Orthogeriatric Anaesthesia

-Studies on the bone cement implantation syndrome, risk prediction and intraoperative haemodynamics

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“When you can measure what you are speaking about, and express it in numbers, you know something about it; but when you cannot measure it, when you cannot express it in numbers, your knowledge is of a meagre and unsatisfactory kind.”

-Lord Kelvin

ABSTRACT

The bone cementation implantation syndrome (BCIS), as seen in orthopaedic patients, is characterised by intraoperative hypotension and hypoxia and loss of consciousness around the time of bone cementation. In a retrospective study, the incidence of and risk factors for the BCIS and its impact on mortality during cemented hemiarthroplasty for hip fracture were evaluated. Data were retrieved by an in-depth analysis of medical records of more than 1000 patients for patient characteristics and comorbidity. A follow-up study on a population operated without cement was then reviewed and compared with patients undergoing cemented hip arthroplasty in order to isolate the effects of bone cement use on perioperative haemodynamics and mortality. For the prognostication of 30-day mortality after hip fracture surgery, we attempted an external validation and performed a recalibration of the Nottingham Hip Fracture Score (NHFS) in a large cohort of Swedish patients. Finally, we performed a prospective study on systemic haemodynamics following the use of a fractionated low-dose continuous spinal anaesthesia (CSA) in a group of 15 hip fracture patients with a high-risk score and age, using invasive haemodynamic monitoring. This neuraxial technique is not commonly used but has the potential to cause less intraoperative haemodynamic aberrations.

The incidence of BCIS was 27%, with the more severe forms present in 7% of cases. Risk factors for severe BCIS were: chronic obstructive pulmonary disease, ASA grade III-IV risk, and medication with warfarin and diuretics. The incidence of hypoxia or and/or hypotension were higher in the cemented (28%) compared to the uncemented group (17%). The use of bone cement was an independent risk factor for one-year mortality. External validation of the NHFS failed in its present form. Following recalibration of the formula, we could perform an internal validation in a subset of our cohort. Fractionated low-dose CSA showed a minor/moderate fall in mean arterial pressure caused by a decrease in cardiac output, in turn caused by systemic venodilation and a fall in stroke volume.

In conclusion, BCIS is commonly seen in the elderly hip fracture population. Its occurrence is strongly associated to the use of bone cement and is a separate entity from anaesthesia related intraoperative hypotension. Failed external validation of the NHFS in our population implies a difficulty in applying externally developed risk prediction scores without validation. Fractionated low-dose CSA provided stable intraoperative haemodynamics. A decline in cardiac output due to reduced stroke volume was the defining trait of the minor fall in blood pressure after spinal anaesthesia.

Keywords: bone cement implantation syndrome, cemented hip hemiarthroplasty, bone cement, Nottingham hip fracture score, cardiac output monitoring, continuous spinal anaesthesia

SAMMANFATTNING PÅ SVENSKA

Höftfraktur hos äldre är en vanlig skada med stor påverkan på överlevnad och livskvalitet. I Sverige sker ca 18 000 höftfrakturer årligen där kvinnor drabbas 2–3 gånger oftare än män. Höftfraktur drabbar den äldre befolkningen, med en genomsnittsålder på 82 år. Frakturer uppstår vanligen efter fall i samma plan och är klassade som lågenergiskador. Benskörhet är en väsentlig bidragande faktor. Om lårhalsen är felställd, störs blodförsörjningen till höftkulan. För att återfå funktionen och undvika bencellsdöd, måste man vid operation ta bort höftkulan och lårhalsen och ersätta den med en halvprotes. Förankring av protesen i lårbenet görs antingen med bencement eller med en teknik utan cement. För att använda den cementfria tekniken krävs en bra benkvalité, vilket oftast inte är fallet.

Det så kallade bencement implantationssyndromet (BCIS) är ett känt fenomen som kan förekomma vid operationer där bencement används, till exempel vid proteskirurgi på grund av höftfrakturer. Vid BCIS ses en plötslig blodtryckssänkning, syresättning och i värsta fall medvetslöshet och död. Det definieras, enligt en rekommendation från 2009, som en akut försämring av cirkulation, andning eller medvetande i samband med cementering och graderas I-III. Olika förklaringsmodeller har framförts för hur detta fenomen uppstår, där den mest underbyggda teorin är att benmärg, fett och skelettfragment förs från märghålan till lungorna där det utlöses en

kärlsammandragning. Detta kan framkalla en akut högersidig hjärtsvikt, med i värsta fall död som följd.

Delarbete I undersöker förekomsten av BCIS och dess riskfaktorer genom en noggrann journalgranskning. Över 1000 patienter granskades under 3,5 år. Vi upptäckte att 7% av patienterna upplevde svår BCIS, vilket var mycket starkt kopplad till tidig död. Riskfaktorer för BCIS identifierades också.

I **delarbete II** undersökte vi förekomsten av blodtryckssänkning, syresättning, medvetslöshet och död hos patienter som opererats med en halvprotes efter en höftfraktur med eller utan bencementering. Resultaten visar att cement i sig ger större förekomst av detta fenomen och att användandet av bencement i sig ökar risken för död.

Att som äldre opereras för höftfraktur är inte riskfritt och flera olika studier visar att risken för att avlida inom 30 dagar efter operationen är 10%. Flera faktorer är förknippade med ökad dödlighet och en forskargrupp i Nottingham har utvecklat en enkel modell, Nottingham Hip Fracture Score (NHFS), som preoperativt anger risken för död inom 30 dagar. NHFS baseras på faktorer som är lättillgängliga vid inskrivning och ger 0–10 poäng beroende på t.ex. kön, ålder, blodvärde, boendesituation och vilka sjukdomar man har.

Delarbete III utvärderar giltigheten av NHFS för en svensk patientgrupp. Vi undersökte alla patienter opererade för en höftfraktur

vid Mölndals sjukhus under en 2 års period och noterade faktorerna som ingår i NHFS tillsammans med uppgifter om överlevnad. NHFS förmåga att förutspå risk för tidig död var låg. Denna förbättrades efter en justering av verktyget. Vi anser att NHFS har en plats i handläggningen av höftfrakturpatienter då den är enkel att använda och att data finns tillgängliga redan vid inskrivning.

Vår kunskap om hur hjärta/kärlsystemet beter sig i samband med ryggbedövning hos äldre är begränsat. I **delarbete IV** studerade vi cirkulationsförändringar vid kontinuerlig låg-dos spinal anestesi hos höftfrakturpatienter med hög ålder och hög samsjuklighet. Metoden används sällan men ger en stabil cirkulation i jfr med traditionell anestesiteknik som ofta leder till blodtrycksfall. Patienterna fick en tunn plastslang inlagd i ryggmärgskanalen. Därefter mättes blodtryck samt hjärtminutvolym mättes före och under ryggbedövningen. Denna anestesiteknik bibehåller en stabil cirkulation och att det lindriga blodtrycksfallet beror på en minskning i hjärtminutvolymen som i sin tur beror på ett minskat återflöde av blod till hjärtat.

Sammanfattningsvis har denna avhandling studerat förekomsten av BCIS, dess riskfaktorer och betydelse för dödlighet. BCIS är vanlig förekommande och är ansvarig för en majoritet av dödsfallen på operationsbordet. Att avgöra vilka patienter som löper störst risk för att avlida efter höftfraktur är svårt på individnivå. Fraktionerad kontinuerlig spinal anestesi är en teknik som ger en stabil cirkulation hos äldre, sjuka patienter som opereras för en höftfraktur.

LIST OF PAPERS

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

I. Olsen F, Kotyra M, Houltz E, Ricksten SE. **Bone cement implantation syndrome in cemented hemiarthroplasty for femoral neck fracture: incidence, risk factors, and effect on outcome.** Br J Anaesth 2014; 113:800-6

II. Fredrik Olsen, Mathias Hård Af Segerstad, Bengt Nellgård, Erik Houltz, Sven-Erik Ricksten **The role of bone cement for the development of intraoperative hypotension and hypoxia and its impact on mortality in hemiarthroplasty for femoral neck fractures**. Acta Orthopaedica 2020, 91:3, 293-298

III. Olsen F, Lundborg F, Kristiansson J, Hård af Segerstad M, Ricksten S-E, Nellgård B. **Validation of the Nottingham Hip Fracture Score (NHFS) for the prediction of 30-day mortality in a Swedish cohort of hip fractures.** Under review in Acta Anaesthesiologica Scandinavica

IV. Olsen F, Hård af Segerstad M, Dalla K, Ricksten SE, Nellgård B. **Fractional spinal anaesthesia and systemic haemodynamics in frail elderly hip fracture patients.** In manuscript

CONTENTS

ABBREVIATIONS

AHF = Acute Hip Fracture

AMI = Acute Myocardial Infarction

ASA = American Society of Anesthesiology

AUC = Area Under Curve

BCIS = Bone Cement Implantation Syndrome

BSA = Body Surface Area

CHF = Congestive Heart Failure

CI = Confidence Interval/Cardiac Index

CO = Cardiac Output

COPD = Chronic Obstructive Pulmonary Disease

CPR = Cardio Pulmonary Resuscitation

CVP = Central Venous Pressure

DAG = Directed Acyclic Graph

DOAC = Direct Oral Anticoagulants

ECMO = Extracorporal Membranous Oxygenation

FES = Fat Embolism Syndrome

GA = General Anaesthesia

HR = Hazard Ratio

MAP = Mean Arterial Pressure

MMTS = Mini Mental Test Score

NHFS = Nottingham Hip Fracture Score

NOF = Neck of Femur

OR = Odds Ratio

MACCE = Major Adverse Cardiac or Cerebral Event

MINS = Myocardial Injury after Non-cardiac Surgery

NE = Norepinephrine

NOF = Neck of Femur

PA = Pulmonary Artery

PAP = Pulmonary Artery Pressure

PDPH = Post Dural Puncture Headache

PMMA = Polymethyl Methacrylate

PVP = Peripheral Venous Pressure

PVR = Pulmonary Vascular Resistance

ROC = Receiver Operator Curve

SVRI = Systemic Vascular Resistance Index

TEE = Trans esophageal echocardiography

THA = Total Hip Arthroplasty

TKA = Total Knee Arthroplasty

TTE = Transthoracic Ultrasound

1 INTRODUCTION

1.1 HIP FRACTURE

Hip fracture is a common fracture type in the elderly. Sweden has one of the highest incidences per capita with 18000 cases annually.

Hip fracture is a typical osteoporotic or fragility fracture. A typical patient is 82 years old, with women outnumbering men by 2 to 1. The mean American Society of Anesthesiology (ASA) risk score is 3, on a scale from 1-6. A fall from standing position to the floor, i.e. a low-energy trauma by definition, is the most common mechanism of injury.[1–3] This patient group has normally a number of medical comorbidities and the complexity seems to increase over time.[4] Early surgical repair is associated with reduced morbidity and mortality following surgery.[5,6] After surgery, one third of patients require ongoing community support after discharge from hospital.[6,7] The combination of an aging patient group with pre-existing chronic diseases in need of emergency surgery poses a challenge for those involved in their care. 30-day mortality following hip fracture surgery is reported in the 5-10% range.[7–13] Multidisciplinary care, including geriatric co-management pre- and post-surgery, is associated with a 20% relative reduction of 30-day mortality as shown in a large German study.[13] Emergency laparotomy, which is recognized as an extremely dangerous procedure, has a similar 30-day mortality rate as hip fracture surgery.[14,15]

Hip fractures vary depending on the location of the fracture in the proximal femur. Neck of femur (NOF) fractures are located in the anatomical neck of the femur and are referred to as cervical.[16] More distal fractures are called trochanteric or sub-trochanteric fractures. NOF and trochanteric fractures are normally equally distributed in frequency. Even more distal fractures are denoted as femoral shaft fractures. They constitute another entity, as femoral shaft fractures are often caused by high-energy trauma and are beyond the scope of this work.

