde till viss del förhindra ökningen av det lungvaskulära kärlmotståndet. Resultatet tolkas som lovande, trots studiens utforskande karaktär, och prostacyklin och kan möjligtvis användas som profylax eller behandlingen av BCIS.

Sammanfattningsvis kan det noteras att BCIS observeras ganska ofta och är orsak till majoriteten av perioperativa dödsfall hos patienter med lårbenhalsfraktur som genomgår cementerad höft- eller halvprotes. Ökningen av det lungvaskulära motståndet betraktas som grundläggande i patofysiologin av BCIS. Patienter med mycket hög risk att drabbas av BCIS ska handläggas noggrant i samråd med kirurgen och om möjligt borde användas icke-cementerade förankring av protesen. Inhalationsbehandling med prostacyklin, kommer eventuellt ta plats i framtiden vid profylax och behandling av BCIS.

List of Papers

This thesis is based on the following papers, which are referred to in the text by their Roman numerals.

The change of the surname from Kotyra to Hård af Segerstad was due to a marriage in 2013.

I. Olsen F, Kotyra M, Houltz E, Ricksten S-E. Bone cement implantation syndrome in cemented hemiarthroplasty for femoral neck fracture: incidence, risk factors, and effect on outcome. Br. J. Anaesth. 2014; 113: 800-06.

II. Kotyra M, Houltz E, Ricksten SE. Pulmonary haemodynamics and right ventricular function during cemented hemiarthroplasty for femoral neck fracture. Acta Anaesthesiol. Scand. 2010; 54: 1210-16

III. Segerstad MHA, Olsen F, Patel A, Houltz E, Nellgard B, Ricksten SE. Pulmonary haemodynamics and right ventricular function in cemented vs uncemented total hip arthroplasty-A randomized trial. Acta Anaesthesiol. Scand. 2019; 63: 298-305

IV. Segerstad MHA, Olsen F, Houltz E, Nellgard B, Ricksten SE. Inhaled prostacyclin for the prevention of increased pulmonary vascular resistance in cemented hip hemiarthroplasty - A randomised trial. Accepted. Acta Anaesthesiol. Scand. May 2019

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Abbreviations

5-HT	5-Hydroxy-Tryptamine
ACE	Angiotensin-Converting Enzyme
ADP	Adenosine Diphosphate
ARDS	Acute Respiratory Distress Syndrome
ASA	American Society of Anaesthesiologists
ATP	Adenosine Triphosphate
BCIS	Bone Cement Implantation Syndrome
BMI	Body Mass Index
BSA	Body Surface Area
cAMP	Cyclic Adenosine Monophosphate
CHF	Congestive Heart Failure
CI	Cardiac Index
CO	Cardiac Output
COPD	Chronic Obstructive Pulmonary Disease
COX	Cyclooxygenase
CPR	Cardiopulmonary Resuscitation
CVP	Central Venous Pressure
DAP	Diastolic Arterial Pressure
EPAC	Exchange Protein Early Activated by cAMP
ET-1	Endothelin-1
ET-CO_2	End-tidal Carbon Dioxide
FDA	U.S. Food and Drug Administration
FES	Fat Embolism Syndrome
FiO_2	Fraction of inspired Oxygen
HR	Heart Rate
IVC	Inferior Venae Cava
LA	Left Atrium
LV	Left Ventricle
MAP	Mean arterial Pressure
MMA	Methyl Methacrylate
MPAP	Mean Pulmonary Arterial Pressure
MPSS	Methyl Prednisolone Sodium Succinate
NO	Nitric Oxide

OR	Odds Ratio
PA	Pulmonary Artery
PAC	Pulmonary Artery Catheter
PAF	Platelet Activating Factor
PAH	Pulmonary Arterial Hypertension
PaO_2	Partial Pressure of Oxygen
PAOP	Pulmonary Arterial Occlusion Pressure
PAP	Pulmonary Arterial Pressure
pCO_2	Partial Pressure of Carbon Dioxide
PCWP	Pulmonary Capillary Wedge Pressure
PDGF	Platelet-Derived Growth Factor
PEEP	Positive End-Expiratory Pressure
PGI_2	Prostacyclin
PKA	Protein Kinase A
PMMA	Polymethyl Methacrylate
PV	Pulmonary Vein
PVR	Pulmonary Vascular Resistance
PVRI	Pulmonary Vascular Resistance Index
RA	Right Atrium
RV	Right Ventricle
RVEDV	Right Ventricle End-Diastolic Volume
RVEDVI	Right Ventricle End-Diastolic Volume Index
RVEF	Right Ventricle Ejection Fraction
RVESV	Right Ventricle End-Systolic Volume
RVESVI	Right Ventricle End-Systolic Volume Index
SAP	Systolic Arterial Pressure
SBP	Systemic Blood Pressure
SPAP	Systolic Pulmonary Arterial Pressure
SpO2	Oxygen Saturation
SV	Stroke Volume
SVC	Superior Vena Cava
SVI	Stroke Volume Index
S_VO_2	Mixed Venous Oxygen Saturation
SVR	Systemic Vascular Resistance
SVRI	Systemic Vascular Resistance Index
THR	Total Hip Replacement
Tx-A_2	Thromboxane-A_2

Introduction

Background

The German surgeon and university professor Themistocles Gluck must be considered as one of the founders of modern endoprosthesis. On the 20th of May 1890 in Berlin, Gluck successfully implanted the first total knee prosthesis, consisting of hinged ivory, in a 17-year-old woman who was suffering from tuberculosis.[1] Three weeks later he implanted a wrist prosthesis and subsequently a knee prosthesis in different patients. In all three cases, he achieved good short-term results. He solved the problem of the existing unevenness between the bone and prosthesis with a "glue" that consisted of plaster and colophony (rosin).[2] Degussa's and Kulzer's patent in 1943 in relation to the mechanism of polymerisation of methyl methacrylate (MMA) must be considered as another milestone in the development of modern endoprosthetics.[3] Finally, the first use of a polymethyl methacrylate (PMMA)-based bone cement is credited to the famous surgeon Sir John Charnley. He anchored a hip prosthesis with bone cement in 1958.[4] In 1970, the FDA approved the use of bone cement (PMMA) for the fixation of hip or knee prostheses. Today, bone cementation is the Gold standard in orthopaedic surgery, particularly in the field of joint replacement.

Femoral neck fracture is common among the elderly population world-wide, representing a heavy burden on health-care systems. Most hip fractures (90%) occur in the age group of ≥50 years and 52% of hip fractures occur in the age group of ≥80 years.[5] Dhanwal *et al* reported on the geographical

variation of the incidence of femoral neck fracture, with the highest rates seen in the US and Sweden.[6]

In Sweden in 2017, 6,033 patients received either total hip replacement (THR) or hemiarthroplasty due to femoral neck fracture.[7] Most of these patients (N=3,937) were treated with hemiarthroplasty. Techniques that employ bone cement are preferred by orthopaedic surgeons in Sweden for the treatment of femoral neck fractures.

Bone cement

Bone cement (polymethyl methacrylate; PMMA) is a polymer based on methyl methacrylate that is formed in an exothermic reaction of a mixture of two components: a liquid MMA monomer, and a powdered MMA-styrene co-polymer.[2] Depending on the presence of additives, e.g., antibiotics, bone cement has distinct chemical and physical properties. The addition of a stabiliser and inhibitor, usually hydroquinone, prevents premature polymerisation. The addition of an initiator and accelerator, di-benzoyl peroxide (BPO) and N,N-dimethyl-p-toluidine (DmpT), respectively, is necessary to facilitate the polymerisation of the polymer and monomer at room temperature (cold-curing cement). Finally, zirconium dioxide (ZrO_2) or barium sulphate ($BaSO_4$) is added to create a radiopaque bone cement (Table 1).

Definition of Bone Cement Implantation Syndrome (BCIS)

Case reports of intra-operative deaths that are clearly associated with cementation and prosthesis insertion appeared more frequently in the early 1970s.[8-10] Air and fat embolisms with fatal outcomes were reported in patients who were undergoing a procedure using bone cement, mostly in conjunction

with hip replacement.[11-14] The observed symptoms vary widely, although hypoxia, hypotension, cardiac arrhythmias, loss of consciousness, and cardiac arrest are the most frequently reported. The term Bone Cementation Implantation Syndrome (BCIS) emerged and is generally accepted today.

First in 2009, Donaldson and colleagues proposed a standard definition of BCIS, which is mainly based on the cardinal symptoms, and they defined BCIS as a condition characterised by hypoxia, hypotension or both and/or unexpected loss of consciousness that occurs around the time of cementation and prosthesis insertion.[15] In addition, they proposed a severity score that reflects the grade of hypoxia, hypotension, the occurrence of loss of consciousness, and cardiovascular collapse (Table 2).[15]

Table 1: Components of bone cement.

Liquid	**Powder**
1. Monomer (Methyl methacrylate) (MMA))	1. Polymer (Polymethyl methacrylate/co-polymer (PMMA)
2. Accelerator (N, N-Dimethyl para toluidine (DMPT)/dimethyl para toluidine (DMpt))	2. Initiator (Benzyl peroxide (BPO))
3. Stabilizer (Hydroquinone)	3. Radio-opacifier Barium sulphate ($BaSO_4$)/Zirconium dioxide (ZrO_2)
	4. Antibiotics

Table 2: Severity score of BCIS. SpO_2, Oxygen saturation; SAP, systolic arterial pressure; CPR, cardiopulmonary resuscitation.

	Grade 1	**Grade 2**	**Grade 3**
SpO_2	< 94	< 88	
SAP	20% drop	40% drop	
Other		unexpected loss of consciousness	Cardiovascular collapse requiring CPR

Epidemiology of BCIS

Background

Currently, there is a lack of consensus regarding the standard definition of BCIS. The true incidence of fatal outcomes due to BCIS is unknown, BCIS-related mortality is not systematically reported, and cases of less-severe BCIS are under-reported. Furthermore, few studies to date have focused on the incidence and mortality of BCIS. The rate of intra-operative death due to cemented total hip arthroplasty was reported as 0.11%, and these deaths usually occurred around the time of cementation.[15] Parvizi *et al* related all intra-operative deaths to the use of bone cement and reported mortality rates of 0.16% for cemented total hip arthroplasty and 0.4% for cemented hip hemiarthroplasty.[16] The risk of intra-operative death increased with the type of fracture and certain pre-operative conditions, such as pathological fractures. Intra-operative mortality was reported to be 4.3% in patients undergoing cemented hemiarthroplasty due to pathological fractures and 1% in patients undergoing procedures using bone cement and long-stem components.[16, 17] Other researchers have reported significantly higher rates of peri-operative mortality, i.e., death within 48 hours of the surgery, in patients undergoing cemented hip hemiarthroplasty, as compared to patients undergoing un-cemented hip hemiarthroplasty.[18, 19] The use of bone cement must be considered as the factor that most likely accounts for these findings.

Incidence, mortality and risk factors of BCIS

Incidence

Currently, there are no studies that focus on investigating the true incidences of BCIS attributable to surgical procedures that use bone cement, especially cemented total hip replacement (THR) and hip hemiarthroplasty. Several studies have estimated the peri-operative mortality related to the use of bone cement.[16, 20, 21] Milder severities of BCIS and the impact on mortality are under-reported. However, our investigation involving 1,016 patients who received cemented hip hemiarthroplasty for displaced femoral neck fracture showed a total incidence of BCIS (according to Donaldson's criteria) of 28% (283/1,016 patients), regardless of the BCIS severity score. In our study, BCIS grades 1, 2 and 3 were detected at frequencies of 21%, 5.1% and 1.7%, respectively (**Paper I**).

Mortality

Older studies have reported only the peri-operative mortality (death within 48 hours of surgery), while more recent studies have reported the peri-operative mortality rate, as well as the mortality rates at 30 days and 12 months for patients undergoing cemented THR or hip hemiarthroplasty, as compared with patients undergoing un-cemented THR or hip hemiarthroplasty. Coventry *et al* reported, as early as 1974, a peri-operative mortality of 0.06% for patients undergoing cemented THR.[21] Ereth *et al* presented data with a peri-operative mortality of 0.12% for patients undergoing cemented THR, although no patient died when un-cemented THR was used.[20] The incidence of intra-operative death was in the range of 0.16%–0.68% for cemented THR, depending of the type of fracture (non-pathological, pathological), whereas no deaths occurred when un-cemented THR was used.[16] The frequently observed low peri-

operative mortality rate for cemented THR reflects the fact that this procedure was more often performed electively on younger patients with a more favourable ASA-score. In contrast, when cemented hip hemiarthroplasty for femoral neck fracture was the preferred treatment option, mortality rates in the range of 0.4%–4.3% were observed, depending of the type of fracture (intra-capsular, inter-trochanteric, non-pathological, pathological).[16] Two more recent studies have reported that the intra-operative mortality and early post-operative mortality (within 7 day) in patients undergoing cemented hip hemiarthroplasty for femoral neck fracture are as high as 2.54% (8/314 patients)[18] and 3% (3/108 patients)[22], respectively. Pripp *et al* reported that about 50% of the observed peri-operative mortalities were associated with cementation in patients who were treated with hemiarthroplasty.[23]

The overall 30-day and 1-year mortality rates reported for patients undergoing hip surgery due to hip fractures, independent of the chosen fixation method, are 2.5%–8%[24, 25] and 25%[26, 27], respectively. For patients who underwent cemented hip hemiarthroplasty, Costain *et al* observed 30-day and 1-year mortality rates of 7% and 21%, respectively.[19] Other groups have observed 30-day mortality rates of 3.5% and 4%[22, 28] and 1-year mortality rates of 19% and 25% [22, 29]

Interestingly, the initially higher rates of death seen within 48 hours for patients who underwent either cemented THR or hip hemiarthroplasty (as compared to patients who underwent un-cemented THR or hip hemiarthroplasty) were not seen at 7 days post-surgery and the rates were even reversed at 30 days and at 1 year post-surgery.[19, 30, 31] A possible explanation for this is that high-risk patients are more likely to die early in the peri-operative period.

In **Paper I**, we observed an overall peri-operative mortality rate of 2.0%. 95.0% for those patients were suffering from BCIS grade 3 intra-operatively. The 30-day and 1-year overall mortality rates were 9% and 29%, respectively.

Applying the severity score scale of Donaldson *et al* (Table 2), the 30-day mortality was 5.2% for patients with no symptoms of BCIS (grade 0) and 9.3%, 35%, and 88% for patients with BCIS grades 1, 2, and 3, respectively. The corresponding percentages for the 1-year mortality were 25.2% (grade 0), 29.9% (grade1), 48.1% (grade 2), and 94.1% (grade 3) (Figure 1). The observed differences in mortality were not statistically significant ($p=0.15$) when comparing BCIS grade 0 and BCIS grade 1, while the mortality rates of patients with BCIS grade 2 and 3 were significantly higher than those of patients with grade 0 ($p<0.001$ and $p<0.001$, respectively) or grade 1 ($p<0.009$ and $p<0.001$, respectively). Mortality was also higher for patients with BCIS grade 3 than for those with BCIS grade 2 ($p<0.001$).