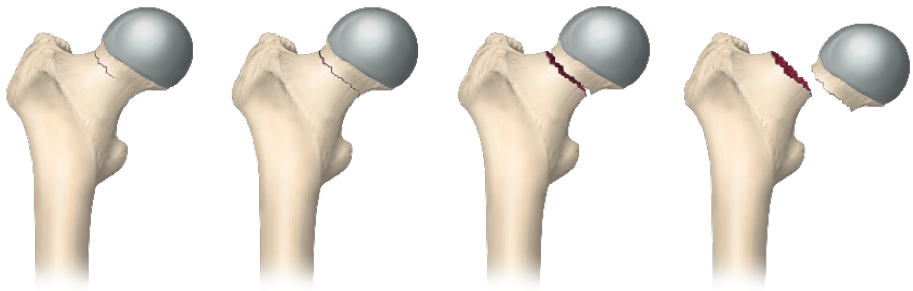

Figure 1 Garden classification I, II, III and IV

Neck of femur fractures are further classified by the Garden system.[17,18] There are four grades, I-IV, implying grades of dislocation or impaction on frontal x-rays (figure 1). Garden grades III and IV imply dislocation so great that blood supply to the head of femur is compromised.[17,18] This is because the femoral head is supplied with blood from the inferior aspect and not through the ligamentum teres.[19]

1.2 BONE CEMENT

Bone cement's chemical name is polymethyl methacrylate (PMMA).[20,21] It is more commonly known as Plexiglass, Perspex or

Lucite.[21] It was discovered in 1933 by the German chemist Dr. Otto Röhm.[20] The substance was useful due to its optical properties and shatter resistance.[20] Further advances in the curing of PMMA allowed for curing in room temperature. Bone cement was first adopted for dentistry in fixtures and is referred to as dental acrylic.

In a field hospital during the second world war, an English ophthalmologist, Dr Harold Ridley, noticed that Hurricane fighter-pilots with plexiglass splinters in the eye, did not develop rejection or inflammation.[22,23] This led him to develop the intraocular lens, made of acrylics after the war. His insights paved the way for the use of acrylic materials in many other areas of medicine. Thus, it is utilized for

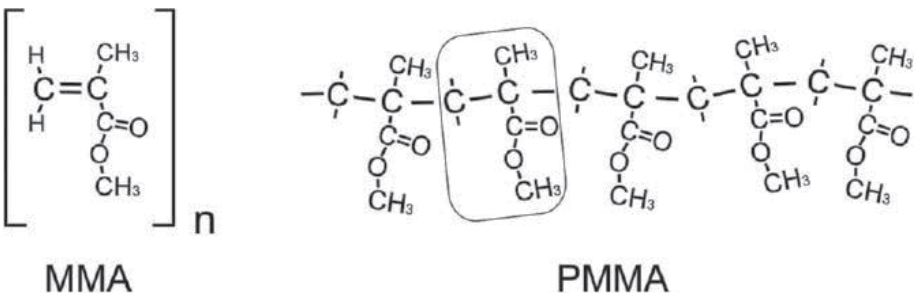

Figure 2 Structural formula of Bone Cement, as a monomer (left) and polymer (right)

cranial and maxillofacial reconstruction, in dentistry, in vertebroplasty after compression fractures, in skeletal cancer surgery to replace large skeletal excisions, in neurosurgery to reconstruct cranial defects and in arthroplasty mainly in shoulder, knee and hip joint replacement.[21]

In bone cement for arthroplasty, compounds are added to increase the radioopacity, usually barium or zirconium.[20,21] For revision surgery antibiotics are usually added, often gentamycin.[24] For increased

visibility in the surgical field, chlorophyll is added giving the cement a greenish tint.[20,21] In addition, there are small amounts of benzoyl-peroxide, which acts as an initiator and diMethyl para-toluidine (DPMT) acting as an accelerator. This composition allows the polymerization (chain-building) to take place at room temperature, creating monomer chains as polymer (figure 2). Even though the cement itself can reach temperatures of 85° Celsius, there is little energy transfer to the surrounding tissue due to the relatively thin layer of cement (5mm), large surface area and the high thermal capacity of the metal femoral shaft.[25] Being a well-vascularized area also contributes to rapid heat dissipation, reducing the risk of thermally induced complications in the patient.[21,25,26]

In arthroplasty, the use of bone cement was pioneered by Sir John Charnley. Starting in the late 1950s, he developed the surgical technique upon which modern arthroplasty surgery is based.[27,28] The material comes as a dry and wet component that is mixed prior to use in the operating theatre by vacuum mixing. This is commonly referred to as the third generation mixing technique. By mixing under vacuum the cement will have less air entrapped, thus increasing mechanical strength and homogeneity. Modern cementing also includes the use of a cement restrictor, pulsatile lavage and retrograde cement insertion with a cement gun.[29] By changing temperature, mixing and waiting time, it is possible to get the desired viscosity for the procedure at hand.

However, bone cement does not have many of the properties we associate with common cement. It has no adhesive properties in itself, but functions as a space filler in the space between the prosthesis and the femoral canal. Due to the uneven surface of both the prosthesis shaft and the inside lumen of the femur, the components interlock mechanically.[21,25,27]

1.3 HIP HEMIARTHROPLASTY

Cemented hemiarthroplasty is the preferred technique in the elderly, the frail and those with compromised blood supply to the femoral head. Uncemented total hip replacement or internal fixation is preferred in younger and more active patients.[16,30]

Several approaches are used for arthroplasty surgery of the hip. At our institution the anterolateral approach is the preferred method.[31,32] The patient is placed in the lateral position on a custom-built operating table and is supported on both sides, (front and back). The fracture side is placed superiorly and the leg is not fixated, (Figure 3). This position is necessary to allow for dislocation and reduction of the joint perioperatively.

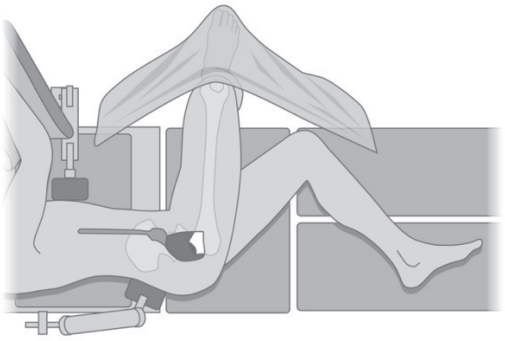

Figure 3 Patient positioning for hip hemiarthroplasty

After incision and dissection, the neck and head of the femur are removed and the femoral medullary canal is reamed to a uniform diameter, a cement restrictor is inserted and after pulsatile lavage, (vigorous washing with saline), the cavity is filled with cement. Modern cementation techniques imply the use of retrograde cementation. The cement gun is placed with its nozzle distal in the femoral cavity and the cement is filled in a distal to proximal direction under pressure, (Figure 4). Pressurization is needed to minimize the entrapment of air bubbles in the cement, limiting its strength after curing. In elderly patients undergoing fracture surgery, pressure is kept low as to minimize the risk of embolization. The femoral component of the prosthesis is then inserted, (Figure 4). Such force is normally applied that will extrude bone marrow from the exposed trochanter, the so-called “sweating trochanter” sign.[21,27] After insertion, the femur component is then held in place waiting for the hardening of the bone-cement. Then, the femoral head prosthesis is applied, the hemi-prosthesis is repositioned in the acetabulum and soft tissue is closed.

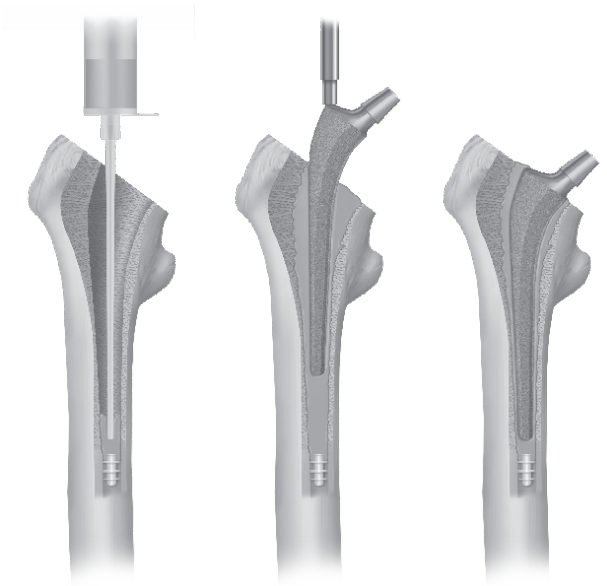

Figure 4 Retrograde cementation and insertion of the femoral component

In comparison, a non-cemented technique requires a press-fit of the femoral component. Therefore, this method requires a higher femur bone quality and is associated with a higher incidence of complications such as residual thigh pain and perioperative femur fractures.[33–37]

Cemented *vs.* uncemented hip hemiarthroplasty is an area of extensive research in orthopaedics and beyond the scope of this introduction.

1.5 BONE CEMENT IMPLANTATION SYNDROME (BCIS)

BCIS, being a rather unchartered field of research, has been a growing topic of scientific interest in the last few decades, see Figure 5. The syndrome as described and defined by Donaldson et al[38] from 2009, serves as the basis of our classification.

During cementation and insertion of the femoral component, the pressure generated forces the remaining organic material in the femoral canal into the venous circulation. After entering the pulmonary circulation, it is stipulated that it reacts with the endothelium where it may trigger a vasoconstrictory response. This sudden onset of pulmonary vasoconstriction increases the afterload of the right ventricle.[39–41] Elevated right ventricular afterload will decrease the performance of the right ventricle, causing a decreased filling of the left ventricle. This will, in turn, cause a reduction of cardiac output and arterial blood pressure, which will impair coronary perfusion to the right ventricle and thereby lower its contractile force. Thus, the right ventricle may be faced with an increased pressure simultaneous to a reduced ability to contract against an elevated pressure. This chain of events occurs in a majority of patients undergoing cemented procedures but remain mostly unnoted. However, in a subset of patients, the right ventricle is unable to handle the strain and an acute right sided ventricular failure occurs, possibly causing circulatory shock and, if severe enough, cardiovascular collapse.[42,43] This phenomenon is called BCIS and was defined as late

as in 2009 in a review article by AJ Donaldson.[38] The article graded the severity of BCIS in three grades 1–3, based on clinical presentation (table 1).

Grade	Clinical Manifestations of BCIS
1	Arterial oxygen saturation <94% Fall in systolic blood pressure 20%
2	Arterial oxygen saturation <88% Fall in systolic blood pressure 40% Unexpected loss of consciousness
3	Cardiovascular collapse requiring CPR

Table 1 Definitions of BCIS

Studies examining the BCIS incidence have found rates of 1.4-6.4% for grades 2 and 3. More recent studies showed a total incidence of 37% in a cohort of 208 patients.[44–46]

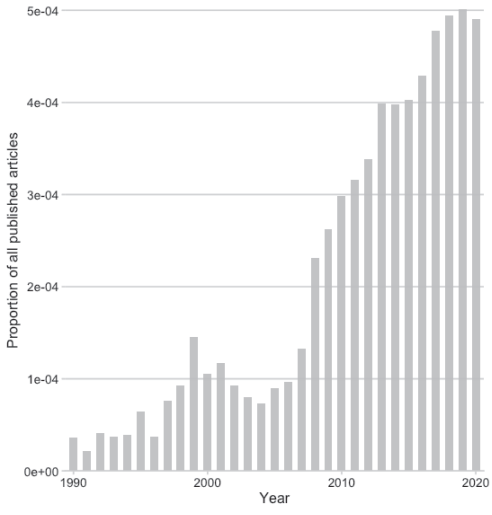

Figure 5 Research interest in BCIS the last 30 years

Cancer patients receiving cemented arthroplasty are recognized as especially susceptible to BCIS due to metastatic fractures, and subsequently have a very high incidence (75%) of BCIS [47] However, they are not treated with conventional hemiarthroplasty, but

rather with individualized longer stems and in some cases rather large amounts of bone cement to compensate for the excised bone.[48]

Perioperative instability as seen in BCIS was well described by Thomas et al[49] in 1971 in an investigation triggered by a typical presentation of an intraoperative grade 3 BCIS reaction with fatal outcome. They showed that a transient fall in blood pressure was commonly seen early after cementation, but with large individual differences. In their investigation they quote Sir John Charnley's personal communication with the authors "*there is commonly a small transient fall in blood pressure, which rarely lasts more than three minutes. This fall is most likely to occur if the surgeon inserts the cement very early, while the odour of the monomer is very strong or he continues mixing the cement until the very moment of inserting it instead of allowing time for monomer to evaporate from the surface.*"

In contrast to the emergency perioperative presentation of BCIS, hip fracture patients also have a 1% risk of fatal pulmonary embolism (PE) in the postoperative period.[50]

1.5.1 AETIOLOGY OF BCIS

Different aetiological models have been proposed to explain the relation between cemented arthroplasty and the cardiovascular collapse as described in BCIS.

The Monomer model: Sir John Charnley firmly believed in the "monomer model", where it was stipulated that the MMA monomer

itself had a direct chemical effect, inducing vasodilation peripherally through relaxation of smooth muscle cells.[49] This model was partially based on the fact that MMA is, in fact, toxic through direct contact with mucosal tissues such as the eyes and airways. The model has currently little support due to the fact that other surgeries involving larger amounts of bone cement, though without pressurization (craniofacial plastic surgery, percutaneous vertebroplasty and total knee replacement), do not elicit a clinical response like BCIS. One study showed a dose/response correlation between levels of soluble MMA injected in dogs and subsequent size and duration of hypotension.[51,52] Several studies subjecting animals to large concentrations of MMA monomer have failed to replicate the cardiovascular effect.[53] Further studies in dogs showed cardiovascular effects of MMA injected intravenously, but at concentrations 50-fold of what is measured in a human clinical setting.[54,55]

The Histamine mediated model: A study in 1991 tested the levels of histamine in blood samples taken perioperatively during elective cemented hip replacement surgery. Twenty patients received interventions with antihistamine medications and 20 patients served as controls without antihistamine medication. The control group had an increase in the levels of plasma histamine large enough to have clinical implication while the medicated group had significantly less histamine release.[56] Other studies have failed to replicate these findings, but the authors are open to the possibility that histamine release may play a part in the cardiovascular compromise associated with BCIS.[57,58]

The Complement activation model: Complement factors C3a and C5a are biomarkers of activation of the complement system. In a study from 1987, complement release was detected in blood samples during cemented but not in uncemented hip arthroplasty surgery. The authors further propose this release as a contributing factor inducing hemodynamic instability in BCIS.[59] In 1988 Dahl and colleagues published a study where they sampled blood perioperatively during cemented arthroplasty. Consumption of complement factors (C3 and C4) was detected as well as a distinct rise in the short-lived fibrinopeptide A, indicating intrapulmonary fibrinogen to fibrin conversion.[60] These findings have also been corroborated by Thordardottir et al in 2016.[61]

The Embolic model: More recent research pinpoints endothelial activation in the pulmonary vasculature and the release of thrombin and thromboplastin involved in the BCIS. Due to friction forces of the emboli on the wall of the pulmonary arterial vasculature, a release of endothelin-1 occurs.[62,63] This, in combination with a reflex vasoconstriction by smooth muscle cells triggers an abrupt rise in pulmonary vascular resistance (PVR).[64] This is evident as there is a mismatch between the degree of mechanical obstruction and the degree of hemodynamic detoriation.[62,65–67]

The effect on pulmonary haemodynamics has been shown in a study from our research group utilizing perioperative Swan-Ganz catheters.

Results demonstrate an increase of 10-15% in pulmonary arterial pressure (PAP) and of 45% in PVR.[39] These phenomena were temporally associated with cement application and prosthesis insertion as well as with negative changes in mean arterial pressure (MAP) through a lowered stroke volume index (SVI), thereby reducing cardiac output.[39,40] Further studies with invasive pulmonary hemodynamic monitoring confirm these findings and show that the elevated PA pressure remains significantly higher at least until postoperative day one, when invasive monitoring was terminated. These results were found in patients with elective bilateral total hip arthroplasties with a mean age of 61 and mean ASA grade of II.[68]

Studies utilizing trans-oesophageal echocardiography (TEE) as well as conventional trans-thoracic echocardiography have shown a "flurry" of emboli at the time of cementation and prosthesis insertion.[69–71] Small series of patients undergoing TEE during resuscitation for manifest BCIS grades 2 and 3 also consistently present with emboli.[44] Direct ultrasound of the inferior vena cava in a sheep model showed the presence of embolic matter at an intramedullary pressure of 50 mmHg, a level associated with manipulation in an unstable fracture.[72]

In a series of total hip replacement from 1973, blood samples from an pulmonary artery was analysed for the presence of fat particles. Samples were taken during both acetabular and femoral prosthesis insertion showing presence of fat particles in 25% and 75% of cases respectively.[73]

Other substances with known vasoconstrictory effects have been detected to be elevated after cemented procedures, like platelets release thromboxane A2, serotonin and platelet-derived growth factor (PDGF) upon activation.[62,74–79]

1.5.2 PRIMARY AND SECONDARY PREVENTION OF BCIS

A recommendation from the British Association of Anaesthetists entitled "Guideline for the management of hip fractures 2020"[80] emphasizes the role of multidisciplinary communication and the implementation of specific guidelines as laid out in "*Safety guideline: reducing the risk from cemented hemiarthroplasty for hip fracture 2015*".[81] This document recommends the following preventive steps.

- Identification of high-risk patients; increased age, cardiopulmonary disease, diuretic therapy and male sex
- Preparation of teams and roles in case of severe reaction
- Specific intra-operative roles; Surgeon informs the anaesthetist that cementation is imminent, thoroughly wash and dry femoral canal, retrograde cement application with cement gun, suction catheter and cement restrictor and avoidance of excessive pressurization in risk patients. Anaesthetist ensures adequate pre optimization, confirm that patient is ready for cementation, vigilance for signs of cardiorespiratory collapse e.g., fall in systolic BP or

fall in $ETCO_2$ in intubated patients, keep BP within 20% of preinduction value and have vasopressors prepared.

The primary prevention strategy of BCIS is dependent on which patho-physiological model one regards as valid, as several possible solutions have been proposed. Drilling a distal venting hole in the femur prior to cement insertion has been proposed and tested.[44,82–84] This does indeed lower the intramedullary pressure, but increases the risk of peri-operative fractures and suboptimal fixation of the femoral component.[33–35] Another method, that has been shown to reduce the embolic load measured by perioperative ultrasound, is aspiration through a cannula located in cancellous bone attached to a suction source during cementation.[70]

Further, normovolemia seems to mitigate hemodynamic instability during cementation as noted in a small study of 109 patients undergoing total knee arthroplasty in spinal anaesthesia.[85]

By lowering the viscosity of the cement, the peak intramedullary pressure is expected to be lower. This triggered a cadaveric study by Rothberg et al showing this by examining 10 pairs of cadaveric femurs with low and high viscosity cement. By measuring pressure, via sensors in intramedullary space, and performing mechanical tests to check for strength reduction, they failed to show any discernible difference.[86] Further, low molecular weight heparin has been proposed

as a prophylactic treatment with administration prior to surgery to reduce the effects of thrombin generation.[87]

The use of TEE-guided goal-directed hemodynamic therapy in an RCT of 90 patients has been tested without finding a reduction in the incidence of BCIS.[88] Prostacyclin (PGI_2) is a derivative of arachnoidonic acid, produced by endothelial tissues, more so in the pulmonary arteries *vs.* the pulmonary veins. PGI_2 inhibit platelet aggregation and enhance vasodilatation. By utilizing prostacyclin inhalation during cemented hemiarthroplasty in patients undergoing surgery for cemented hemiarthroplasty, our research group showed a significant reduction in pulmonary vasculature resistance index and pulmonary arterial pressure, by Swan-Ganz catheter monitoring, during cementation compared to placebo.[41] Furthermore, systemic vasodilators such as sildenafil have been shown to reduce embolic pulmonary load and cardiovascular effect in a sheep and a rat model of cemented vertebroplasty.[89,90]

In another study, Lamade et al, (1995), based on the histamine model, performed a RCT comparing histamine blocking agents to placebo in cemented hemiarthroplasty without finding any difference between groups in either outcomes or haemodynamics.[58]

Our routine is to administer high flow oxygen on a non-rebreathing mask and alerting the attending anaesthesiologist. Furthermore, we have an alertness to turn the patient from the lateral to the supine

position if needed. Secondary prevention relates to the management of a patient with manifest BCIS.

Extracorporeal membranous oxygenation (ECMO) in manifest BCIS has been proposed as a directed therapy, however the authors claim no experience with ECMO for this indication and the logistic issues and potential bleeding complications seem prohibitive.[91] There is, however, a published case report on an 80-year female who developed acute RV failure after cement implantation for a fractured hip. She was successfully treated with veno-arterial (VA) ECMO and continuous renal replacement therapy for 3 days, after which she recovered.[92]
Further, the use of "Lipid Rescue" with Intralipid administration has been proposed. References to animal studies and in vitro trials are made but not to human trials.[93]

Stellate ganglion block (SGB), an old technique to effectively block sympathetic transmission in the pulmonary vasculature, has been used as treatment for pulmonary embolism.[94] There have been animal and human studies of sympathetic block either with epidural catheter or SGB to alleviate pulmonary vasoconstriction in PE or in weaning from cardiopulmonary bypass.[95–97] There are not, to our knowledge, any literature supporting its use in manifest BCIS.