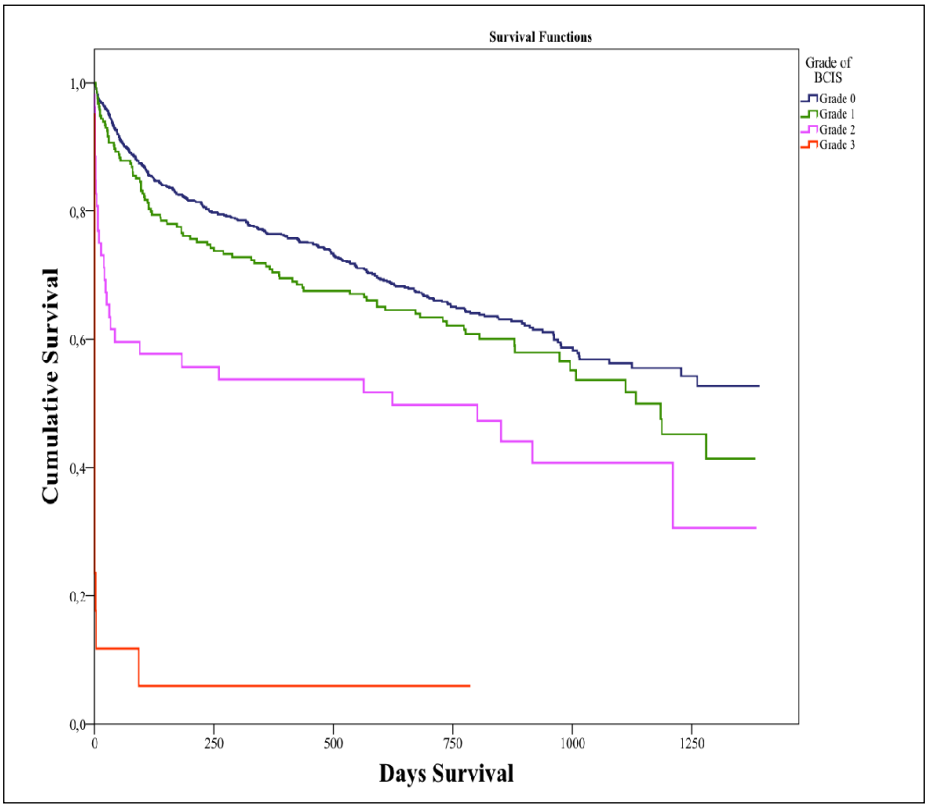

Figure 1: Impact of BCIS on cumulative long-term survival of patients. The differences in survival rate between BCIS grades 1 and 0 are non-significant (p=0.15). The survival rate is significant lower for patients with BCIS grades 2 and 3 than for those with BCIS grade 0 ($p<0.001$ and $p<0.001$, respectively) or grade 1 ($p<0.009$ and $p<0.001$, respectively). The rate of survival is also lower for patients with BCIS grade 3 than for those with grade 2 ($p<0.001$).

We divided the patients into two groups: the first group contained patients with BCIS grade 0 or 1, while the second group had patients with BCIS grade 2 or 3. In Figure 2, it is evident that: deaths related to severe BCIS (grade 2 or 3) in cases of cemented hemiarthroplasty occur intra-operatively and in the immediate post-operative period; and, thereafter, the survival rate of these patients does not differ from that of the group of patients with BCIS grade 0 or 1.

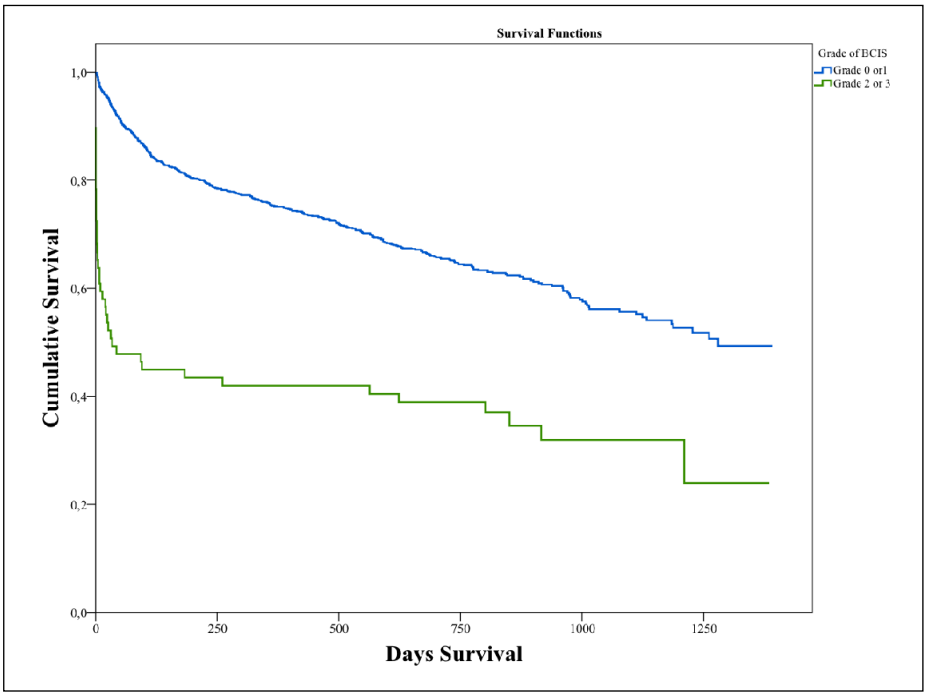

Figure 2: Cumulative long-term survival following cemented hemiarthroplasty for displaced femoral neck fracture in relation to the grade of BCIS. Patients were dichotomised into two groups: the first group had BCIS grade 0 or 1 (blue), while the second group had BCIS grade 2 or 3 (green). Survival was lower in the patients with severe BCIS ($p<0.005$).

Risk factors

It is important to evaluate and identify risk factors for post-operative mortality and the development of BCIS, particularly when considering potential strategies for prevention or treatment. Several large retrospective registry-based investigations have reported that advanced age, male gender, worse ASA-score (>2), and a high number of comorbidities, e.g., renal insufficiency, significant cardiovascular and pulmonary disease, and dementia, are risk factors for post-operative mortality in patients undergoing THR.[24, 32-35] Hossain *et al* found that pre-existing cardiovascular disease and a high ASA-score

increased the risk for mortality in patients who were receiving cemented hip hemiarthroplasty.[18]

In the study described in **Paper I**, we reviewed the medical records and the anaesthesia charts of 1,016 patients who were admitted to the Sahlgrenska University Hospital/Mölndal with dislocated femoral neck fracture and who received cemented hip hemiarthroplasty during the period 2008–2011. The goal was to identify and evaluate risk factors related to mortality and the development of BCIS. The collected data included age, body mass index (BMI), gender, current drug therapy, history of smoking, ASA-score, and pre-operative haemoglobin and serum creatinine levels. We also retrieved information on the presence of pre-operative cardiac disease, and co-existing diseases, e.g., liver disease, renal impairment, diabetes mellitus, previous stroke, peripheral vascular disease, hypertension, chronic obstructive pulmonary disease (COPD), cancer, dementia, and arrhythmias (Table 3).

Table 3: Clinico-pathological parameters of the patients. Data obtained from the medical records and anaesthesia charts.

Age	Disease
BMI	Cancer
Gender	Dementia
ASA classification (1-4)	Arrythmia
Medical history	Medication
Liver disease	Betablocker
Renal failure	Diuretics
Diabetes	Antiplatelet drugs
Stroke	Organic nitrates
Peripheral arterial disease	Calcium antagonists
Atherosclerosis	ACE inhibitors
Hypertension	Insulin
Angina pectoris	Warfarin
Previous myocardial infarction	Statins
Congestive heart failure	Pre-operative Haemoglobin (g/L)
Chronic obstructive pulmonary	Serum creatinine (μmol/L)

We found that high ASA-score (ASA >2), COPD, the use of diuretics, and treatment with anti-coagulants (warfarin) were independent risk factors for the development of BCIS (Table 4). Thus, patients who exhibit one or more of these risk factors must be carefully assessed and alternatives should be considered to avoid or prevent BCIS.

Table 4: Predictors and Odds Ratios (ORs) for developing BCIS grade 2 or 3. Renal failure is defined as a creatinine level >150 µmol/L or diagnosed. ASA. American Society of Anaesthesiologists (ASA) score; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; ACE, angiotensin-converting enzyme. Adjusted ORs are only presented for independent predictors of severe BCIS.

Predictors	Odds ratio (unadjusted)	(95% CI)	p-value	Odds ratio (adjusted)	(95% CI)	p-value
Age>85 years	0.85	0.52-1.39	0.535			
Male sex	0.92	0.54-1.57	0.784			
ASA 3 or 4	2.65	1.48-4.77	0.001	1.97	1.07-3.61	0.029
Medical History						
Renal failure	1.45	0.60-3.50	0.44			
Diabetes	1.57	0.83-2.96	0.195			
Stroke	1.14	0.62-2.19	0.632			
Peripheral vascular disease						
Arteroscleroses	3.18	1.04-9.66	0.056			
Hypertension	1.34	0.82-2.19	0.255			
Angina pectoris	1.99	1.10-3.58	0.029			
Previous myocardial infarction	1.39	0.69-2.80	0.326			
CHF	1.97	1,04-3,72	0.045			
COPD	2.30	1.27-4.16	0.012	2.02	1.10-3.72	0.024
Cancer	0.77	0.27-2.18	0.811			
Dementia	0.77	0.43-1.40	0.478			
Arrythmia	1.72	1.01-2.91	0.051			
Medication						
Beta-blockers	2.20	1.34-3.60	0.002			
Diuretics	2.52	1.53-4.14	<0.001	1.92	1.15-3.22	0.013
Anti-platelet drugs	1.16	0.71-1.90	0.615			
Organic nitrates	1.63	0.88-3.01	0.147			
Calcium antagonists	0.52	0.24-1.10	0.085			
ACE inhibitors	2.11	1.27-3.51	0.005			
Insulin	1.67	0.73-3.81	0.209			
Warfarin	3.41	1.73-6.74	0.001	2.69	1.33-5.43	0.006
Statin	1.19	0.61-2.33	0.589			

COPD is often complicated by the presence of pulmonary hypertension.[36] The mechanisms involved in the pathogenesis of pulmonary hypertension and high pulmonary vascular resistance (PVR) in patients with COPD are, in addition to hypoxia, academia, and the destruction of lung parenchyma, likely to involve vascular remodelling, inflammation, and endothelial dysfunction.[36] The latter mechanisms may alter the responsiveness of the pulmonary vascular bed and may explain why patients with COPD have a higher risk for developing BCIS. Although a diagnosis of congestive heart failure (CHF) or chronic atrial fibrillation, each in itself, was not found to be an independent risk factor for BCIS, pre-operative treatment with diuretics or warfarin was statistically significantly correlated to the development of BCIS. Patients with CHF, particularly when it is associated with chronic atrial fibrillation, are known to develop pulmonary venous hypertension due to an increased left-sided filling pressure.[37] In patients with chronic CHF, the PVR is higher owing to endothelial dysfunction, and there is reduced expression of nitric oxide and increased availability of endothelin, as well as structural remodelling.[37] One could, therefore, speculate that patients with COPD and CHF, with or without chronic atrial fibrillation, share common pathophysiological mechanisms, including pulmonary vascular hyperactivity, when exposed to a certain level of pulmonary embolism at the time of bone cementation and insertion of the prosthesis.

Independent factors that predicted 30-day mortality were age >85 years, male gender, CHF, dementia, use of diuretics, and BCIS grade 2 or 3 (Table 5). The development of BCIS grade 2 or 3 resulted in a 16-fold increase in the 30-day post-operative mortality. Aside from the other factors, severe BCIS must be considered as the factor with the strongest impact on 30-day mortality in patients who are undergoing cemented hemiarthroplasty.

Table 5. Predictors and Odds Ratios for 30-day mortality following cemented hemiarthroplasty. Liver disease is defined as primary liver failure or liver metastasis. Renal failure is defined as a serum creatinine level >150 µmol/L. Diabetes includes both Type I and Type II. ASA, American Society of Anaesthesiologists (ASA) score; COPD, chronic obstructive pulmonary disease; ACE, angiotensin-converting enzyme; BCIS, bone cement implantation syndrome.

Predictors	Odds ratio (unadjusted)	(95% CI)	p-value	Odds ratio (adjusted)	(95% CI)	p-value
Age > 85	2.21	1.41-3.47	0.001	2.58	1.54-4.32	<0.005
Male sex	2.08	1.34-3.23	0.001	2.15	1.31-3.54	0.02
ASA 3 or 4	2.85	1.69-4.80	<0.005			
Medical history						
Liver disease	2.30	0.49-10.79	0.257			
Renal failure	2.54	1.30-4.96	0.011			
Diabetes	1.10	0.59-2.04	0.746			
Stroke	1.19	0.70-2.02	0.571			
Peripheral vascular disease	0.85	0.20-3.64	1			
Arteroscleroses	3.12	1.12-8.65	0.039			
Hypertension	0.72	0.46-1.14	0.18			
Angina	2.32	1.39-3.87	0.002			
Previous myocardial infarction	1.51	0.82-2.76	0.22			
Congestive heart failure	2.50	1.46-4.29	0.002	1.91	1.0-3.64	0.049
COPD	1.57	0.88-2.80	0.133			
Cancer	1.26	0.58-2.71	0.526			
Dementia	1.89	1.21-2,95	0.008	2.81	1.67-4.74	<0.005
Arrythmia	2.15	1.37-3.40	0.001			
Medication						
Beta-blockers	1.51	0.98-2.33	0.069			
Diuretics	2.61	1.69-4.05	<0.005	1.95	1,17-3,26	0.012
Anti-platelet drugs	1.86	1.21-2.88	0.005			
Organic nitrates	1.86	1.09-3.17	0.026			
Calcium antagonists	0.72	0.40-1.30	0.334			
ACE inhibitors	1.27	0.78-2.07	0.363			
Insulin	0.81	0.32-2.07	0.826			
Warfarin	1.21	0.53-2.72	0.656			
Statins	0.84	0.43-1.61	0.751			
Haemoglobin < 100 (g/L)	1.98	0.47-8.34	0.575			
BCIS grade 2 or 3	14.05	8.17-24.16	<0.005	16.35	8.84-30.24	<0.005

Pathophysiology of BCIS

The aetiology and pathophysiology of BCIS are not fully understood. Several theories have been proposed and discussed. The earliest theory focused on MMA release into the circulation and its toxicity. More recently published studies have proposed mechanisms based on an increased pulmonary embolic load that occurs as a result of a high intramedullary pressure and other mechanisms, such as mediator release and complement activation subsequent to cementation and prosthesis insertion.