Experimental studies examining the possibility to reverse thromboxane-caused pulmonary artery vasoconstriction has been performed in rats. Researchers administered a selection of resolvins

(E1, D1 and D2) and found that especially resolvin E1 inhibited vasoconstriction caused by thromboxane.[98]

1.5.3 HISTOPATHOLOGICAL FINDINGS AFTER BCIS

There are few studies investigating histopathological findings post-mortem following BCIS. Those existing describe findings of bone marrow, fat, bone and MMA microparticles in the lungs and right ventricle of the heart (figures 6 and 7).[99–103] de Froidmont et al studied 6 patients who had died intraoperatively during cemented total hip arthroplasty, with all of them having massive fat embolism in the pulmonary vasculature.[100] Further, a study by Sevitt in 1972 correlated the finding of pulmonary fat embolism with cemented arthroplasty of the hip following fracture. The study stipulated that the rise in intramedullary pressure forced fat into the venous circulation.[101] The findings are dominated by fat embolism in the lungs but also to some extent the kidneys and brain were affected.[101] Neri et al reported an illustrative case describing fat embolism syndrome (FES), but with all the hallmarks of BCIS.[102] The patient in question received a cemented arthroplasty for NOF after trauma. During insertion of the femoral component in the bone cement filled femur, the patient went into shock. TEE demonstrated several echogenic bodies in the right atrium and ventricle interpreted as fat embolism from the site of injury. An initial improvement was achieved, but the patient died from respiratory failure 4 hours post-surgery. A post mortem was performed and platelet aggregates and fat emboli were found. In contrast, no mention

of bone cement in the pulmonary vasculature was mentioned or implied.

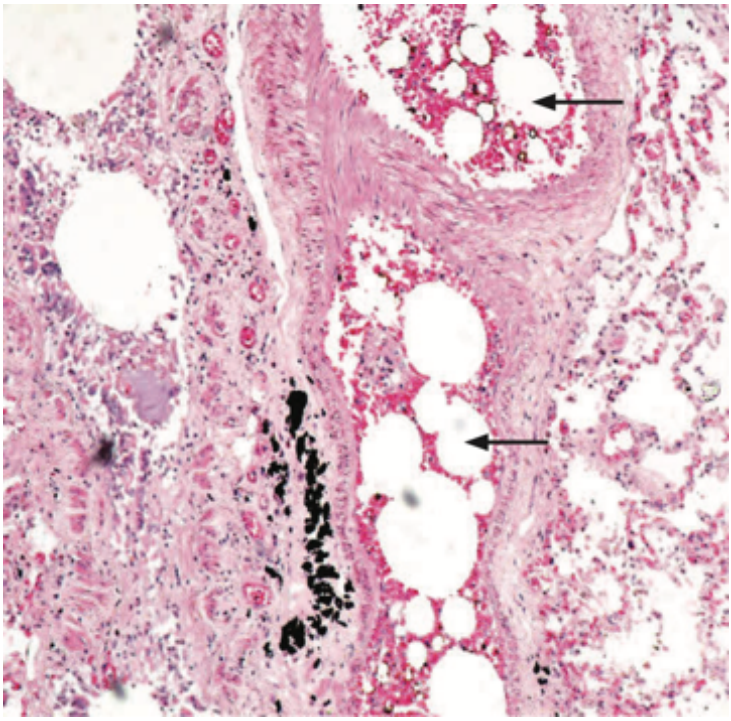

Figure 6 Right ventricle showing fat globules (arrows) in blood vessels (from Razuin et al, 2013, with permission)

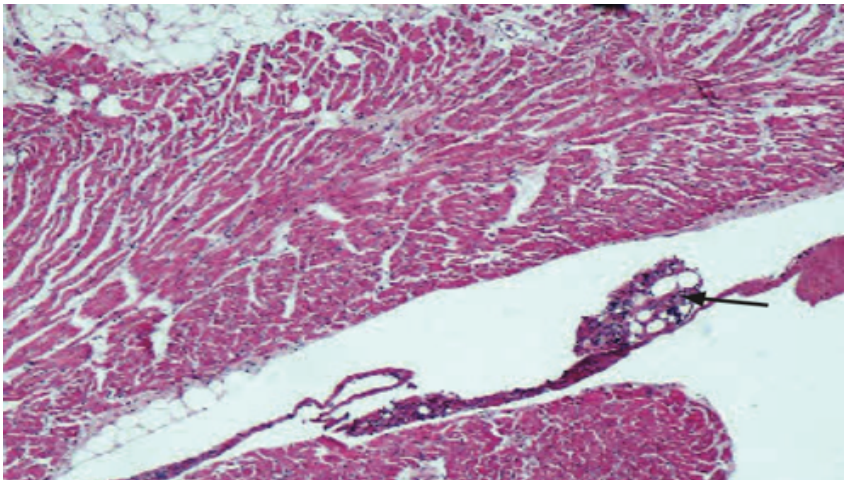

Figure 7 Lung tissue showing fat globules in blood vessels (from Razuin et al, 2013, with permission)

1.6 NOTTINGHAM HIP FRACTURE SCORE

Nottingham Hip Fracture Score (NHFS) is a risk stratification tool specifically designed for the hip fracture population. It was first developed in 2008[10] and was revised in 2012 and 2016.[10,11,104] The score is based on multivariate regression analysis, from the results of univariate regression on a pool of almost 5000 patients. Factors included in NHFS are weighed based on the result from the initial regression.

From intercept and beta values a formula with the NHFS score as an independent variable and risk of 30-day mortality as the dependent variable according to the following formula has been developed.

$$\%risk = {}^{100}/_{1 + e^{(Intercept - (\beta * NHFS))}}$$

The revised formula from 2012 adjusted the intercept value to 5.012 and the β to 0.481, giving us the final formula below. The formula is represented graphically in figure 15.

$$\%risk = {}^{100}/_{1 + e^{(5.012 - (0.481 * NHFS))}}$$

A score from 0–10, (see below), is generated based on clinical and demographic data present upon admission as well as laboratory values, predicting 30-day-mortality after surgery, on a group level (table 2).

- Pre-existing comorbidities included in the NHFS are;[10]
  Cardiovascular disease: previous myocardial infarction, angina pectoris, atrial fibrillation, valvular heart disease and/or hypertension
- Cerebrovascular disease: Previous stroke or TIA

- Respiratory disease: Asthma, COPD, not current chest infection
- Renal disease, not isolated raised urea or creatinine
- Malignancy within the last 20 years, non-melanoma skin malignancy excluded.

Variable	Value	Score
Age	<66	0
	66-85	3
	>85	4
Sex	Male	1
Admission Hb	<10 g/dl (100g/l)	1
MMTS	>6 out of 10	1
Living in an institution	Yes	1
Number of comorbities	≥2	1
Malignancy	Yes	1

Table 2 Variables and scoring for NHFS, Hb=Haemoglobin, MMTS=Mini Mental Test Score

1.6.1 OTHER RISK PREDICTION SCORES USED FOR HIP FRACTURES

A large number of risk prediction tools for the use in the hip fracture population have been constructed and studied. Two variants occur, where the first use existing scores for a broader population and then validated in a hip fracture population and while the second have developed and validated scores in a hip fracture population. Some

score are complex and require comprehensive databases or time consuming coding, others are based on more easy to assess variables.[11,105]

Donati score, a scoring system based on age, ASA, urgency and severity of surgery. Cardiac surgery and caesarean delivery are excluded. Hip fracture is always urgent and is to be regarded as moderate severity of surgical trauma. However, for the hip fracture population, it is in effect based on ASA and age.[106]

Almelo score, an adaptation of NHFS from a research team in the Netherlands. The MMTS criteria is simplified to cognitive impairment yes/no. In addition, the Parker mobility Score and ASA grades are included. The maximum scores from Parker mobility score and ASA of 4 is 9, compared to the total of 10 from the NHFS part. The Almelo score is weighted heavily on high ASA and reduced mobility. The score is developed with the same method as NHFS with multivariate logistic regression. The Almelo score shows an AUC of 0.82 in the original paper.[107]

Brabant score, another risk prediction score from the Netherlands with similar methodology as NHFS and the Almelo score. They have opted to keep age and haemoglobin levels as numeric variables. Other factors included are gender, institutionalization, presence of COPD, diabetes or malignancy. The Brabant score comes in two varieties, one for prediction of 30-day mortality and one for 1-year mortality. The

latter includes cognitive impairment and renal failure in the prediction model. For the BHFS-30 (Brabant Hip Fracture Score for 30-day mortality) model the original study showed an AUC of 0.71.[108]

Surgical Outcome Risk Tool (SORT), a score developed in the United Kingdom, based on the same methodology as seen prior with the use of logistic regression to selected and weighted risk factors in the cohort. The development cohort of over 11000 patients consisted of patients undergoing a wide variety of surgeries. SORT consists of the following variables; ASA score, urgency of surgery, high risk surgery, cancer and age. The initial study reported an AUC in their test dataset of 0.91.[109] A comparison of NHFS and SORT in a hip fracture population yielded an AUC of 0.70.

Physiological and Operative Severity Score for enUmeration of Mortality and morbidity. **(POSSUM)** A score consisting of six operative factors and twelve physiological factors. POSSUM has been studied in a Swedish hip fracture population, with an AUC of 0.62 indicating moderate prognostic performance.[110,111]

Elixhauser Comorbidity Measure (ECM) is a score based on the presence of 30 conditions defined by the original study in 2008 for a range of outcomes in a general surgery population. The model was designed for use in administrative databases and not for prediction on an individual basis.[112] The ECM has been trialled in a hip fracture population showing an AUC of 0.70.[113]

Charlson Comorbidity Index (CCI) is a widely used score that originally was used as a predictor of 1-year mortality in patients admitted to a medical ward. The score is based on 19 weighted variables where only pre-existing diagnosis are included and no physiological or functional scores.[114] It has been tested in hip fracture populations with reported OR 2.6[115] and another study reported an AUC of 0.72 in a large Australian study.[116]

Equations for estimation of physiologic ability and surgical stress, (E-PASS) A score involving preoperative risk factors as well as intraoperative factors such as blood loss and surgical duration.[117]

CEU17 is developed from the National hip fracture database in the United Kingdom. It is based on the following variables; ASA grade, sex, source of admission, walking ability, and fracture type. The study group reported an AUC of 0.75 with good calibration.[118]

Modified Frailty Index (mFI), is based on the more known Frailty Index from the Canadian Study of Health and Aging.[119] The original Frailty index is comprised of 70 variables, whereas mFI comes in an 11-variant and 5-variant edition. The 11-variant edition was a result of the authors choosing variables to include based on potential influence on mortality, but also on the availability of robust data. All variables were categorized. No measures of compromised physiology were included. The AUC for one-year mortality was 0.74 in the original

study.[120] The mFI with 5 variables assesses diabetes mellitus, CHF, COPD or current pneumonia, hypertension under treatment and non-independent functional status. The original study does not report AUC for mFI-5 but report a OR of 1.337 per point increase.[121]

Sernbo score. Originally developed to grade patients in a study comparing internal fixation to hemiarthroplasty. The score consists of 4 variables; age, habitat, walking aids and mental status, all dichotomized. No details are given regarding how these variables were selected. Other studies have reported an AUC of 0.71[122] and 0.69 in a Swedish registry-based study for one-year mortality.[123]

1.8 INTRAOPERATIVE HYPOTENSION IN HIP FRACTURE SURGERY

A fall in blood pressure during hip fracture repair surgery is common with a prevalence ranging from 22% - 89%.[124] Several definitions as to what constitutes intra-operative hypotension (IOH) exist; either as a relative decrease *vs.* baseline value or an absolute decrease. If using relative change, 20-30% reduction of either systolic or mean arterial pressure is used. In absolute terms both systolic and mean pressures are used as well, with cut-off values of 100-90 mmHg for systolic pressure or values from 55 to 70 mmHg for MAP. From the grading of BCIS by Donaldson et al, a relative reduction of systolic pressure is used to define the phenomenon.[38] IOH also includes cumulative duration of hypotension either as absolute or relative change from baseline.[125] A surrogate factor for IOH is the amount of vasoactive drugs required to maintain normotension, as described by Kristiansson et al.[126]