MMA-mediated model

A strong vasodilatory effect of MMA, involving relaxation of vascular smooth muscles with increased coronary blood flow, has been described.[38, 39] Furthermore, MMA has direct toxicity for the airways, skin and eyes.[40] However, there is currently no evidence to suggest that circulating MMA causes the pulmonary and systemic haemodynamic disturbances seen in BCIS. The plasma concentration of MMA after cementation is lower than that needed to induce pulmonary[41] and hemodynamic deterioration.[39, 42-44]

Embolic model

The echogenic material in the right-side of the heart during cementation, as detected by echocardiography, suggests that embolization occurs due to the increasing intramedullary pressure rather than MMA toxicity, thereby inducing the pulmonary and systemic haemodynamic changes early after prosthesis insertion and cementation.[20, 45-48] Fat[13, 16, 49-51], air[12, 52], bone marrow[13, 16, 49-51] and aggregates of platelets and fibrin[49, 53] have been observed in the embolic

material.

The origin of the embolic material is the instrumented femoral canal. As the bone cement hardens, the exothermic reaction, which occurs with a temperature of up to 96°C, expands the interface between the bone and prosthesis. The resulting high intramedullary pressure, which can reach values >900 mmHg, forces the trapped air, fat, bone marrow, and other debris into the femoral venous channels. The use of a cement gun usually generates a higher intramedullary pressure than does manual packing of the bone cement.[54] In comparison, un-cemented anchored prostheses generate intramedullary pressures of <100 mmHg.[43]

The emboli detected by trans-oesophageal echocardiography vary widely in terms of size and quantity.[20, 45-48, 55] Lafont *et al* has described multiple small emboli as "snow flurry".[47] One-third of the patients had emboli of diameter >10 mm in that study.[47] Some patients generated vermiform-shaped emboli with a length of approximately 5–7 cm.[45, 48] However, patients who underwent un-cemented prosthesis insertion generated fewer emboli (snow flurries) than those who underwent cemented prosthesis insertion.[20, 45] Interestingly, there are no correlations between the size and quantity of the embolic load and the pulmonary or haemodynamic disturbances.[20, 45, 47, 48] Furthermore, the correlation between the degree of mechanical obstruction and the haemodynamic manifestations of pulmonary embolism due to venous thromboembolism is weak.[56] Mechanical obstruction of the left or right pulmonary artery during surgical procedures causes only modest haemodynamic changes, and right-sided heart failure is uncommon.[56] These findings suggest that additional mechanisms to embolization account for the development of BCIS.

Mediator model

Massive fat and bone marrow emboli, micro-emboli, and intra-vascular thrombi have been regularly detected in the pulmonary vascular beds of patients who were autopsied after death resulting from cardiopulmonary collapse due to cementation and prosthesis insertion.[13, 16, 50]

Already in 1974, Modig *et al* observed in the pulmonary vasculature an increase in the levels of tissue thromboplastic products associated with the cementation procedure. These products initiate intra-vascular coagulation and the formation of micro-emboli (thrombocyte and fibrin aggregates). This notion is strengthened by the observation of transient accumulations of radioactively marked thrombocytes and fibrinogen after cementation and prosthesis insertion.[49, 57] Furthermore, fat and MMA appear to be of minor or no importance for these reactions.[49] An amorphous, eosinophilic, fine granular material was detected in blood samples taken from the right atrium when "snow flurries" appeared in the trans-oesophageal echocardiograph. This material was composed of bone dust, i.e., fine particles that originated from reamed bone rather than materials from bone cement or fat and air.[53]

Micro-emboli exert a frictional force on the vascular endothelium of smaller pulmonary arterial vessels and compromise their integrity. The consequences are reflex vasoconstriction[58] and the release of endothelial vasoconstrictive mediators such as endothelin-1 (Figure 3).[56, 59] The appearance of activated platelets and their release of mediators seem to play important roles in the manifestation of pulmonary and cardiovascular disturbances in BCIS. Activated platelets release vasoconstrictive mediators, such as thromboxane-A_2 (Tx-A_2),[56, 60] platelet-derived growth factor (PDGF), and serotonin (Figure 3).[56] The release of potent vasoactive mediators (such as histamine, leukotrienes, and prostaglandins) mediated by the complement

anaphylatoxins C_{3a} and C_{5a}, is another possible pathway.[61, 62]

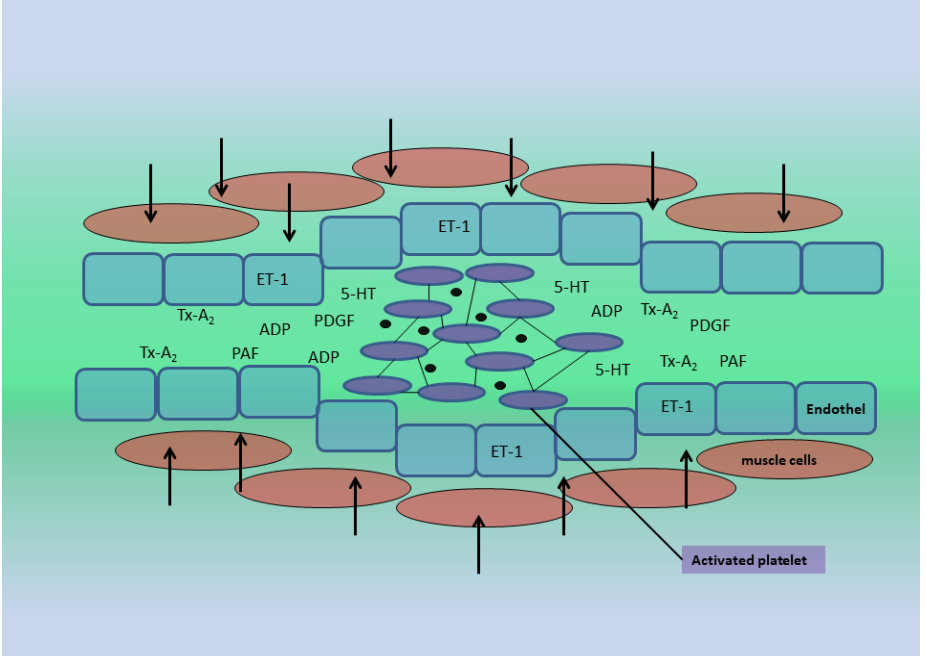

Figure 3: Micro-emboli and their vasoconstrictive consequences. Shown are reflex vasoconstriction and mediator release and consecutive vasoconstriction. PDGF, platelet-derived growth factor; ET-1, endothelin-1; 5-HT, 5-hydroxy-tryptamine); PAF, platelet-activating factor; ADP, adenosine diphosphate; Tx-A_2, thromboxane-A_2. Adapted from Donaldson *et al.*[15]

Multi-modal model

The mechanical effects of embolic load and the pulmonary vascular action of mediator release may act in concert to provoke the pathophysiological changes seen around the time of cementation and prosthesis insertion.[63, 64] The extents to which each of these models contribute to the clinical manifestations may depend on the patient`s physiological responses and co-morbidities.

Clinical manifestations of BCIS

Embolic obstruction of the pulmonary vascularity and subsequent mediator release are considered to be the causative events in BCIS. The symptoms are similar to thromboembolic pulmonary embolism and vary widely in their severity. Mild forms of BCIS show a transient reduction in oxygen saturation[16, 49, 64, 65] and arterial blood pressure.[11, 16, 49, 66-69] In contrast, severe forms of BCIS are associated with significant hypoxia, hypotension, arrhythmias, and cardiac arrest.[11, 16, 51, 69] An acute increase in PVR must be considered as the most important factor. Consecutive right-sided heart strain and in severe cases, right-sided heart failure lead to cardiovascular collapse, usually with fatal outcome.

Pulmonary vascular resistance

In general, vascular resistance is the resistance that must be overcome to force blood through the circulatory system and create a blood flow. The resistance offered by the pulmonary vascular bed is known as the PVR. The equation to calculate PVR is conceptually equivalent to:

$$R=\Delta P/Q$$

where R is the resistance (fluid resistance), ΔP is the pressure difference across the pulmonary circuit, and Q is the rate of blood flow through the lungs. PVR can be calculated according to the following equation, expressed by the unit, dynes × sec^{-1} × cm^{-5}:

$$PVR = 80 \times (MPAP\text{-}PCWP) / CO$$

where MPAP is the mean pulmonary arterial pressure, PCWP is the pulmonary capillary wedge pressure, CO is the cardiac output, and 80 is a conversion factor. The normal level of PVR is 100–200 dynes × sec^{-1} × cm^{-5}.

The regulation of pressure and flow in the pulmonary vasculature is complex and depends on both active and passive mechanisms (Figure 4).[70, 71] However, embolic events, which obstruct the pulmonary vascularity, initiate several vascular, humoral and reflexive responses that increase the MPAP and PVR.[71] For patients without pre-existing cardiovascular disease, the angiography-detectable obstruction of the pulmonary vascular bed correlates well with the MPAP, CVP, PaO_2 and heart rate.[72-74] Obstruction of 50% of the pulmonary vascularity results in MPAP values in the range of 30–40 mmHg or PVR values ≥500 dynes × sec^{-1} × cm^{-5}.[71, 73, 74] An acute embolic obstruction of more than 75% usually results in an increase in MPAP of approximately 40 mmHg, an after-load that exceeds the capacity of the healthy right ventricle to generate an adequate stroke volume, which may lead to right-sided heart failure.[75] On the other hand, patients with pre-existing cardiovascular diseases should be considered to be more susceptible to sudden increases in MPAP and PVR, as evidenced by a poor correlation between the degree of embolic obstruction and changes in MPAP and PVR, especially when the MPAP and PVR are already chronically elevated.[71] Finally, patients with femoral neck fractures who are undergoing cemented hip hemiarthroplasty are often older and more likely to have a history of cardiovascular diseases. Therefore, the changes in pulmonary haemodynamic are unpredictable, and these patients should be considered highly susceptible to severe manifestations of BCIS.

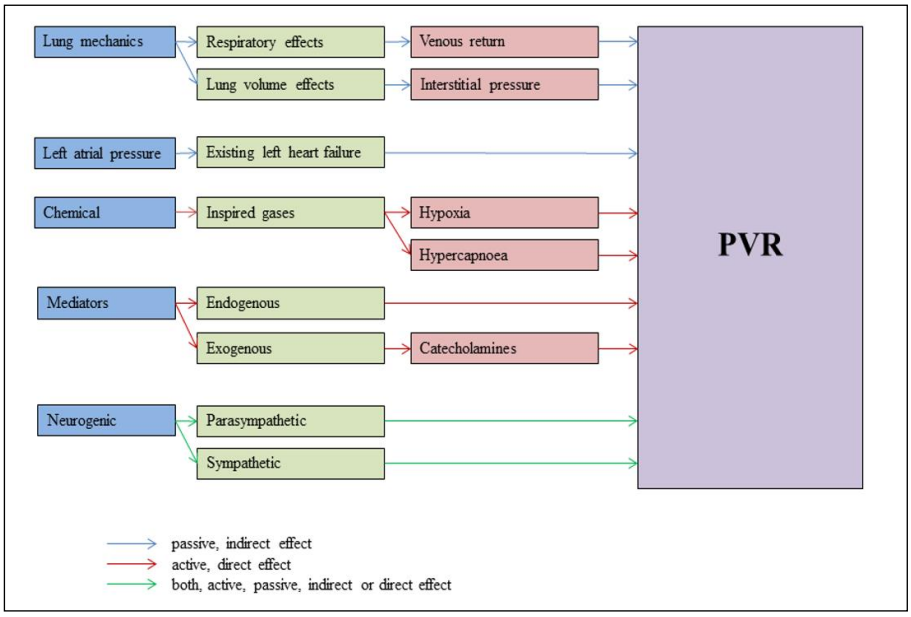

Figure 4: Factors that influence pulmonary vascular resistance (PVR).

Few clinical trials have been conducted to evaluate the effects of bone cementation on the pulmonary haemodynamics in patients undergoing hip arthroplasty or hemiarthroplasty for femoral neck fracture. In a non-randomised study, Ereth *et al* looked at the effects on pulmonary haemodynamics of bone cement use in patients who were undergoing elective total hip arthroplasty, using a pulmonary artery catheter. They found that the PVR was increased by 5%–10%.[20] In another study, Urban *et al* examined the effects of bone cementation on the pulmonary haemodynamics variables of patients who were undergoing elective revision total hip arthroplasty under hypotensive epidural anaesthesia. During femoral prosthesis insertion, they noted that all the patients exhibited transient haemodynamic changes, which were small and clinically insignificant in the majority of the patients.[66] In striking contrast, in all the patients who were undergoing cemented hip arthroplasty (**Paper III**) or hip hemiarthroplasty (**Papers II** and **IV**) for femoral neck fracture, bone cementation and prosthesis insertion *per se* caused

a ≈45% increase in pulmonary vascular resistance index (PVRI) (Figure 5), and this increase was sustained throughout the surgical procedure. Furthermore, the observed maximal changes in PVRI, defined as the difference between PVRImax and PVRImin, were significant, as shown in **Papers II**, **III** and **IV** (Figure 6).

In summary, the magnitude of the increase in PVR and the consequences thereof must be considered as the fundamental factors in the development of the haemodynamic disturbances seen in BCIS.

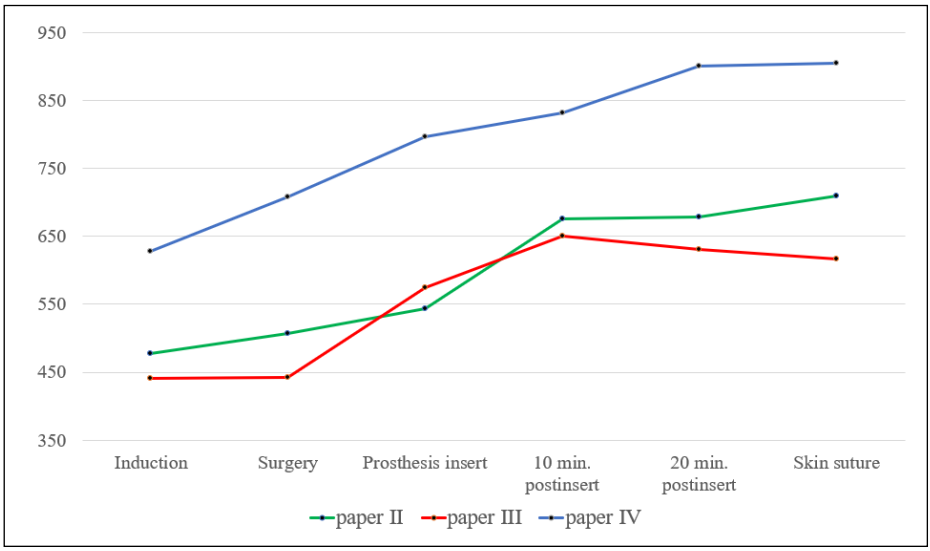

Figure 5: Significant increases in pulmonary vascular resistance index (PVRI) seen in all patients undergoing cemented hip arthroplasty (**Paper III**, $p<0.001$) or cemented hip hemiarthroplasty (**Paper II**, $p<0.001$ and the saline group in **Paper IV**, $p<0.001$) for femoral neck fracture.