Studies correlating IOH to postoperative mortality and/or morbidity show a strong association between the two.[125–129] Common post-operative morbidities closely linked to IOH is myocardial injury after non-cardiac surgery (MINS), delirium and kidney injury.[126,127,130,131]
IOH can be related to anaesthetic management but may also be an effect of surgery as volume depletion, vessel clamping, tourniquet release or BCIS. Large registry based studies based on the availability of electronically documented haemodynamic variables has enabled researchers to associate both occurrence and duration of both relative

and absolute changes in blood pressure.[127] In a systematic review from 2018, Wesselink et al, a MAP under 80 mmHg for more than 10 minutes seemed to be associated with increased risk of organ injury.[128]

Bone cement implantation syndrome is specific cause of intraoperative hypotension, derived from the coupling of pulmonary and central haemodynamics. Invasive haemodynamic studies have established a causal relationship between cementation and a distinct increase in pulmonary arterial pressure due to an increase of pulmonary vascular resistance.[39] Elevated PVR results in a ventilation/perfusion (V/Q) mismatch, leading to acute hypoxaemia.[132] As the right ventricle blood flow is hindered by the increase of PVR, its thin walls will dilate. A dilated right ventricle will obstruct left ventricle filling. Reduced left ventricle filling invariably leads to a fall in cardiac output and systemic hypotension.[133]

1.9 ASSESSMENT OF INTRAOPERATIVE CARDIAC OUTPUT BY ARTERIAL WAVEFORM ANALYSIS

The extrapolation of traditional invasive hemodynamic parameters from arterial waveform analysis is a growing field in hemodynamic monitoring. Most methods rely on some kind of initial calibration by thermodilution, where cold saline is injected in a central vein and a temperature drop is recorded on the arterial side of the circulation. The integral temperature change over time curve is then used to extrapolate cardiac output (CO). Systemic (SVRI) or pulmonary vascular

resistance index (PVRI) are then calculated by standard formulas. At calibration, the arterial waveform is used as a baseline and both the integral/area under the curve and the waveform is used to track changes in the parameters. Thermodilution requires a central venous access not otherwise indicated in our patient group.

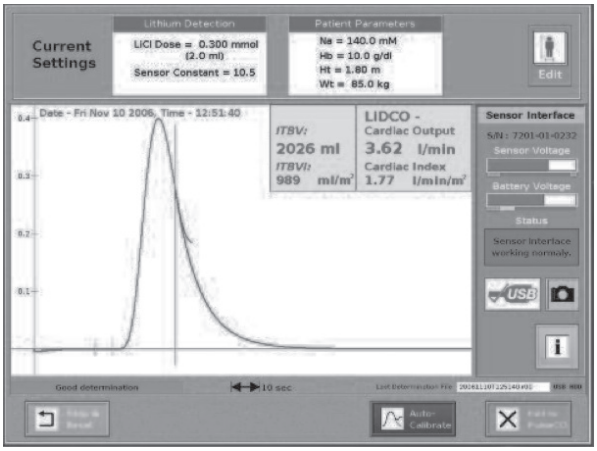

Figure 8 Calibration of the LiDCOplus system (LiDCO™)

Instead of thermodilution, a chemical calibration with lithium can be used. This technique was first described in 1993 by Linton et al.[134] who by measuring dilution of Lithium over time determined CO based on the Stewart-Hamilton principles.[135]

$$Flow = C_0V_0 / \int C(t)\mathrm{d}t$$

The C_0V_0 represents concentration and volume of the injectate. The denominator is the integral of concentration over time of the indicator giving us an area under the curve (AUC).

CO monitoring is based on two stages where the calibration with a lithium bolus is subsequently followed by a pulse contour analysis.[136] Thus, a bolus of lithium chloride 0.3mmol is injected in a peripheral vein(figures 8 and 9). A lithium sensor is attached to an indwelling arterial catheter (usually in the radial artery) and through a peristaltic pump, blood is then aspirated at a fixed rate from the artery. An ion-selective membrane senses Li concentration through voltage change. A correction for levels of plasma Na concentration is done and CO is determined through the following adaption of the Stewart-Hamilton formula.[134,136,137]

$$CO = Lithium\ dose(mmol)/Area\ x\ (1 - PVC)$$

Lithium is distributed solely in plasma at the time frame of calibration. Packed cell volume (PVC) is calculated from the patient's haemoglobin level prior to calibration by dividing the level in g/dL with a factor of 34.

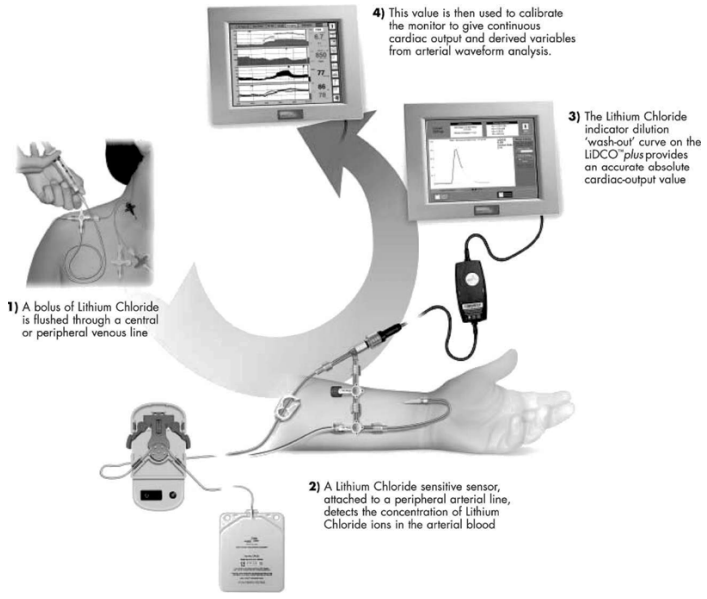

Figure 9 Schematics of the lithium bolus calibration system in LiDCOPlus (LiDCO™)

The LiDCO® system utilized, in paper IV, delivers CO based on arterial waveform analysis after calibration. The system also registers mean arterial blood pressure (MAP) and heart rate (HR) by the formula below, whereas systemic vascular resistance (SVR) is calculated. The algorithm assumes a central venous pressure (CVP) of 7 mmHg unless another value is given. The constant of 80 is to convert the value from mmHg/l/min (Woods Units) to a metric variable; dynes/sec/cm^{-5}.

$$SVR = {}^{MAP - CVP}/_{CO} \; x \; 80$$

By further utilizing the calculated CO we can estimate the stroke volume (SV) based on the formula.

$$SV = {}^{HR}/_{CO}$$

SV, SVR and CO are often indexed by using the body surface area (BSA) of the patient and are referred to as cardiac index (CI), stroke volume index (SVI) and systemic vascular resistance index (SVRI). Several formulas exist for the calculation of BSA based on patient weight and height. The formula incorporated in the LiDCO system is by du Bois and du Bois, also used by us throughout the study.[138]

In our study we chose to use lithium dilution to calibrate the arterial waveform analysis. This method is clinically established and does not require a central venous catheter and allows us to calibrate the waveform analysis and monitor CO and SVR in real-time. [139]

The algorithms translating arterial waveform to cardiac output are proprietary. Lithium dilution and its subsequent waveform analysis is a product of LiDCO and has been validated in several studies.[140] A monitoring setup for study use is shown in figure 10.

Figure 10 Monitoring using the LiDCOPlus system in Paper IV

1.10 CONTINUOUS SPINAL ANAESTHESIA

The predominant method of anaesthesia in Sweden for hip fracture surgery is by tradition a single shot spinal anaesthesia with isobaric bupivacaine and a fast-acting opioid.[7] However, several studies have not shown any significant difference in mortality between spinal- and general anaesthesia in these patients.[141,142]

Continuous spinal anaesthesia (CSA) was first described in 1907 by the British surgeon Henry Dean.[143] Initially the technique relied on the spinal needle left in place during surgery, with all the possible mechanical complications that entailed. Touhy, giving name to the famous epidural needle, introduced a thin urethral catheter in the

intrathecal space by way of a Huber-tipped needle.[144] The practice of CSA earned notoriety due to complications with caudal equina syndrome[145], leading to banning its use in non-research settings by the FDA in the USA.[144] Better understanding of the effects of local anaesthetic toxicity in the intrathecal space and the use of more delicate microcatheters has led to resurgence of CSA use.[144] Thus, indwelling spinal catheters are part of the arsenal in treating chronic pain and lower body spasticity in patients with neurological injury. In the perioperative setting it is mostly used for labour analgesia in the case of an accidental dural puncture and for pain relief in expectant mothers with severe heart disease.[146] In orthopaedic surgery the most common indication is anaesthesia for lower extremity fractures in patients with severe heart disease, commonly aortic stenosis.[147]

CSA allows a more direct control of the spinal block, minimizing risk for hemodynamic deterioration in a group of patients with limited reserves. Several studies have shown a lower incidence and duration of perioperative hypotension using CSA compared to a single shot spinal anaesthesia.[148]

Complications of CSA have decreased and the incidence of post dural puncture headache (PDPH) is between 1 and 2% as described in a CSA-review from 2017. The authors also deemed the risk of neurological and haemorrhage complications as comparable to single shot spinal and epidural anaesthesia.[149]

Hypotension following spinal anaesthesia can originate from a reduction either in CI or SVRI. The traditional belief is that the spinal anaesthesia blocks the sympathetic outflow causing a peripheral vasodilation, resulting in a fall in SVRI inducing hypotension.[150–152] Contrary, other studies claim that hypotension is mainly the result of a fall in CI through a decrease in SVI.[153–155]

Undoubtedly, there is an association between higher doses of intrathecal anaesthetics and IOH.[156] An indwelling spinal catheter allows for the incremental dosing of, in our case, bupivacaine. Another advantage of CSA is that a failure of a single shot spinal anaesthesia either leads to termination of surgery or an unplanned perioperative conversion to general anaesthesia (GA). In order to minimize haemoynamic changes as small as possible, doses of bupivacaine are titrated, achieved by evaluating the level of anaesthesia by pin-prick or altered sense of cold. A cleverly designed dose-response study by Szucs et al (2015) concluded that a dose of 0,4 ml of 0,5% isobaric bupivacaine (2 mg) provided adequate surgical anaesthesia in elderly hip fracture patients.[157] Another small study compared 4 mg and 10mg bupivacaine in a single shot spinal for hip fracture surgery, where the group with the lower dose had satisfactory anaesthesia but with significantly reduced need for blood pressure support.[158] Based on these studies we can assume that the required dose of bupivacaine is probably lower than expected, and an indwelling catheter gives us the option of starting low and titrating the dose to the desired effect.

2 AIMS OF THE THESIS

The aims of this thesis were;

- To assess the incidence and risk factors for the development of BCIS and its impact on mortality in an unselected population undergoing cemented hemiarthroplasty?

- To evaluate whether the use of bone cement itself is an independent risk factor for mortality and for the development of intraoperative hypotension and hypoxia in hip fracture surgery.

- To evaluate whether the Nottingham Hip Fracture Score can be externally validated and used as a predictor of postoperative 30-day mortality in a Swedish hip fracture population?

- To measure changes in systemic haemodynamics during titrated continuous spinal anaesthesia in elderly hip fracture patients.

3 PATIENTS AND METHODS

3.1 PAPER I

Paper I is a retrospective study of all cemented hemiarthroplasty operations performed in the period from January 2008 through June 2011 at SU/Mölndal Hospital. All patient charts were reviewed and the grade of BCIS was determined from perioperative journal and journal documentation. The incidence of BCIS is presented as descriptive statistics. We went on to elucidate the effect of increasing grades of BCIS on mortality. In order to differentiate grades of BCIS the population was divided first in groups according to their grade of BCIS and thereafter we dichotomized grades 0 and I into one group and groups II and III into another.

Mortality was compared using the Kaplan-Meier method. Predisposing factors leading both to death within 30 days and development of BCIS grades II-III were calculated using univariate and multivariate analysis. Differences in mortality between BCIS groups were determined with the Mantel-Cox (log-rank) method. The univariate and binomial multivariate analysis gave us odds-ratios for the associated factors for both the occurrence of BCIS grades 2 and 3 and 30-day mortality.

3.2 PAPER II

Paper II included the original population with cemented hemiarthroplasties from **Paper I** and compared it to a population in another hospital where they exclusively operated hemiarthroplasties with the uncemented technique. This enabled us to collect data based on the same criteria as **Paper I** and compared the incidence of the hemodynamic and oxygenation changes as described by Donaldson et al.[38], to assess whether bone cement itself is an independent predictor for intraoperative hypotension or hypoxia.

In **Paper II** we used the Cox regression model to adjust for differences in patient demographics and in order to allow for the isolation of the effects of cementation itself. The factors included in the Cox regression was partly based on univariate analysis for 1-year mortality and partly on known risk factors gathered from the available literature. The variables were assessed for inclusion using directed acyclic graphs (DAG) to identify mediators. Outcome was the adjusted Hazard Ratio (HR) and E-value. Even after adjusting for our selected confounders there was still the possibility of residual confounders. E-value is a statistical test for quantifying the size of unknown/unmeasured confounders, the test quantifies the size of an unknown HR needed to shift our outcome measure under our level of significance.[159]

3.3 PAPER III

In this study we collected data on all patients operated for hip fracture with any technique during 2015 and 2016 at Mölndal Hospital.

A rigorous data collection process gave us all necessary variables needed to calculate the NHFS for all patients. This was then analysed with respects to 30-day mortality. Discrimination was assessed by calculation of the C-statistic. For comparison, the discriminatory effect of ASA was also calculated.

Calibration was assessed by calculating the rate of 30-day mortality, observed in our entire cohort, stratified by NHFS. Comparing these rates to the predicted 30-day mortality rate based on Moppett et al[104] formula from 2012, gave us a ratio of observed vs predicted rates. Goodness-of-fit is also evaluated with a p-value for the likelihood ratio of miscalibration and presented graphically with a calibration belt.[160]

Finally, we split the cohort into a training and testing dataset (70/30). In the training set we performed the same binomial regression as the original authors in 2008 and 2012 and calculated our own formula for converting NHFS to a percentage risk for 30-day mortality. A new calibration was performed on the test set, with a comparison of observed vs. expected rates of 30-day mortality based on the recalibrated formula.

3.4 PAPER IV

Paper IV is a prospective exploratory study where we enrolled 15 patients, all ASA grades 2-4, scheduled for emergency hip fracture repair surgery. After informed consent, the patients were, in addition to continuous arterial pressure monitoring, also attached to the LIDCOplus system. This gave us data on CI, SVI and SVRI after calibration. Patients were managed intraoperatively according to a fixed protocol based on clinical guidelines regarding BP limits. Thus, maintenance of MAP >65 mmHg was managed by norepinephrine infusions if needed. Anaesthesia was maintained with an indwelling spinal catheter dosed with 1.5mg/ml isobaric bupivacaine and 10μg/ml fentanyl in 1.5 ml aliquots, (2.25mg isobaric bupivacaine and 15μg fentanyl per aliquot).

Prior to placing the patient in the lateral position without sedation or opioid treatment, all patients received a femoral inguinal compartment block (FIC) or ultrasound guided femoral block, in order to avoid drugs with potential cardio-depressant effects prior to monitoring.

Baseline characteristics were recorded prior to spinal catheter positioning. Subsequent registrations were recorded every 5 minutes following the first dose. A second dose of the bupivacaine/fentanyl mixture was administered after 25 min. Further dosing was given at the discretion of the anaesthetist responsible in the OR after study registration was completed at 45 min after initial dose.

The incidence of hypotension measured both in absolute terms as well as required dose of NE was recorded as well as peri-operative changes in CI, SVRI, SVI and HR.

4 RESULTS

4.1 PAPER I

A total of 1016 out of 1080 available patients were included in the final analysis based on inclusion criteria and availability of medical records. Patients were excluded if having incorrect classification of the performed surgery (n=30), lacking perioperative documentation (n=3) or having cemented hemiarthroplasty as a secondary intervention (n=31), most often after failed internal fixation.

We found that the 30-day mortality in the studied cohort was 9%, while mortality on the day of surgery and the first perioperative day was 2%. The 30-day mortality was strongly linked to BCIS-grades with rates of 9.3%, 35% and 88% in grades 1, 2 and 3 respectively.

Univariate Odds Ratio (OR) was then computed for a list of variables predicting 30-day mortality. Factors with $p>0.05$ were included in the multivariate analysis. The factors retaining significance are described in table 3.

Predictor	Adjusted OR	95% CI	*p*-value
Age over 85	2.58	1.54–4.32	<0.005
Male sex	2.15	1.31–3.54	0.02
Congestive heart failure	1.91	1.00–3.64	0.049
Dementia	2.81	1.67–4.74	<0.005
Diuretics	1.95	1.17–3.26	0.012
BCIS grades 2 or 3	16.35	8.84–30.24	<0.005

Table 3 Multivariate predictors for 30-day mortality

The incidences of BCIS by grades were as follows; all grades of BCIS were 28% and for the two severe grades (2 and 3) the incidence was 6,8% (table 4).

No BCIS	BCIS grade 1	BCIS grade 2	BCIS grade 3
72%	21%	5,1%	1,7%

Table 4 Relative incidence of BCIS

Comparing survival over time between the different grades of BCIS utilizing the Kaplan-Meier method is depicted in Figure 11.

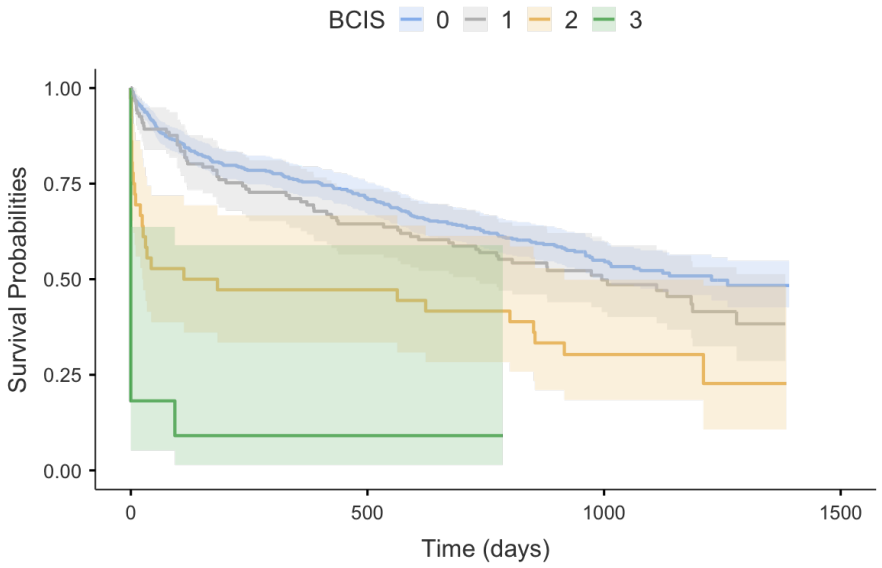

Figure 11 Kaplan-Meier plot of BCIS grades 0 to 3.

By combining BCIS grades 0 and 1 and grades 2 and 3 and plotting survival with the Kaplan-Meier curve we found a clear difference in mortality. This difference was confirmed using the Mantel-Cox (log-rank) method giving us a p-value < 0.005. The confidence intervals, not reported in the original paper, showed a clear discrimination in mortality between the two groups (figure 12).

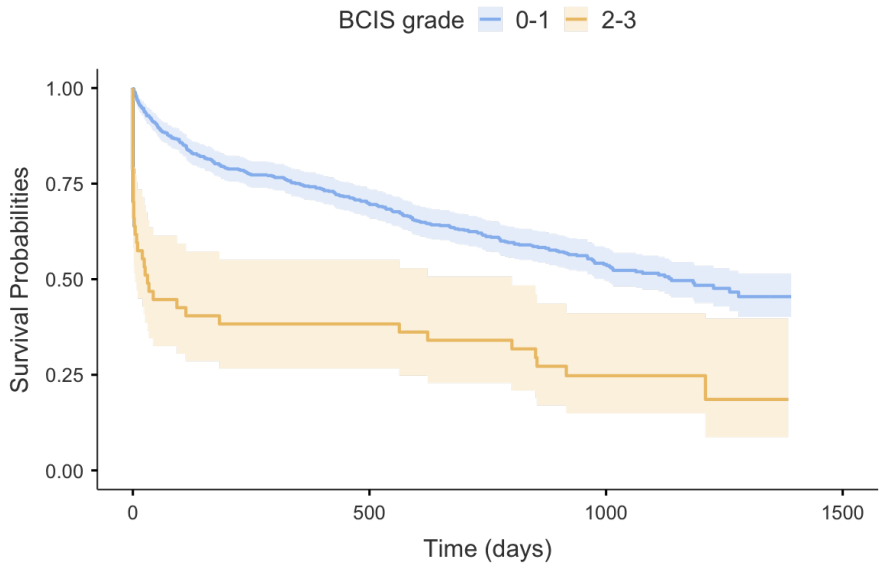

Figure 12 Kaplan-Meier plot of BCIS 0-1 and 2-3

By repeating the univariate and subsequent multivariate analysis using BCIS grades 2 or 3 as the endpoint, we found the following associated factors as described in the table below (table 5).

Predictor	Adjusted OR	95% CI	p-value
ASA III or IV	1,97	1,07-3,61	0,029
COPD	2,02	1,10-3,72	0,024
Diuretics	1,92	1,15-3,22	0,013
Warfarin	2,69	1,33-5,43	0,006

Table 5 Multivariate predictors for developing BCIS grade 2-3

4.2 PAPER II

This paper compared patients operated with cementation at Mölndal vs those without cement at Alingsås Hospitals. A total of 1159 patients were screened for inclusion. Totally, 64 patients were excluded as of errors in registration (n=30), lacking complete perioperative documentation (n=3) and having surgery for other indications than acute hip fracture (n=31). A total of 1095 patients were thus included in the final analysis.

The relative incidence of BCIS equivalent of hemodynamic instability was lower in the uncemented group with no patients having the severe grades 2 and 3. Detailed incidence of BCIS is presented in table 6.