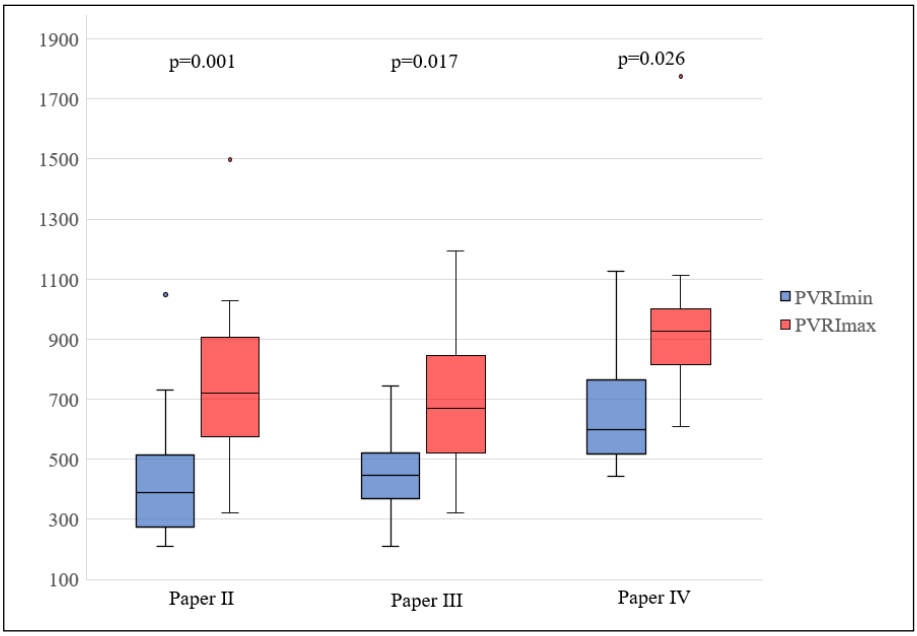

Figure 6: Maximal changes in pulmonary vascular resistance index (PVRI) in patients undergoing cemented hip arthroplasty (**Paper III**) or cemented hip hemiarthroplasty (**Paper II** and the saline group in **Paper IV**). Data that were obtained at sampling points a) and b) in the study protocol were pooled and considered as PVRImin. PVRImax was defined as the highest registered PVRI value after cementation and prosthesis insertion for each patient. Differences with p-values ≤0.05 were considered significant.

Right-sided heart failure

Right-sided heart failure is defined as a complex clinical syndrome that can result from any structural or functional cardiovascular disorder, whereby the right ventricle of the heart fails to deliver an adequate blood flow through the pulmonary vascularity at a normal filling pressure (CVP).[76, 77] Pulmonary hypertension, both primary and secondary left ventricular failure, COPD, and pulmonary embolism must be considered as the most common causes of right-sided heart dysfunction and cardiac failure.

The primary tasks of the right ventricle are to pump oxygen-poor blood

through the lungs, such that the blood is replenished with oxygen and cardiac output is maintained. The pulmonary vascular bed is a low-pressure system that allows the relatively thin-walled right ventricle to perform with around 25% of the needed stroke work, as compared to the left ventricle. Volume load (pre-load) is well-tolerated by the right ventricle and represents the physiological response to conditions that require an increased cardiac output. In contrast, an increased pressure load (after-load) that arises under conditions that increase the PVR and MPAP is less-well-tolerated and may lead to right-sided heart failure. Furthermore, it has been shown previously that moderate-to-severe pulmonary hypertension often leads to right-sided heart dysfunction.[78]

Acute embolic load and the subsequent mediator release, as seen in BCIS, lead to acute increases in the PVR and MPAP. On the one hand, there are increases in the extent of the resulting embolic obstruction, vasoconstriction, and PVR, while on the other hand, the ability of the right-side of the heart to handle these changes may determine the severity of BCIS. An increase in right ventricular after-load may cause the right ventricle to dilate and decompensate. As a consequence, the stroke volume from the right side of the heart will decrease, which will cause decreased filling of the left ventricle. Furthermore, the increased right ventricular volume will cause a left-ward shift of the septum, which will decrease distensibility, i.e., compress the left ventricle, thereby further impairing the pre-load of the left ventricle. The low output from the left ventricle will cause a drop in systemic arterial pressure, and this will impair right coronary perfusion, which together with the distended right ventricle may induce right ventricular ischaemia with further aggravation of right-sided heart performance. (Figure 7, a–c).

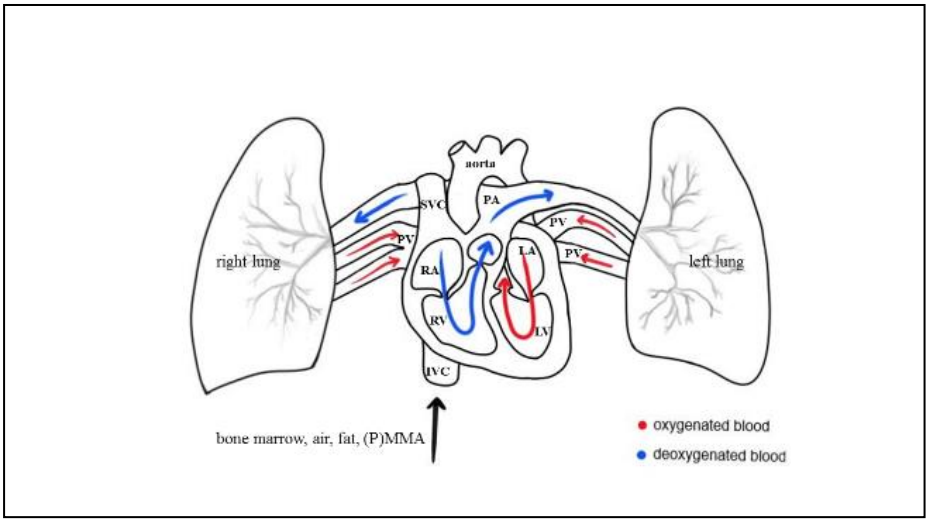

Figure 7a: Schematic of normal heart function before cementation and prosthesis insertion. PA, pulmonary artery; PV, pulmonary vein; SVC, superior vena cava; IVC, inferior vena cava; RA, right atrium; LA, left atrium; RV, right ventricle; LV, left ventricle; (P)MMA, Polymethyl Methacrylate.

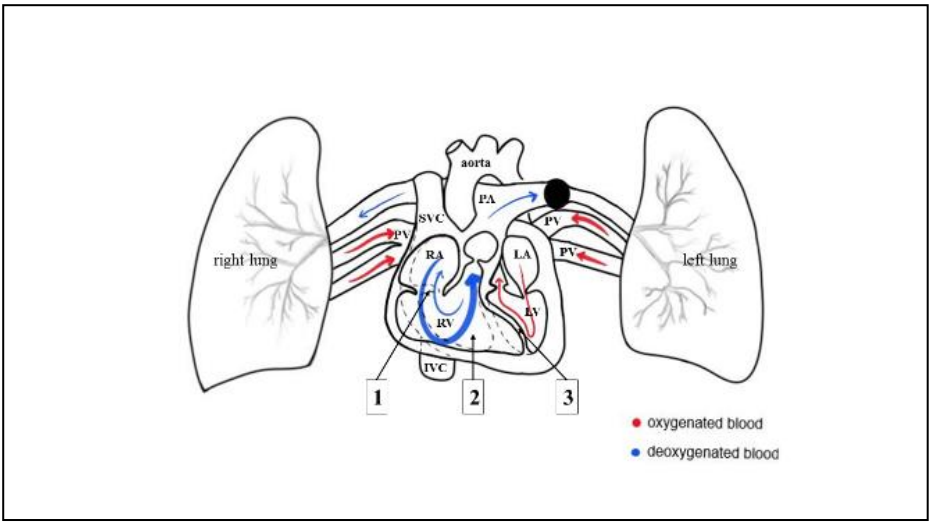

Figure 7b: Schematic of heart function immediately after cementation and prosthesis insertion due to an embolic obstruction. PA, pulmonary artery; PV, pulmonary vein; SVC, superior vena cava; IVC, inferior vena cava; RA, right atrium; LA, left atrium; RV, right ventricle; LV, left ventricle. **1**, Tricuspid insufficiency; **2**, dilation and wall distension, **3**, inter-ventricular septum shift.

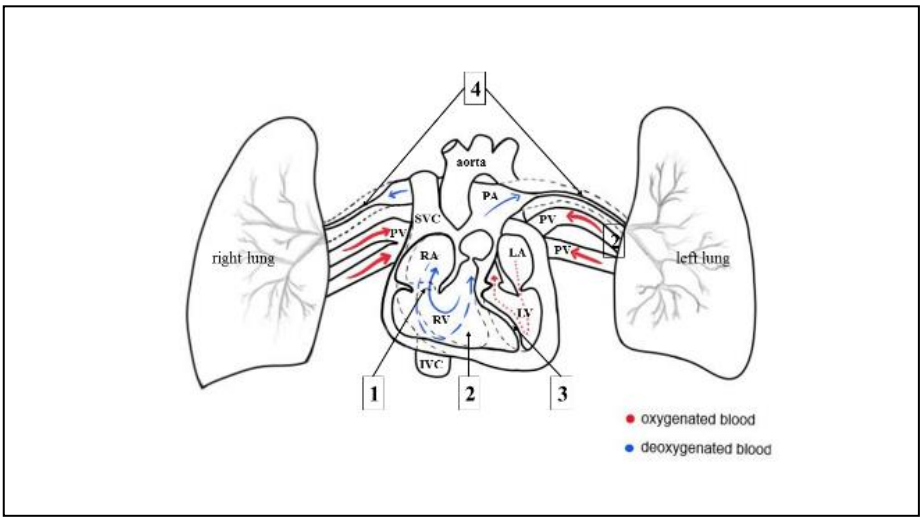

Figure 7c: Schematic of heart function around 20 min after cementation and prosthesis insertion with increased pulmonary vascular resistance. PA, pulmonary artery; PV, pulmonary vein; SVC, superior vena cava; IVC, inferior vena cava; RA, right atrium; LA, left atrium; RV, right ventricle; LV, left ventricle. **1**, Tricuspid insufficiency; **2**, dilation and wall distension, **3**, inter-ventricular septum shift; **4**, pulmonary vasoconstriction.

Only a few studies have been performed that have provided data regarding the advanced haemodynamic variables in patients who are undergoing cemented hip arthroplasty or hemiarthroplasty. Clark *et al* showed, using a trans-oesophageal Doppler probe, that in patients who were undergoing cemented hemiarthroplasty for femoral neck fracture cementation produced a transient reduction in cardiac output of 33%.[79] The authors did not provide data on the pulmonary haemodynamics or RV function. Ereth *et al* compared, using a pulmonary artery catheter, the haemodynamics of patients undergoing cemented versus non-cemented elective total hip arthroplasty and found only minor changes (5%–10%) in cardiac output and PVR.[20] Neither did this investigation present data on pulmonary artery pressures or RV functions. Urban *et al* studied the effects of bone cementation on the pulmonary haemodynamic of 18 patients who were undergoing elective revision total hip arthroplasty. They found that during femoral prosthesis insertion, all the

patients exhibited transient haemodynamic changes, which were small and clinically insignificant in the majority of the patients.[66] The cardiac index was not significantly altered by bone cementation and prosthesis insertion, and the decrease in right ventricle ejection fraction (RVEF) was transient and had normalised upon wound closure. However, four patients in their study demonstrated a decrease in RVEF of ≥10% and an increase in MPAP of ≥10 mmHg, which required intervention.[66] In that study, no data on PVR or RV volumes were presented. A significant fall in RVEF accompanied by a significant decrease in CI and SVI, sustained throughout the surgical procedure, could be observed after cementation in **Papers II**, **III** (cemented group), and **IV** (saline group) (Figure 8), which contrasted with the findings of Urban *et al*. A possible explanation for this is that a previously instrumented femoral canal, as in revision hip surgery, may place the patient at lower risk of developing BCIS, as seen in the study of Urban *et al*.[66] It is possible that there is less embolic material present in the previously instrumented canal and that the inner surface of the femoral canal becomes smooth and sclerotic and less-permeable to the bone marrow content.[15]

In conclusion, in contrast to previous studies, changes in the right-sided heart performance due to cemented hip arthroplasty or hemiarthroplasty were regularly detected in our studies as an increase in right ventricular after-load followed by decreases in the RVEF, stroke volume index, and cardiac index.

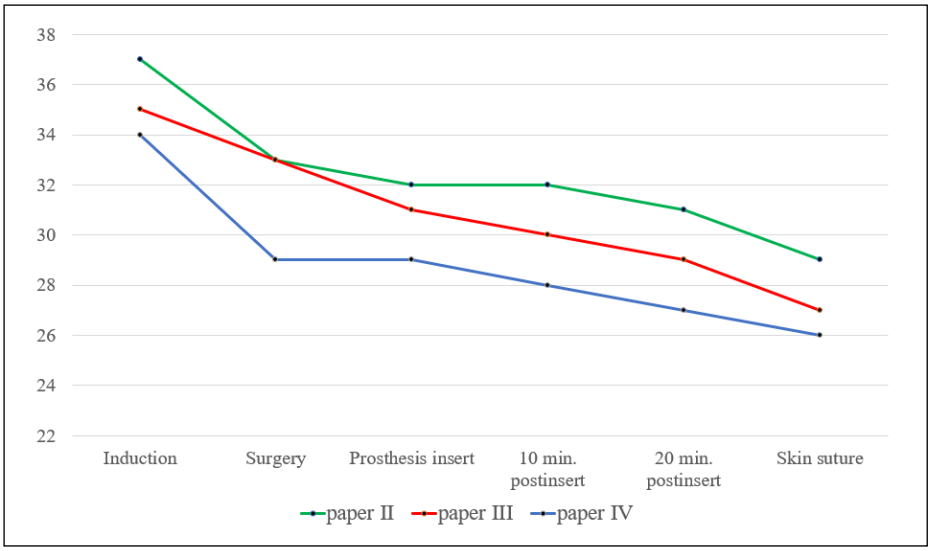

Figure 8: Significant decreases in the right ventricle ejection fraction (RVEF) in all patients undergoing cemented hip arthroplasty (**Paper III**, $p<0.05$) or cemented hip hemiarthroplasty (**Paper II**, $p=0.001$ and the saline group in **Paper IV**, $p=0.031$) after cementation and prosthesis insertion.