Grade of hypotension/ hypoxia	**Uncemented (n=108)**	**Cemented (n=983)**
0	90 (83)	711 (72)
1	18 (17)	204 (21)
2	0 (0,0)	51 (5,2)
3	0 (0,0)	17 (1,7)

Table 6 Incidence of intraoperative hypotension/hypoxia and frequency (%). p=0,003

Unadjusted survival was also markedly lower in the uncemented group. This is clearly illustrated in the Kaplan-Meier curve below (figure 13).

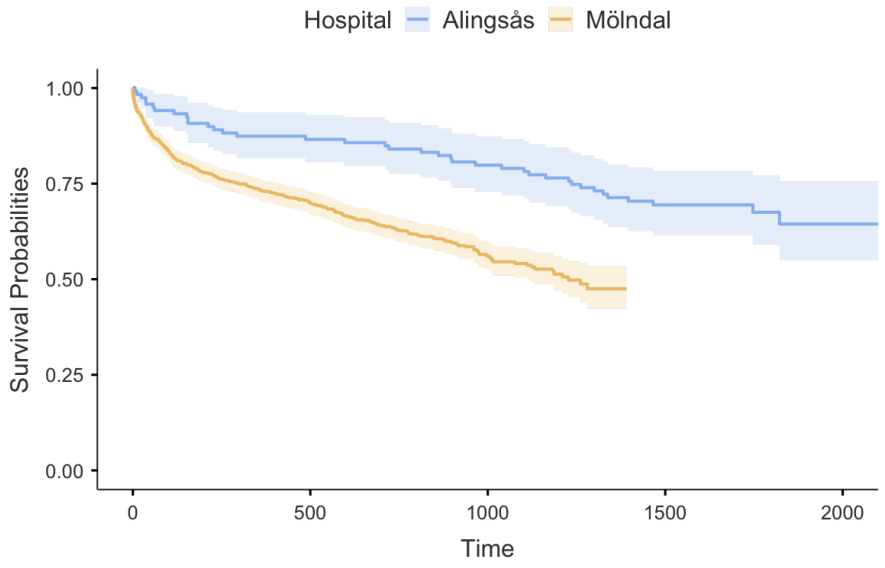

Figure 13 Kaplan-Meier curve describing cemented vs uncemented hemiarthroplasty survival

The uncemented group had lower age and ASA grades as well as a higher proportion of male patients. As shown in table 6, a large number of known risk factors for mortality after hip fractures are over-represented in the cemented group. The Cox regression used all these variables based on statistical significance in the univariate analysis, as well as factors known to be associated with poor outcome from the literature (table 7). The variable selection was also aided be the use of directed acyclic graph (DAG) method. The incidence of BCIS in the cemented group and its equivalent in the uncemented group also differed significantly. This was deemed as being a mediator factor and was not included in Cox regression model.

Table 7 Included factors in the final Cox regression model

Demographic	**Comorbidities**	**Medication**
Institutional living	Liver disease	Beta blockers
Reduced mobility	Diabetes	Diuretics
Male sex	Stroke	Antiplatelet drugs
Age	Peripheral vascular disease	Statine
	Arteriosclerosis	
	Myocardial infarction	
	Congestive heart failure	
	Cancer	
	Dementia	
	Arrythmia	
	Renal failure	
	Anaemia	

After adjusting for the above-mentioned confounders, bone cement use in itself showed a hazard ratio (HR) of 1.9 with a confidence interval of 1.3-2.7. We calculated the E-value to be 3.1 (95% CI 1.9-4.8) indicating the need for an unmeasured confounding factor to have an equal HR to the E value for the model to lose its significance regarding bone cement use.

4.3 PAPER III

Totally 1959 patients were screened for study enclosure and 1864 patients were finally included after excluding 95 patients due to duplicate surgery in the study period, revision surgery and age <60

years at time of surgery. NHFS showed a normal distribution in our dataset (figure 14). Demographics are presented in table 8.

Table 8 Demographic variables of the study cohort, stratified by survival status

	Dead at 30 days (N=213)	***Survivors at 30 days (N=1651)***	***Overall (N=1864)***
Age			
Median [Min, Max]	88.0 [63.0, 103]	84.0 [61.0, 105]	85.0 [61.0, 105]
Sex			
Male	74 (34.7%)	509 (30.8%)	583 (31.3%)
Female	139 (65.3%)	1142 (69.2%)	1281 (68.7%)
Haemoglobin (g/l)			
Mean (SD)	122 (17.3)	126 (16.6)	125 (16.7)
Dementia			
Yes	116 (54.5%)	439 (26.6%)	555 (29.8%)
No	93 (43.7%)	1189 (72.0%)	1282 (68.8%)
Institutional living			
No	148 (69.5%)	1192 (72.2%)	1340 (71.9%)
Yes	61 (28.6%)	438 (26.5%)	499 (26.8%)
Nr of comorbidities			
Median [Min, Max]	2.00 [0, 8.00]	1.00 [0, 7.00]	1.00 [0, 8.00]
Cancer			
Yes	33 (15.5%)	212 (12.8%)	245 (13.1%)
No	171 (80.3%)	1373 (83.2%)	1544 (82.8%)

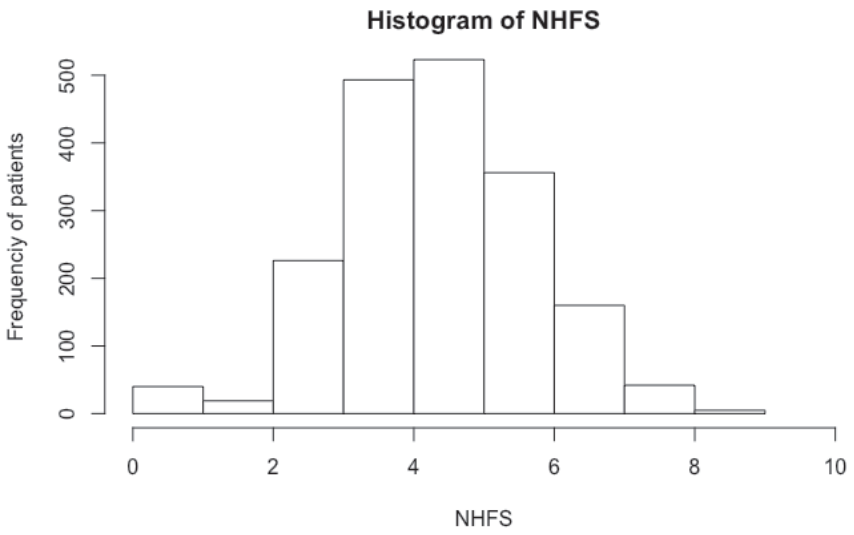

Figure 14 Histogram of NHFS in our total cohort

Overall, 30-day mortality rate was calculated to be 11.4% (213/1864). AUC for NHFS for the whole dataset was 0.64. For comparison AUC for ASA was 0.62 as shown in figure 15.

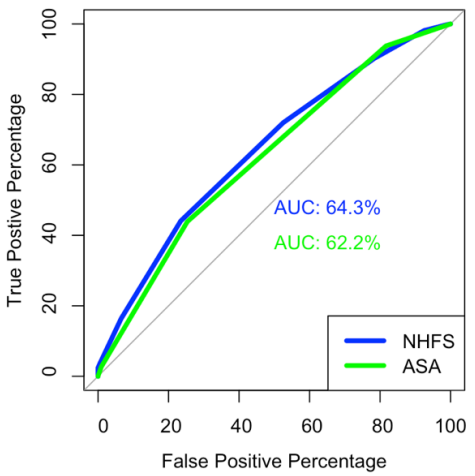

Figure 15 AUROC for NHFS and ASA for comparison.

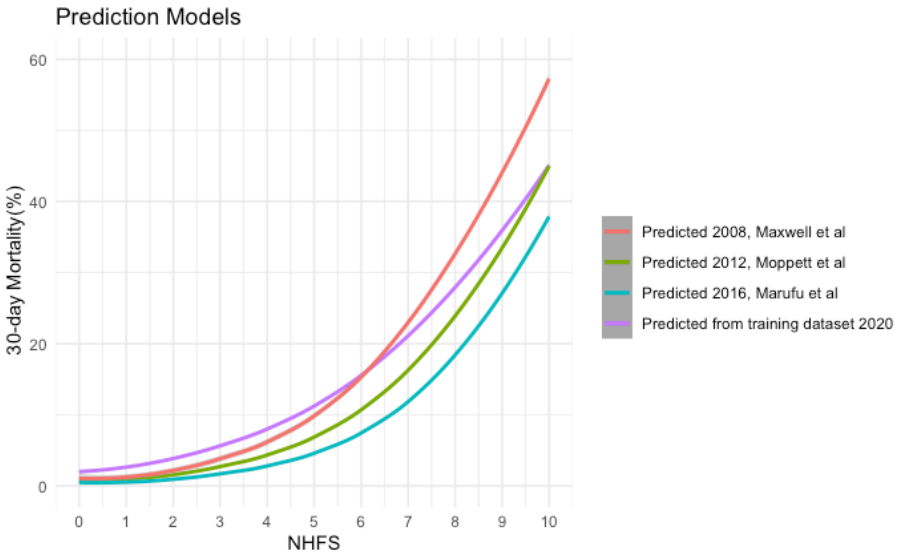

Figure 16 Estimated 30-day mortality rates by NHFS points. Prediction derived from the training dataset (70%).

Comparison of observed 30-day mortality in our cohort, with the predicted mortality from Moppett et al 2012 iteration, gave an observed vs. expected ratio of 1.37(figure 17A).

By a division of our cohort to a training (70%) and a test (30%) partition gave us the opportunity to replicate the process of translating NHFS score to a predicted 30-day mortality risk. The original NHFS article and the two subsequent recalibration's methodology were replicated, giving us the following formula (figure 16).

$$\%risk = {}^{100}/_{1 + e^{(4.07 - (0.39 * NHFS))}}$$

Applying the formula above to the remaining 30% of our dataset, (test or validation portion), and plotting the expected vs observed values, gave us figure 17B, with a O/E ratio of 0.97. Both the model from Moppett and our own model are visualized in figure 18A and 18B with the calibration belt method where the red line indicates perfect fit.

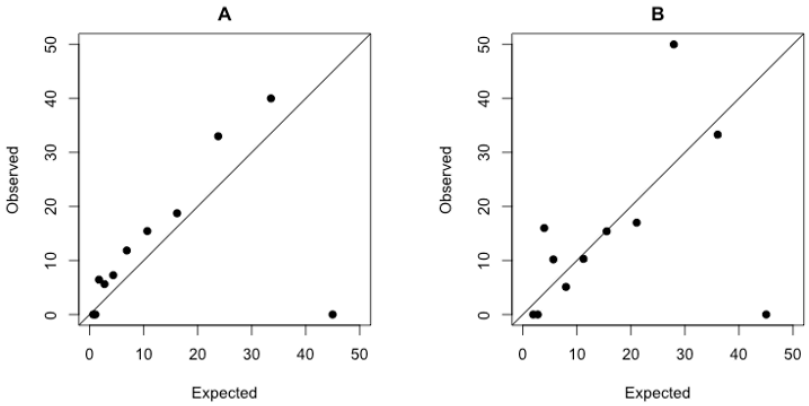

Figure 17 O/E plots of A) Moppett et al 2012 compared to our total cohort and B) Recalibrated formula compared to test cohort (30%). Each point representing one step of NHFS.