Gas-exchange abnormalities

Hypoxia in BCIS manifests itself in almost all patients as a transient, or in severe cases, as a pronounced and prolonged reduction in oxygen saturation. The acute embolic obstruction and the subsequent mediator release with increasing PVR must be considered as the causal factors for the observed hypoxia. The extent of hypoxia reflects the size and character of the embolic load and pre-existing cardiopulmonary diseases.[71, 80] The mismatch between ventilation (V) and perfusion (Q) with a regional shift of the V/Q ratio results in a re-distribution of the blood flow from embolised towards non-embolised lung areas, which will cause a fall in the V/Q ratio and hypoxia. [81] Atelectasis due to loss of surfactant and induced bronchoconstriction, resulting in right-left shunting, are other conceivable mechanisms.[82, 83] Post-embolic pulmonary

oedema and a patent foramen ovale due to an acute increase in right atrial pressure, with intra-cardiac shunting of blood have also been discussed as mechanisms of hypoxia.[84] High V/Q ratios in embolised areas of the lung lead to dead-space ventilation with a decrease in end-tidal pCO_2 and hypercapnia.

Several investigations have shown alterations in the pulmonary ventilation/perfusion relationship caused by the embolic load during cementation.[48, 66] We could demonstrate pulmonary ventilation/perfusion abnormalities, detected by a significantly increased V_D/V_T ratio, as a measure of dead-space ventilation, in **Papers II** and **IV** (Figure 9), as well as intra-pulmonary shunting resulting from a significant decrease in the paO_2/FiO_2 ratio in **Papers II**, **III** and **Paper IV** (Figure 10). The observed changes were most pronounced immediately after bone cementation and prosthesis insertion. These findings are in line with those of Pitto *et al*, who showed decreases in arterial oxygen saturation and end-tidal CO_2 after cementation and prosthesis insertion.[85] In contrast, a pulmonary ventilation/perfusion analysis, using the multiple inert gas elimination technique as performed by Ereth *et al* on six patients who were undergoing elective cemented total hip arthroplasty, did not demonstrate significant changes in the venous admixture or physiological dead-space fraction during cementation and prosthesis insertion.[20] However, several investigations have shown decreases in the pO_2 and pO_2/FiO_2 ratios as a result of the immediate deterioration in the pulmonary ventilation/perfusion relationship due to the embolic load.[64, 65, 69, 86]

In summary, a reduction in the level of oxygen saturation immediately after cementation and prosthesis insertion is common and must be considered as the result of embolic obstruction and the increase in PVR, which may induce pulmonary ventilation/perfusion abnormalities that lead to hypoxia and increased dead-space ventilation.

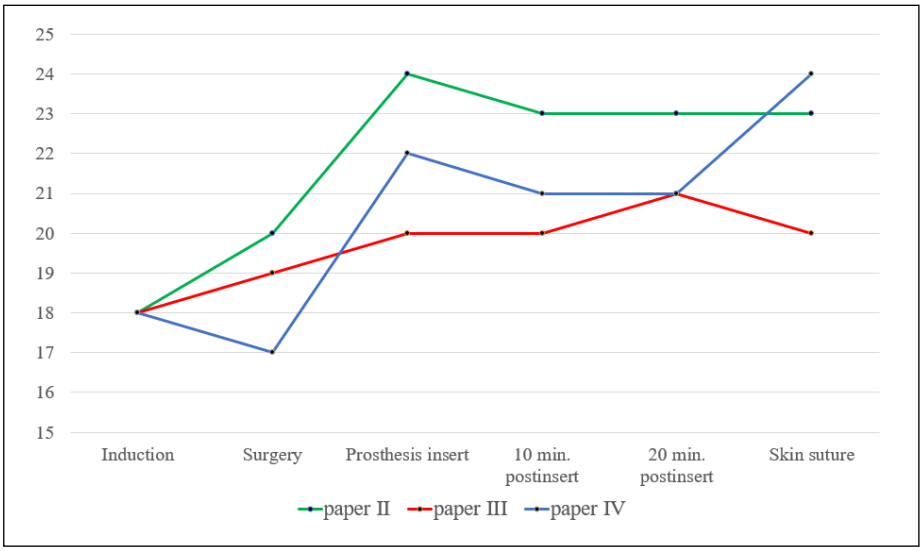

Figure 9: Changes in the V_D/V_T ratio in all patients undergoing cemented hip arthroplasty (**Paper III**, p=0.567) or cemented hip hemiarthroplasty (**Paper II**, p=0.004 and the saline group in **Paper IV**, p=0.046) after cementation and prosthesis insertion.

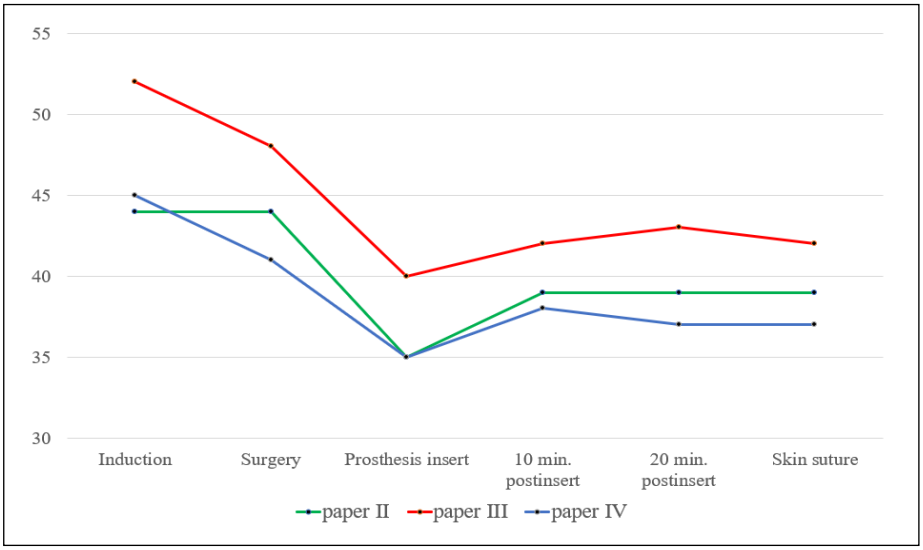

Figure 10: Changes in the PaO_2/FiO_2 ratio in all patients undergoing cemented hip arthroplasty (**Paper III**, p=0.003) or cemented hip hemiarthroplasty (**Paper II**, p=0.018 and the saline group in **Paper IV**, p=0.011) after cementation and prosthesis insertion.

Haemodynamic measurements, study protocol, clinical setting and monitoring

Pulmonary artery catheter (PAC)

The balloon-tipped pulmonary artery catheter (PAC), which was developed and introduced by Swan *et al* in 1970, allowed the use of advanced hemodynamic (heart) monitoring outside laboratory or research settings.[87] The use of PAC was limited primarily to patients with myocardial infarction, shock or heart failure. Gradually, the indications for PAC application widened to include surgical patients requiring advanced haemodynamic monitoring.[88] Over the next 20 years, the PAC was used in the intensive care units for the assessment of advanced haemodynamic parameters.[88] By 1996, the "golden era" of the PAC`s was coming to an end with the publication of the investigation of Connors *et al*, who showed increased mortality, higher costs, and longer length of stay in hospital when PACs were used.[89] The results of the ESCAPE (Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness) trial, which showed an overall neutral impact of PAC-guided therapy when compared to therapy guided by clinical evaluation and judgment alone, promoted a further decrease in the routine use of PACs.[90] Today, the use of PAC`s is reserved for the management of refractory heart failure and selected conditions, such as pulmonary hypertension and after heart transplantation.

In principle, the PAC measures changes in blood temperature *via* a thermistor at the catheter tip, which is placed in the pulmonary artery. If one knows the temperature and the volume of a saline solution that is injected into the superior vena cava or right atrium from a proximal catheter port, one can

derive the typical thermo-dilution curve computed from the change in blood temperature as it flows over the thermistor surface (Figure 11).

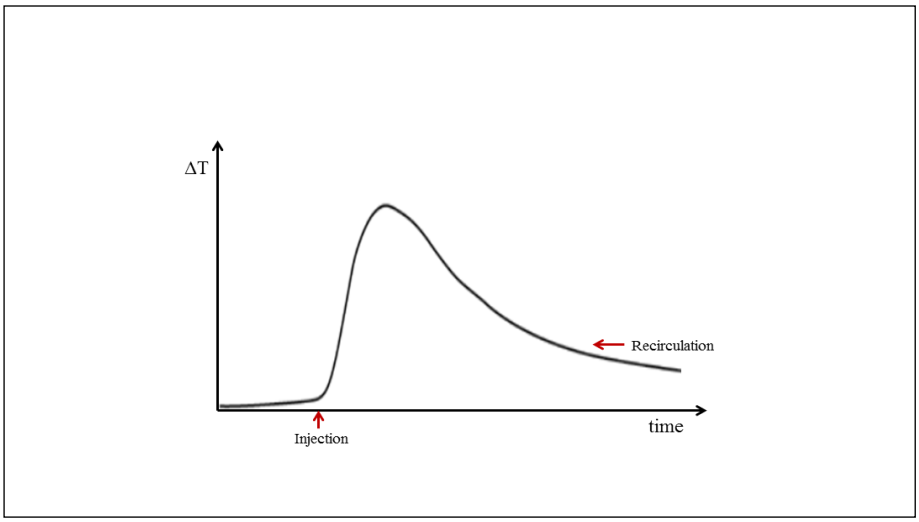

Figure 11: Thermo-dilution curve derived from a pulmonary artery catheter.

The cardiac output can be calculated using the blood temperature information, and the temperature and volume of the injected saline solution are calculated using the modified Stewart Hamilton equation:

$$Q = \frac{V(T_B - T_I)\,K_1K_2}{T_B(t)^{dt}}$$

where Q is the cardiac output (CO), T_B is the blood temperature, T_I is the injectate temperature, K_1 and K_2 are the corrections for the specific heat and density of the injectate and for the blood and dead-space volume, and $T_B(t)^{dt}$ represents the change in blood temperature as a function of time [area under the curve (AUC)].

The fast-response thermo-dilution PAC has mounted thermistors with a response time of approximately 50 msec, which enables a beat-to-beat measurement of the temperature variation (Figure 12).

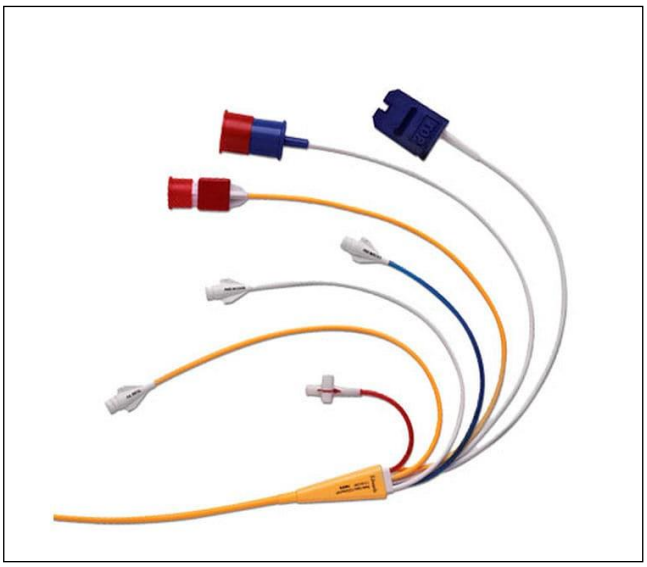

Figure 12: Fast-response thermo-dilution pulmonary artery catheter (Edwards Lifesciences Inc., Irvine, CA).

The thermo-dilution curve derived from the values recorded by the thermistors shows characteristic plateaus, which represent the beat-to-beat changes in temperature (Figure 13); when synchronised with the R-wave obtained from the ECG the ventricular contraction can be identified. Then, the RVEF, which is defined as the percentage of blood in the ventricle at end-diastole that is ejected at end-systole, can be calculated based on the changes in temperature using the following equation:

$$RVEF=1-(Tb-T2)/(Tb-T1)$$

where Tb is the incoming blood temperature, T1 is the ejected blood temperature 1, and T2 is the ejected blood temperature 2 (Figure 13).

Thereafter, the right ventricle end-diastolic volume (RVEDV) and right ventricle end-systolic volume (RVESV) can be calculated from the RVEF and CO.

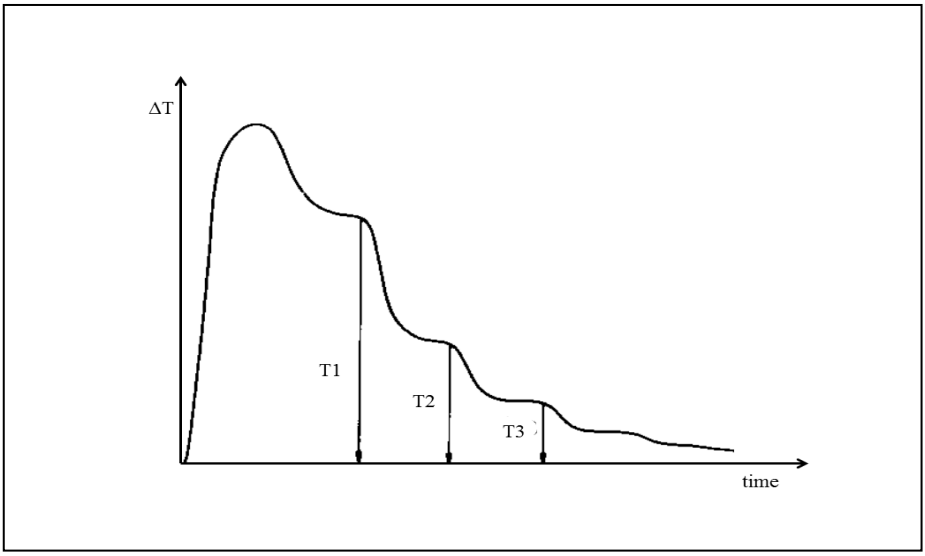

Figure 13: Thermo-dilution curve derived from the fast-response thermo-dilution pulmonary artery catheter.

The use of a fast-response thermo-dilution PAC may provide not only the parameters relevant for pulmonary haemodynamics, but also important information on the function of the RV in various conditions involving the cardiopulmonary system. The reproducibility and accuracy of this technique for repeated bolus measurements of RVEF have been validated and confirmed, as compared to other methods for the measurement of RVEF.[91-93] Zink *et al* have demonstrated that measurements of RV function by PAC match the results obtained with trans-oesophageal echocardiography with regards to bias and precision.[94]

Study protocol

In **Papers II**, **III** and **IV**, haemodynamic measurements and blood gas analyses were performed on six occasions: a) after induction of anaesthesia before surgery; b) during surgery before cementation and insertion of the prosthesis stem; c) immediately after cementation and insertion of the prosthesis stem; d) 10 minutes after insertion of the prosthesis; e) 20 minutes after insertion of the prosthesis; and f) at the time of skin closure (Figure 14).

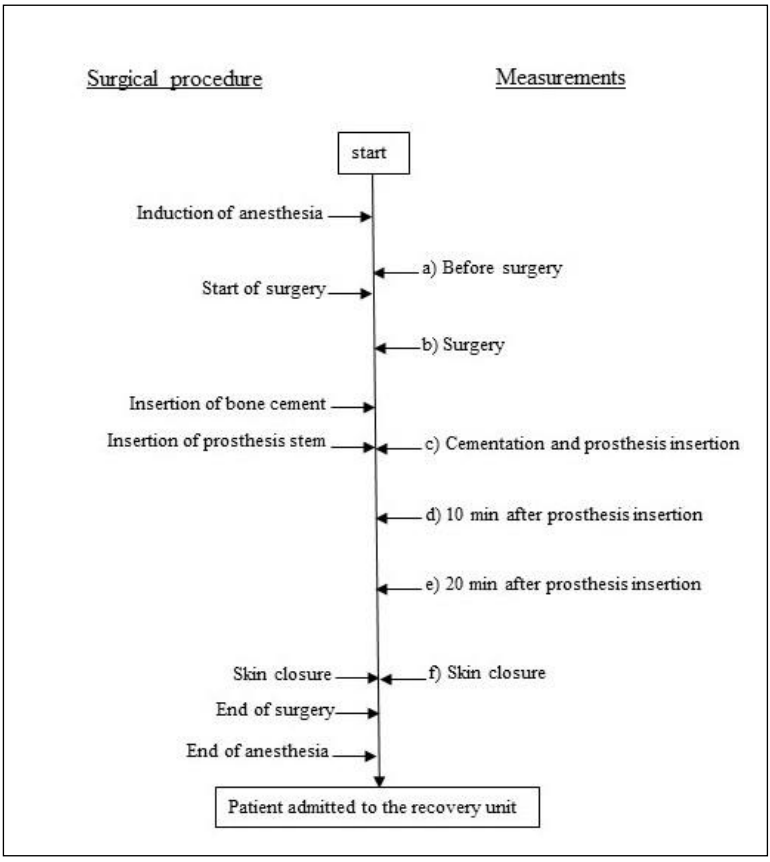

Figure 14: Study protocol used in **Papers II–IV.**

Clinical setting and monitoring

All patients included in **Papers II**, **III** and **IV** received general anaesthesia and were induced and maintained with total intravenous anaesthesia using propofol (Propolipid®; Fresenius Kabi AB, Uppsala, Sweden) and remifentanil (Ultiva®; GlaxoSmithKline, Solna, Sweden). The depth of anaesthesia was guided by spectral entropy monitoring. After muscular relaxation with rocuronium (Rocuronium Fresenius Kabi®; Fresenius Kabi), all the patients were endotracheally intubated. A standard anaesthetic monitoring procedure with continuous heart rate and SPO_2 registration was performed in all the patients (Datex-Ohmeda Anaesthesia Monitor; GE Healthcare, Stockholm, Sweden; and Flow-I® C30; Maquet Critical Care AB, Solna, Sweden). Mechanical ventilation was used to achieve normocarbia, guided by the end-tidal carbon dioxide (ET-CO_2) with 2–3 cmH_2O of positive end-expiratory pressure (PEEP). The target ranges for mean arterial pressure (MAP) and central venous pressure (CVP) were 70–80 mmHg and 5–8 mmHg, respectively, and the target range for haemoglobin was 100–110 g/l. Patients received norepinephrine when needed to counteract the vasodilatory effect of the intravenous anaesthetics. Patients were administered colloids, crystalloids and erythrocytes at the discretion of the attending anaesthetist (Figure 15).

Arterial blood pressure was measured continuously via a preoperatively inserted radial arterial cannula (Becton Dickinson AB, Stockholm, Sweden). After induction of anaesthesia, a 7.5 F CCOmbo Volumetrics Pulmonary Artery Catheter (Edwards Lifesciences Inc., Irvine, CA) was inserted via the right internal jugular vein. The Vigilance II Monitor (Edwards Lifesciences) was used for continuous measurements and for registrations of the central venous pressure (CVP), pulmonary arterial pressure (PAP), cardiac output (CO), mixed venous oxygen saturation (S_VO_2), right ventricular end-diastolic volume (RVEDV), and right ventricular ejection fraction (RVEF) (Figure 16).

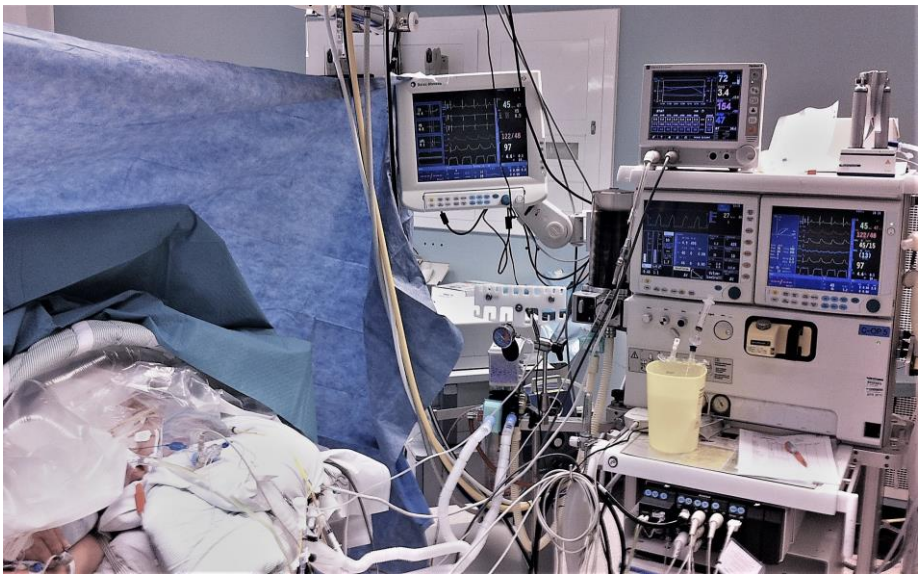

Figure 15: Intra-operative milieu.

The pulmonary artery occlusion pressure (PAOP) was measured intermittently. All transducers were referenced to the mid-axillary line. Cardiac output was measured using the thermo-dilution method. The average of three rapid injections of 10 ml if ice-cold saline into the proximal port of the PAC was assumed to be accurate. Cardiac output was indexed to body surface area (BSA). Systemic vascular resistance index (SVRI), pulmonary vascular resistance index (PVRI), stroke volume index (SVI), right ventricular end-systolic volume index (RVESVI), and right ventricular end-diastolic volume index RVEDVI were calculated according to standard equations.

Arterial and mixed venous blood gas analyses were performed using an automated blood gas analyser (RAPIDPoint®; Siemens Healthcare Diagnostics AB, Upplands Väsby, Sweden). Lung oxygenation was assessed as a measure of intra-pulmonary shunting and calculated as the arterial PO_2 (PaO_2) divided by the inspired fraction of oxygen (F_IO_2). The V_D/V_T ratio was

calculated using the Enghoff modification of the Bohr formula: ($PaCO_2$ -ET-CO_2)/$PaCO_2$.

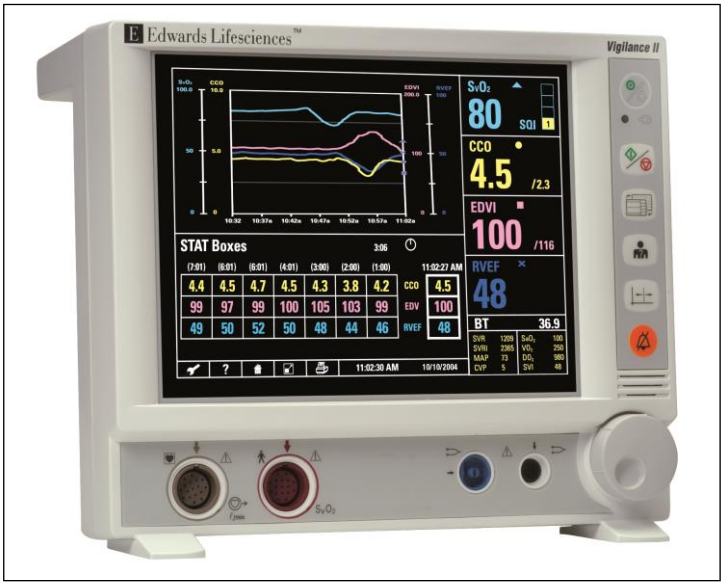

Figure 16: The Vigilance II Monitor (Edwards Lifesciences Inc., Irvine, CA)

Prevention and treatment of BCIS

It is known that BCIS grades 2 and 3 are associated with high peri-operative mortality and lead to a 16-fold increase in the risk of death within 30 days after surgery (**Paper I**). Strategies for the prevention and effective treatment of BCIS should be considered as evidently important. In 2015, Griffith *at al* published safety guidelines to reduce the risk associated with cemented hemiarthroplasty, focusing on multidisciplinary clinical guidance throughout the peri-operative period, involving the anaesthetist, surgeon and orthogeriatrician.[95] After carful assessment of the risk factors for especially frail patients undergoing hip hemiarthroplasty, they made the following recommendations:

1. Discussion between surgeons, anaesthetists and orthogeriatricians as to how best to minimise the early operative risks of mortality and morbidity.
2. Surgeons and anaesthetists should modify the peri-operative practice, both to reduce the risk of cardiovascular events and to improve the outcome if such events should occur.
3. All hip fracture surgery should be undertaken or directly supervised by appropriately experienced anaesthetists and surgeons.[95]

Furthermore, the guidelines contain general recommendations for the surgeon and anaesthesiologist in terms of the prevention and treatment of BCIS. Unfortunately, the body of evidence for particular prevention and treatment options for BCIS is currently unsatisfactory.

Surgical considerations

The over-arching aim of the surgery should be the reduction of the risk of BCIS development, especially in high-risk patients. Table 6 shows the pathological and surgical risk factors for the development of BCIS, as suggested by Hines *at al*.[96] The involvement of an orthopaedic surgeon who is aware of these factors is a fundamental requirement for the management of BCIS.[97]

Table 6: Significant pathological and surgical risk factors for the development of BCIS.

Osteoporosis
Bony metastasis
Presence of hip fracture (especially pathologic or inter-trochanteric fractures)
Patients with large femoral canals (≥21 mm)
Revision surgery
Surgery on previously un-instrumented femur
Planned use of long-stem prosthesis
Use of excessive cementing pressure

Surgical techniques should focus on reducing the medullary contents before cementation and effective reduction of the high intramedullary pressure at the time of cementation. High-volume, high-pressure pulsatile lavage of the intramedullary cavity after reaming has been shown to reduce significantly the changes in pulmonary haemodynamics, PaO_2 and intrapulmonary shunt fraction (Qs/Qt) in animal studies.[64, 98-100] Despite a lack of supporting evidence in humans, medullary lavage is strongly recommended as an effective measure to reduce the intramedullary contents before cementation.[15, 96, 101] Another surgical measure to reduce the amount of material forced into the femoral

venous channels upon cementation involves drilling venting holes in the femur so as to allow air to escape from the medullary cavity.[16, 50, 63, 102, 103] Unfortunately, drilling such holes increase the risk of femoral fracture.[63, 100] Retrograde insertion of the cement (from distal to proximal) with a cement gun is associated with significantly less rapid drops in oxygen saturation at cementation, even though the intramedullary pressure is higher when a cement gun is used rather than finger-packing of the cement.[54] The bone-vacuum cementing technique reduces significantly the embolic load during hip arthroplasty, as shown by intra-operative trans-oesophageal ultrasound analysis.[104] Preparation of the bone cement using a partial vacuum results in a significant reduction in the rate of decrease of oxygen saturation at cementation, as compared to preparation of the bone cement under atmospheric pressure.[104, 105] Finally, the choice of length of the prosthesis stem also has an impact on the occurrence of cardiopulmonary disturbances.[15, 17, 103]

Un-cemented vs cemented total hip arthroplasty

Patients at high risk of developing BCIS should be assessed regarding whether an un-cemented fixation method for the prosthesis can be applied. The use of un-cemented prostheses is effective in reducing the intramedullary pressure, as compared to using prostheses anchored by cement.[43] Several investigations have shown a more favourable outcome for at-risk patients regarding pulmonary and cardiovascular disturbances.[18, 20, 43, 45, 79] However, the impact on mortality is not as conclusive. Investigations have revealed a higher peri-operative mortality rate when bone cement is used, although this rate declines after 30 days and is negligible after 1 year.[19, 30, 106, 107] The tendency for high-risk patient to succumb in the early peri-operative period has been discussed above. Interestingly, two recent investigations did not find differences in either the early post-operative mortality[108] or the cumulative 1-year mortality[109] when

comparing un-cemented and cemented hip arthroplasties. Furthermore, the results from several investigations indicate that un-cemented (as opposed to cemented) hip arthroplasty due to hip fracture is linked to higher levels of pain, poorer joint functionality, and a greater need for revisions.[30, 31, 110-112] In contrast, a recently published investigation found no fixation method-related differences regarding pain level, quality of life or the 1-year mortality rate.[113]

The aim of **Paper III** was to contribute with data regarding the differential effects of cemented *vs* un-cemented total hip arthroplasty on pulmonary haemodynamics in patients with femoral hip fracture. The study was a haemodynamics sub-study of the prospective randomised trial *Cemented versus un-cemented stems in total hip arthroplasty in patients with femoral neck fractures* (ClinicalTrials.gov Identifier: NCT01578408), following the study protocol, clinical setting, and haemodynamic, measurements, as described in the section above. Surgically, all the patients were placed in a lateral position and the standard anterolateral approach was used. A cemented IP hip acetabular cup (Waldemar LINK GmbH & Co. KG, Hamburg, Germany) was inserted in those patients who were randomised to the cemented group. A Marathon® cemented cup (DePuy Synthes, Johnson & Johnson AB, Solna, Sweden) was inserted in the patients randomised to the un-cemented group. The femoral canal was prepared with standard Charnley reamers and lavaged (high-pressure pulsatile lavage) with saline in all the patients after insertion of a cement restrictor (cement plug). All the patients in the cemented group received bone cement that was introduced retrogradely at low pressure using a cement gun. Thereafter, a Lubinus® SP II prosthesis stem (Waldemar LINK) (Figure 17) was inserted. The Corail® Hip System (DePuy Synthes) (Figure 17) was inserted in those patients who were randomised to the un-cemented group.

Figure 17: Photographs of the IP hip acetabular cup and Lubinus® SP II prosthesis stem (Waldemar LINK GmbH & Co. KG, Hamburg, Germany) (left) and the Corail® Hip System (DePuy Synthes, Johnson & Johnson AB, Solna, Sweden) (right).

The main finding in **Paper III** was a significant increase in PVRI (p=0.005, Figure 18), which was accompanied by significant increases in SPAP and MPAP, when comparing the cemented and un-cemented groups. The decrease in RVEF was not statistically significant but tended to be more pronounced in the cemented group than in the un-cemented group.

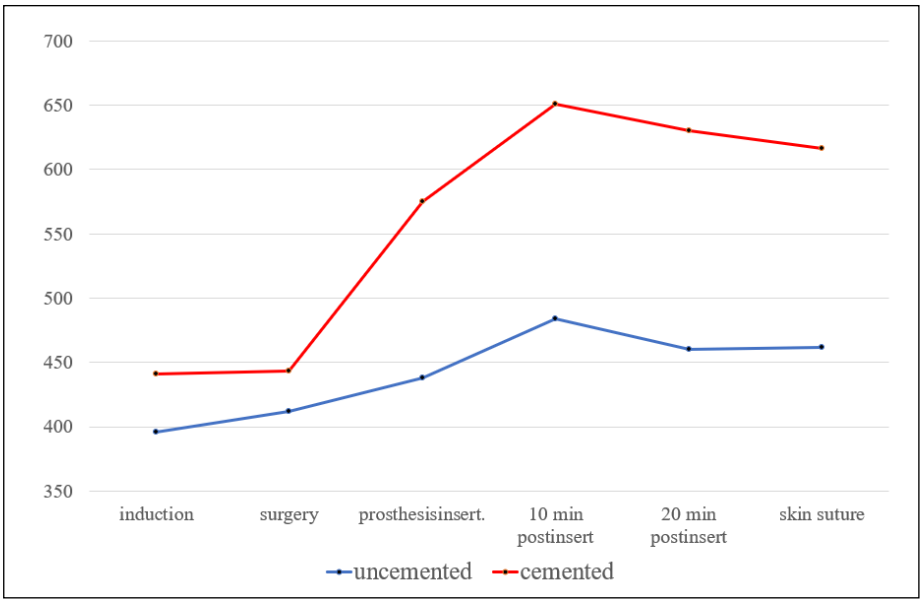

Figure 18: Changes in PVRI for un-cemented *vs* cemented hip arthroplasty. The increase in PVRI is significantly more pronounced in the cemented group (p=0.005).

Only two studies have been published that have investigated the effects of bone cement, comparing cemented *vs* un-cemented hip arthroplasty, on pulmonary haemodynamics and RV performance using advanced monitoring, such as a fast-response PAC. Ereth *et al* could demonstrate only minor changes in pulmonary vascular resistance and cardiac output when comparing cemented *vs* un-cemented fixation of the femoral prosthesis.[20] In another study, using a trans-oesophageal Doppler probe, Clark *et al* demonstrated a non-significant transient reduction in cardiac output in patients who were undergoing cemented hemiarthroplasty, as compared to un-cemented fixation of the prosthesis.[79] Data regarding RV performance were not provided in these studies. In contrast, we observed significant changes in the pulmonary haemodynamics, not only in **Paper III** but also in **Papers II** and **IV**, when bone cement was used. In particular in **Paper II**, where we studied very old patients with ASA ≥3 who were undergoing cemented hemiarthroplasty for

femoral neck fracture, we found that bone cementation and prosthesis insertion caused a 45% increase in the PVRI, which was accompanied by significant decreases in the RVEF, cardiac index, and stroke volume index. While the patients in **Paper III** had ASA II (70%–85%) or ASA III (15%–30%) and were in the age range of 74–76 years so had the majority of patients in **Paper II** had ASA III (93%) and were 86 years old. The lack of significant haemodynamic deterioration in the cemented group compared to the un-cemented group shown in **Paper III** may be explained by the fact that a clear majority of the patients had a low risk of developing BCIS and they had the capability to adapt to the increase in RV after-load during and around the period of prosthesis insertion. These findings are in line with the results of a recent study that noted a more-pronounced decrease in cardiac output in very elderly patients.[68]

In summary, using bone cement increases the pulmonary vascular resistance with potentially fatal consequences for patients who are at risk of developing BCIS. Despite the inconclusive evidence on mortality when comparing cemented and un-cemented prostheses and the findings of higher post-operative pain scores, debilitated functionality, and higher frequency of revision when using un-cemented prostheses, un-cemented fixation of the prosthesis should be considered for elderly patients who have other risk factors for development of BCIS.

Anaesthesia considerations

Currently, there is no specific, agreed protocol for anaesthesia management to prevent or treat the adverse effects of bone cement. Careful assessment and awareness of the risk factors of BCIS are crucial and should be the basis for an optimal anaesthesia plan that is individually tailored to the patient by the anaesthetist. Table 7 shows the anaesthesia-relevant risk factors for the development of BCIS. Strong communication between the anaesthetist and surgeon is essential, and should be considered more important than specific anaesthetic or surgical measures.[95]

Table 7: Anaesthesia-relevant risk factors for the development of BCIS in patients with femoral hip fractures.

ASA class 3 or 4
Older age
Male gender
Medication with diuretics
Medication with warfarin
COPD
Severe cardiopulmonary disease
Pre-existing pulmonary hypertension

There is only limited evidence regarding the effects of the anaesthetic technique on BCIS. General recommendations include peri-operative maintenance of normovolaemia, avoiding anaemia, and delivering a high inspired oxygen fraction (FiO_2), so as to optimise the pre-load, after-load, and oxygen deliveries.[15, 96, 101] Advanced haemodynamic monitoring, including continuous CO measurement, is recommended to detect BCIS early in patients who are at risk, so that supportive therapy and cardiopulmonary resuscitation can be initiate immediately.[96] The initial treatment should focus on securing

the airways and the delivery of high inspired oxygen concentrations. Cardiovascular support with α- and β-adrenergic sympathomimetic agents is important and should not be delayed. However, the choice of anaesthesia, i.e., regional or general, appears to be of minor importance. A retrospective investigation of 56,729 patients designed to evaluate the mortality rate and length of stay in hospital after hip fracture comparing spinal or epidural anaesthesia *vs* general anaesthesia found only that regional anaesthesia was associated with a shorter length of hospital stay than general anaesthesia. No differences in mortality were observed.[114] A recently published Cochrane database review that included 31 investigations comparing regional anaesthesia with general anaesthesia for hip repair after hip fracture revealed no differences in mortality.[115] However, animal investigations showed haemodynamic instability when inhalational anaesthetic agents were used.[116] Khanna *et al* have recommend that intra-operatively high vapour concentrations be avoided, so as to prevent cardiovascular instability around the time of cementation.[101]

Unfortunately, there are currently no specific medical protocols to prevent or treat BCIS. Tryba *et al* have demonstrated a positive effect of pre-operatively administered H_1 and H_2 antagonists on the extent of cardiovascular reactions, with a reduced demand for therapeutic intervention due to low systolic blood pressure.[117] However, they concluded that the cardiovascular deterioration seen in BCIS is multi-factorial and the blockade of histamine receptors alone does not prevent significant drops in blood pressure.[117] Corticosteroids used in the therapy of fat embolism syndrome (FES) associated with post-traumatic lung injury and adult respiratory distress syndrome (ARDS) have been investigated extensively. While older investigations have suggested a protective effect of corticosteroids,[118, 119] more recent studies have failed to confirm the effectiveness of corticosteroids.[120, 121] Methylprednisolone sodium succinate (MPSS) was investigated by Byrick *et al* in an animal model

of pulmonary hypertension after fat embolism, and they concluded that acute hemodynamic changes after cementation were not prevented by MPSS.[122] Another interesting approach is the administration of pulmonary vasodilators. In an investigation conducted in sheep, Krebs *et al* demonstrated that intravenously administered sildenafil could prevent the acute cardiovascular complications of BCIS.[123] The inhalation of nitric oxide (NO) or prostacyclin, which have similar selective pulmonary vasodilation properties, is another interesting option. Both of these agents have been thoroughly investigated and are recommended for the therapy of conditions with elevated pulmonary vascular pressure and right ventricle dysfunction. As the inhalation of NO is technically challenging in peri-operative settings, prostacyclin is a more-favoured alternative.

Prostacyclin

Prostacyclin (PGI_2), which is a prostaglandin that is derived from arachidonic acid by cyclooxygenase and prostacyclin synthase, is produced in all vascular tissues.[124] Endothelial cells are the most prolific producers of prostacyclin.[125] Pulmonary arterial endothelial cells produce in *vitro* more prostacyclin than do pulmonary venous endothelial cells, as demonstrated by Johnson *et al*.[126] Prostacyclin is a potent endogenous inhibitor of platelet aggregation, as well as a strong vasodilator with effects in all vascular beds; its effects are the opposite of those of thromboxane A_2 ($TX\text{-}A_2$), which is produced by platelets and drives platelet aggregation and vasoconstriction. An intracellular increase in the level of cyclic adenosine monophosphate (cAMP) results from prostacyclin-mediated activation of membranous G-protein-coupled receptors, which activate protein kinase A (PKA) and induce relaxation of smooth muscle cells (Figure 19).

Pulmonary arterial hypertension (PAH) is a progressive disease, characterised by remodelling of the pulmonary vascular bed, resulting in increased pulmonary vascular resistance (PVR) and a subsequent increase in the pulmonary arterial pressure (PAP).[127, 128] PAH occurs primarily (idiopathic) or secondarily (e.g., chronic left heart failure or chronic pulmonary embolism), and it is usually progressive, leading to right-sided heart failure and death. Effective lowering of the PAP level will reduce hemodynamic stress, reverse remodelling, and improve the prognosis of the patients.[128] It has been shown that inhaled prostacyclin is more effective at lowering PAP than other treatment options.[128] Currently, prostacyclin and analogues thereof are widely used in the clinical management of patients with PAH.[127-130]

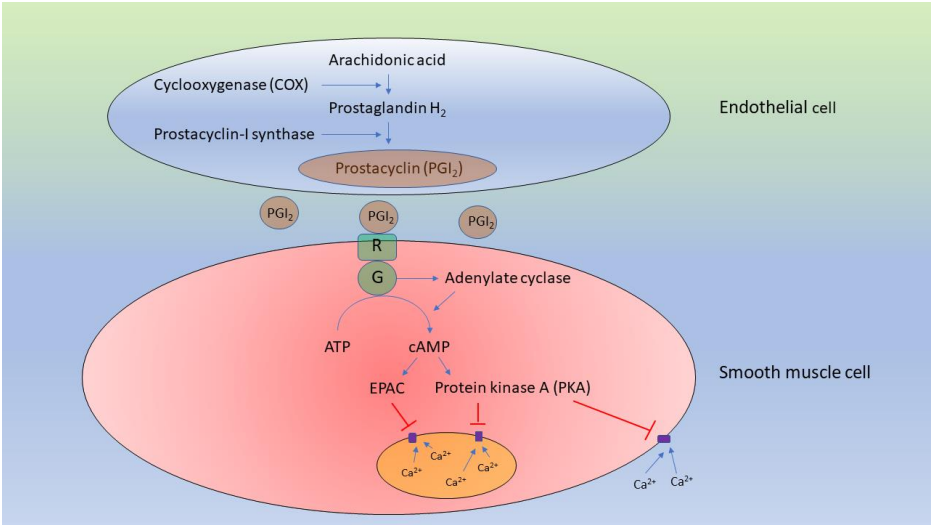

Figure 19: Synthesis and signalling pathway for prostacyclin (PGI_2). Arachidonic acid is metabolised to prostaglandin H_2 by cyclooxygenase (COX). Then, prostacyclin (PGI_2) is synthesised by prostacyclin-I synthase. Released prostacyclin binds to cell-surface receptors (R), thereby activating G-protein (G)-mediated adenylate cyclase, which converts ATP to cAMP. The cAMP activates protein kinase A (PKA), which phosphorylates substrate proteins and exchange proteins (EPAC), resulting in the blockade of calcium channels and a decrease in intracellular Ca^{2+}, which in turns induces the relaxation of smooth muscle cells and leads to vasodilation.

Increased pulmonary vascular resistance is also a problem in patients after cardiac surgery, especially after orthotopic heart transplantation.[131] The consequences of post-operatively elevated PAP levels are acute RV dysfunction and failure with increased risk of death (Figure 20). The reduction of the RV after-load seems to be of particular importance, in addition to maintenance of the systemic blood pressure, optimisation of the RV pre-load, and limiting pulmonary vasoconstriction through high inspired oxygen concentrations[132] Inhaled prostacyclin appears to be an ideal treatment due to its selective pulmonary vasodilatory properties. Several investigations have demonstrated that inhalation of prostacyclin reduces effectively the PAP and improves RV performance.[129, 133]

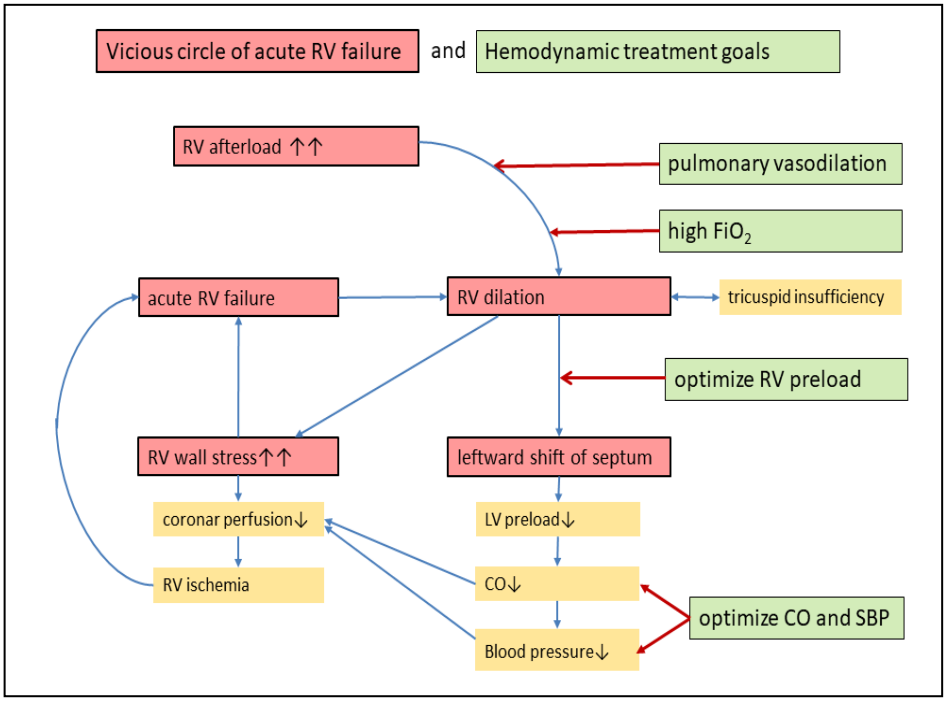

Figure 20: The vicious cycle of acute right ventricle (RV) failure and the haemodynamic treatment goals. FiO_2, Inspired oxygen fraction; RV, right ventricle; LV, left ventricle; CO, cardiac output.

In **Papers II** and **III**, we observed a significant increase in the PVRI around the time of cementation and prosthesis insertion. Pronounced pulmonary vasoconstriction should be considered as the most important pathophysiological factor in the manifestation of BCIS, as already discussed extensively in this thesis. Therefore, the aim of **Paper IV** was to evaluate the effect of a pharmacological intervention to prevent the adverse effects of bone cement on pulmonary haemodynamics, including the PVRI, RV after-load, and RV function (RVEF). This was an explorative, randomised, controlled trial that compared prostacyclin *vs* saline inhalation, following the study protocol, clinical setting, monitoring protocol, and haemodynamics measurements described in the previous section. In addition, after randomisation, continuous inhalation was started with either prostacyclin (10 µg/ml) at 20 ng/kg body-weight/min (Flolan® GlaxoSmithKline) or saline (NaCl, 9 mg/ml) at similar delivery rates (Fresenius Kabi). Inhalation was started after the induction of anaesthesia and was terminated immediately after the last haemodynamic measurement. The Aeroneb® Pro system nebulizer (HealthCap AB, Stockholm, Sweden) with a specified particle size in the range of 1-5 µm (average, 3.1 µm) was used to administer the inhalation compounds. Furthermore, the Agilia® injection pump (Fresenius Kabi) with a maximal delivery rate of 0.24 ml/min was used. (Figure21).

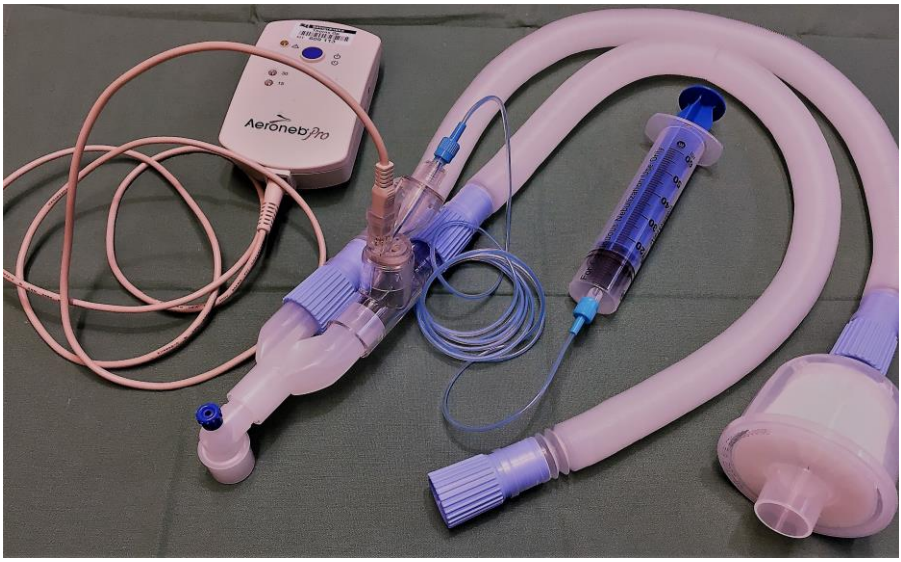

Figure 21: Aeroneb® Pro system nebulizer (HealthCap AB, Stockholm, Sweden).

We found that preventive treatment with inhaled aerosolised prostacyclin attenuated the increases in PVRI (p=0.031) (Figure 22) and RV after-load during cemented hip hemiarthroplasty. In **Papers II** and **III**, we studied the effects of bone cement on the pulmonary haemodynamics and RV function. The results showing a 44% increase in PVRI together with a relative decrease in RVEF of 24% in the saline group confirm the findings of **Papers II** and **III**. Around the time of cementation, an embolic load will increase the PVRI and RV after-load and may induce RV failure. In **Paper IV**, the PVRI was increased to a lesser degree in the group that inhaled prostacyclin, as compared to the group that inhaled saline, which suggests that the mediator-induced pulmonary vasoconstriction can be prevented. However, the difference was not sufficiently large to induce detectable changes in RVEF or SVI between the groups. On the other hand, prostacyclin-induced selective vasodilation in patients with preserved RV function will not necessarily improve RV performance.[134]

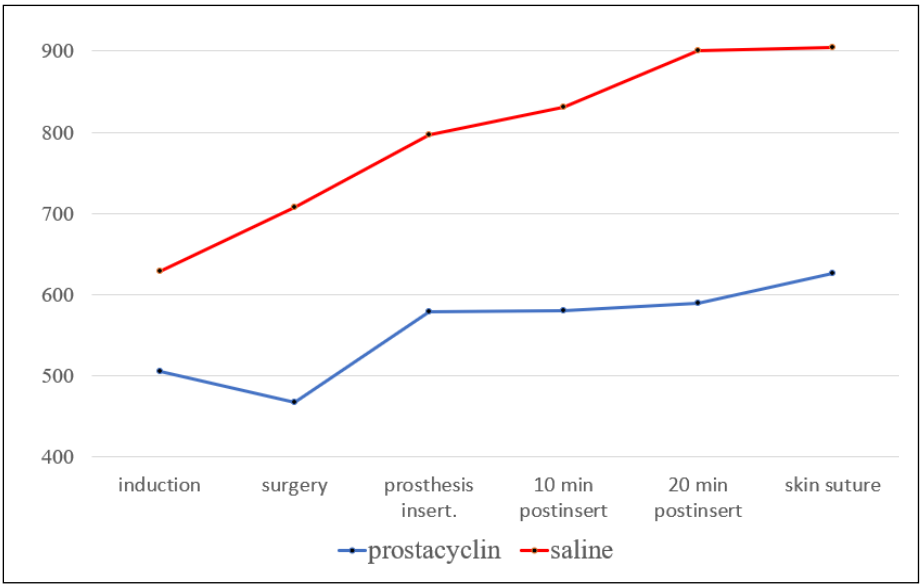

Figure 22: Changes in the PVRI in patients undergoing cemented hip hemiarthroplasty, comparing inhaled prostacyclin with inhaled saline treatment. The increase in PVRI is significantly attenuated in the prostacyclin group (p=0.031).

In summary, inhalation of aerosolised prostacyclin during cemented hip hemiarthroplasty may represent a pharmacological intervention that prevents the deleterious cardiopulmonary consequences of BCIS. Again, it is important to emphasise the explorative character of **Paper IV**. The clinical importance of the findings must be examined in larger randomised investigations.

Conclusions

Bone cement implantation syndrome is often seen in patients with femoral neck fracture who are undergoing cemented hip hemiarthroplasty. While severe grades of BCIS are rare, they can have devastating consequences for patients, in terms of high peri-operative and 30-day mortality rates. The identification of risk factors, such as high ASA-score (ASA>2), COPD, and medication with diuretics or anticoagulants (warfarin), should be a priority in the pre-operative assessment of these patients.

The embolic load during cementation and prosthesis insertion induces acute changes in the pulmonary vascular resistance (PVR), which seems to be crucial for the pathophysiological dysfunctionalities seen in BCIS. An increase in the PVRI by approximately 45% was observed in patients undergoing cemented total hip arthroplasty or hip hemiarthroplasty. Consequently, the right ventricle ejection fraction (RVEF) decreased and significant falls in the cardiac index (CI) and stroke volume index (SVI) could be observed in very old patients with high ASA scores. We propose that the ability of the right ventricle to handle the changes in the PVR determines the severity of BCIS.

Using bone cement to anchor the prosthesis stem regularly led to significant increases in the PVRI, SPAP and MPAP, as compared to un-cemented fixation. Therefore, high-risk patients should be carefully assessed, and un-cemented fixation should be considered.

Inhaled prostacyclin significantly attenuated the increase in PVRI, as compared to a control group that inhaled saline. Differences in the changes in RVEF and SVI were not observed when comparing the groups. Nonetheless, inhaled prostacyclin may be a valuable pharmacological intervention to prevent or treat BCIS.

As the population becomes older the incidence of hip fracture will increase. Patients with acute hip fractures are most frequently seen among the patients with fractures at the orthopaedic surgery departments in Sweden. They generate more than half of all the costs related to fractures, approximately 2.3 billion Swedish crowns (approximately 214 million EUR or 238 million USD) each year. A third of these patients are suffering from femoral neck fractures that are treated with total hip arthroplasty or hip hemiarthroplasty. Techniques that involve cementation are preferred by Swedish orthopaedic surgeons. Systematic research studies on BCIS are needed to improve and expand current clinical treatment options and to increase our understanding of the pathophysiology of BCIS.

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Appendix

Haemodynamic parameters and calculations

Haemodynamic parameter	calculation	normal values	unit
Systolic arterial pressure (SAP)		90-140	mmHg
Diastolic arterial pressure (DAP)		60-90	mmHg
Mean arterial pressure (MAP)	(SAP+(2 x DAP))/3	70-105	mmHg
Systolic pulmonary artery pressure (SPAP)		15-25	mmHg
Diastolic pulmonary artery pressure (DPAP)		8-15	mmHg
Mean pulmonary artery pressure (MPAP)	SPAP+(2 x DPAP)/3	10-20	mmHg
Pulmonary artery occlusions /wedge pressure (PAOP) (PAWP)		6-12	mmHg
Central venous pressure (CVP)		2-6	mmHg
Cardiac output (CO)	HR x SV/1000	4.0-8.0	L/min
Cardiac index (CI)	CO/BSA	2.5-4.0	L/min/m^2
Stroke volume (SV)	CO/HR x 1000	60-100	ml/beat
Stroke volume index (SVI)	CI/HR x 1000	33-47	ml/m^2/beat
Systemic vascular resistance (SVR)	80 x (MAP - CVP)/CO	1000-1500	dyn s/cm^5
Systemic vascular resistance index (SVRI)	80 x (MAP - CVP)/CI	1970-2390	dyn s/cm^5/m^2
Pulmonary vascular resistance (PVR)	80 x (MPAP - PAWP)/CO	<250	dyn s/cm^5
Pulmonary vascular resistance index (PVRI)	80 x (MPAP - PAWP)/CI	255-285	dyn s/cm^5/m^2
Right ventricular ejection fraction (RVEF)	SV/RVEDV	40-60	%
Right ventricular end-diastolic volume index (RVEDVI)	SVI/EF	67-89	ml
Right ventricular end-systolic volume index (RVESVI)	RVEDVI - SVI	20-34	ml
Additional parameters			
Heart rate (HR)		60-80	beat/min
Body surface area (BSA)	DuBois & Du Bois equation		m^2

Statistical analysis considerations

In **Paper I**, comparisons of post-operative survival rates between groups were performed with a log-rank (Mantel-Cox) test. A two-tailed p-value <0.05 was considered statistically significant. The patients were dichotomised according to their individual BCIS score to: Group 1, which comprised patients with no (grade 0) or moderate (grade 1) BCIS; and Group 2, which was constituted by patients with severe BCIS (grade 2 or grade 3). Univariate correlates for the development of severe BCIS, between the baseline and intra-operative characteristics, were tested using the unpaired *t*-test for continuous variables and the χ^2 test or Fisher's exact test for dichotomous data. Independent predictors of baseline and intra-operative variables for the development of severe BCIS were assessed using a step-wise multiple logistic regression. For each variable, the Odds Ratio (OR) and associated 95% confidence interval were calculated. Predictors with an OR <0.5 or >2.0 or a p-value <0.05 were eventually included in the step-wise logistic regression analysis. To evaluate the roles of BCIS and other independent predictors of 30-day mortality, univariate and binomial multivariate regression analyses were performed. Data are presented as OR values with the 95% confidence interval.

In **Papers II**, **III** and **IV**, alterations in PVRI formed the primary end-point. In **Paper II**, a power analysis based on previous studies that investigated changes in PVRI revealed that 14 patients were needed to detect a 30% change in PVRI after cementation and prosthesis insertion with α-value of 0.80 and β-value of 0.05. A power analysis based on the results of **Paper II** was performed for **Papers III** and **IV** and revealed that 11 patients were needed in each group to detect a 50% difference in the maximal increase in PVRI during the procedure with a standard deviation of 100. Intra-group changes during the procedure were determined using a one-way analysis of variance (ANOVA) for repeated measurements. Data obtained at sampling points: a) after

induction of anaesthesia and before surgery, and b) during surgery before cementation and insertion of the prosthesis stem, were pooled and considered as the control value. A two-way time *vs* group interaction ANOVA for repeated measurements was used in **Paper III** to evaluate differences between the cemented and un-cemented group. In **Paper IV**, a two-way time *vs* group analysis of covariance (ANCOVA) for repeated measurements was used. Data obtained at sampling points: a) after induction of anaesthesia and before surgery, and b) during surgery before cementation and insertion of the prosthesis, were pooled and considered as co-variates. Differences were considered as statistically significant at $p<0.05$. In this thesis, we used a Wilcoxon signed-rank test to evaluate the maximal change in pulmonary vascular resistance index (PVRI) in patients who were undergoing cemented hip arthroplasty (**Paper III**) or cemented hip hemiarthroplasty (**Paper II** and the saline group in **Paper IV**). Data obtained at sampling points: a) after the induction of anaesthesia and before surgery, and b) during surgery before cementation and insertion of the prosthesis, were pooled and considered as PVRImin. PVRImax was defined as the highest registered PVRI value after cementation and prosthesis insertion for each patient. Differences with p-values ≤ 0.05 were considered to be statistically significant. The Statistical Package for Social Sciences (IBM SPSS Statistics 25) was used for the statistical analyses.

Papers I-IV