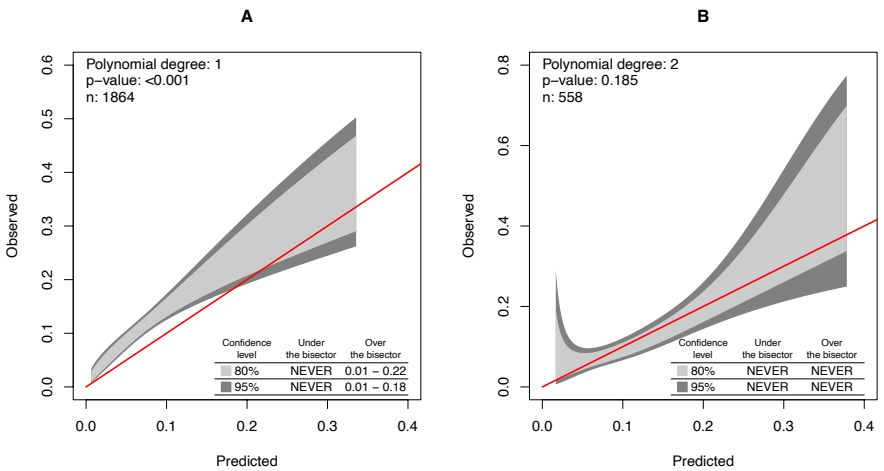

Figure 18 Calibration belt of A) Moppett et al 2012 formula compared to our total cohort and B) Recalibrated formula compared to the test cohort (30%)

4.4 PAPER IV

A total of 24 patients were assessed for inclusion. However, 2 patients withdrew consent, 2 patients were excluded as of logistical reasons, 2 patients were excluded due to agitated dementia and 3 patients had new neurological symptoms prior to surgery, leaving 15 patients to be included in the final analysis. Demographic variables are presented in table 9.

The study population had a median age of 89 years with a 4:1 ratio between female vs male. Hypertension and dementia were the dominating comorbidities with a prevalence of 73% and 47%, respectively. Median ASA score was 3 (range 2-4) and NHFS was 5 (range 4-7).

MAP, SVRI, CI SVI, HR and arterial elastance all had normal distribution according to Shapiro-Wilks test. A normal distribution allowed us to assess variability using the one-way repeated measures ANOVA test, revealing significant variance over time.

Table 9 Demographic summary of Paper IV, Age is presented as median(range), BSA, BMI and haemoglobin are presented as mean (SD)

	Overall (N=15)
Gender, n (%)	
Female	12 (80.0%)
Male	3 (20.0%)
Age, (y)	89.0 (69-94)
ASA, n (%)	
2	4 (26.7%)
3	10 (66.7%)
4	1 (6.7%)
NHFS, n (%)	
4	6 (40.0%)
5	3 (20.0%)
6	4 (26.7%)
7	2 (13.3%)
Body mass index (kg/m^2)	22.0 (3.71)
Body surface area (m^2)	1.64 (0.133)
Serum haemoglobin (g/L)	113 (20.4)
Previous myocardial infarction n (%)	2(13%)
Hypertension n (%)	11 (73%)
COPD n (%)	5(33%)
Dementia n (%)	7(47%)
Malignancy n (%)	5(33%)

No patients required norepinephrine (NE) support prior to the initial spinal dosing. Intermittent dosing of low dose spinal anaesthesia resulted in a significant drop in MAP of 17%, with the need to

commence NE in 5 of 15 cases. Further, we found a significant (ANOVA test) 10% reduction in CI after 10 minutes, 6% reduction of SVRI directly after the first dose and a 7% drop in SVI after 10 minutes. There was a non-significant decrease in HR (6%) and arterial elastance (10%), 5 min after the initial dose. Haemodynamic variables over time are presented in figure 19 and in table 10.

Five of 15 patients required NE-infusions for MAP maintenance according to protocol. The highest dose required was 0.12 μg/kg/min (table10)

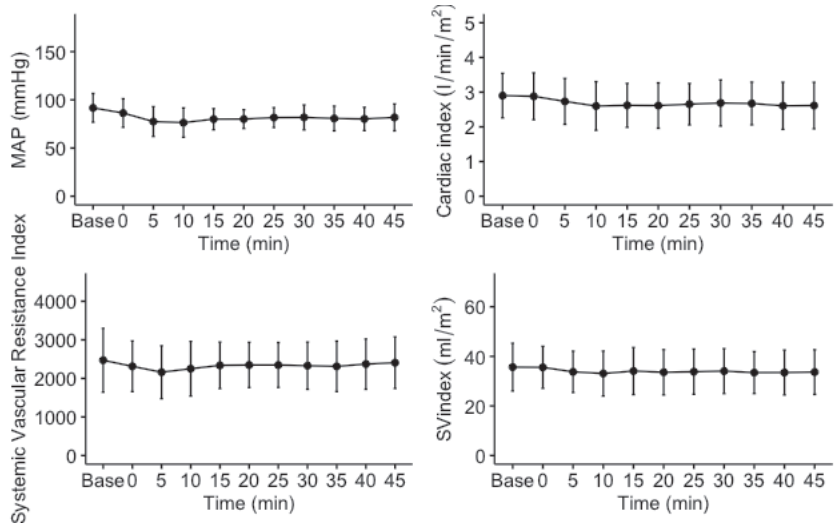

Figure 19 Haemodynamic variables over time

All patients had satisfying levels of sensory block after the second dose at 25 minutes, as measured by an altered sensation to cold at Th12 level or the ability to passively flex the fractured hip. None of the patients received sedation during the study period. After the initial dose was given, we noticed that a majority of patients had retained some motor function.

No patients experienced neurological complications following intrathecal catheter or surgery, including headache. Nor did any patient required prolonged postoperative surveillance.

	Base	0min Dose 1	5min	10min	15min	20min	25min Dose 2	30min	35min	40min	45min	Anova p value
MAP (mmHg)	92±15	86±15	78±15	76±15	80±11	80±10	82±10	82±13	81±13	80±12	82±14	0.00019
CI (l/min/m2)	3.0±0.7	2.9±0.7	2.9±0.7	2.8±0.7	2.8±0.7	2.7±0.7	2.8±0.6	2.8±0.7	2.8±0.7	2.7±0.7	2.8±0.7	0.00015
SVRI (dynes*s/cm5/m2)	2470±827	2310±656	2160±685	2250±708	2340±603	2350±586	2350±582	2330±611	2310±653	2370±651	2410±669	0.017
SVI (mL/m2)	35.7±9.6	35.6±8.5	33.8±8.3	33.1±9.1	34.1±9.5	33.6±9.1	33.8±9.1	34±9.1	33.5±8.4	33.5±9.1	33.7±9	0.021
HR (1/min)	82.3±9.5	82.9±11.6	81.9±10.5	80.3±11.2	79.3±11.5	80.7±11.6	81.2±12.1	79.9±12.2	80.8±12	79.9±12	79.4±12.9	0.472
Ea (mmHg/mL)	2.56±0.91	2.35±0.91	2.31±0.91	2.34±0.88	2.38±0.85	2.40±0.84	2.40±0.87	2.44±0.88	2.51±0.87	2.42±0.96	2.40±0.87	0.086
Norepinephrine dose (µg/kg/min)	0±0	0.003±0.01	0.01±0.02	0.02±0.03	0.02±0.03	0.02±0.03	0.02±0.03	0.02±0.03	0.02±0.03	0.02±0.03	0.02±0.03	0.002

Table 10 Changes in haemodynamic variables over time, values presented as mean (SD), MAP; Mean arterial pressure, CI; Cardiac Index, SVRI; Systemic vascular Resistance Index, SVI; Stoke Volume Index, HR; Heart Rate, Ea; Arterial elastance.

5 DISCUSSION

5.1 METHODOLOGICAL CONSIDERATIONS

Papers I and **II** are based on time-consuming manually reviewed 1400 patient journals from multiple sources. We have been asked if any of the available registries are able to present comparable data to answer our research question? After performing such an extensive review, I am certain that with the use of current registries, the true incidence of BCIS is not possible to identify. Studies relying on registry data and adverse event reporting are likely to underestimate the incidence of BCIS. One such study showed a perioperative mortality incidence due to BCIS of 0.02% (41/180,000)[161]. The authors acknowledge under-reporting as a major weakness in their study. Episodes of severe hypotension are not registered and complications are not reassuringly available.

Paper III is also a retrospective observational study. Similar question arises; can the patient information be easier accessible? With NHFS it is the patient's history at the time of admission that forms the basis of scoring. We could possibly have collected the data automatically from other registries and combined them to our final database. This would need a change in data registration. In **Paper III** though, the relevant data was already collected as part of other studies.

Papers I-III are all based on manually collected observational data. The process of manual review allows for more in-depth verification of data and the possibility to corroborate outliers with other data sources, preventing faulty entries to contaminate our data. This clearly has its limitations regarding the time and effort required and also preventing us from scaling up the process any further.

Paper IV is a prospective study on the change in systemic haemodynamics after intermittent dosing through an intrathecal catheter prior to hip fracture surgery. The recruitment of patients relied upon the presence and availability of the authors. All patients were monitored prior to their planned slot in the surgical program and no patient experienced delayed surgery due to participation in the study.

Hip fracture surgery is a common procedure often performed on elderly patients with several co-morbidities. The 30 day-mortality for all types of hip fractures from ASA 1 to 4 is around 8-10% in Sweden. For comparison, emergency laparotomy has a 30-day mortality of around 12%. Hip fracture patients are a complicated patient group with a high mortality rate associated with the trauma, the surgery and/or the anaesthesia. Frailty is a term often used to describe the typical hip fracture patients and it encompasses variables and conditions not easily encompassed in, for example NHFS or ASA.[119]

As a large centre for the treatment of hip fractures with 1000 patients yearly we have a unique opportunity to perform robust research with the potential to improve all aspects of the care for these patients.

5.2 BCIS IN CEMENTED HEMIARTHROPLASTY

The main finding in **Paper I** was a 28% incidence of BCIS, regardless of its severity. The combined incidence for the severe grades of II and III was 7% combined. In the more severe grades, BCIS showed an odds ratio of 16 for death within 30 days. Other factors such as a high ASA grade, COPD, and medication with diuretics and warfarin were all found to be independent risk factors for the development of severe BCIS.

BCIS in the severe grades was highly associated with 30-day mortality, with an OR of 16. The pre-existing factors associated with the development of BCIS, namely high ASA grade, COPD and warfarin and diuretic medication may be involved in the causality of BCIS. ASA grade is a compound variable of all pre-existing comorbidities known at the time of evaluation. It is known that COPD leads to increased PVR through chronic hypoxia, parenchymal destruction and acidaemia. Warfarin is most likely associated with severe BCIS on the base of its use in atrial fibrillation (AF). Likewise, we believe diuretic use is a proxy for CHF. Both AF and CHF may have direct impact on the hearts ability to cope with a sudden increase in PVR, due to a reduction in EF and pre-existing pulmonary

hypertension.[162] This could lead to pulmonary vascular hyperreactivity diminishing cardio-pulmonary reserves.[163] Through the results of **Paper I**, **Paper II**, and previous clinical studies on BCIS, we believe that BCIS is caused by an inability of the right ventricle to cope with embolic events and pulmonary vasoconstriction. The use of bone cement is a prerquisite to trigger BCIS grades II and III. With reduced reserves, at-risk patients are more exposed to clinically significant reactions to what we assume to be a corresponding embolic load.

The major limitation of **Paper I** is its retrospective nature. In our review, we were therefore limited by the quality of the data presented to us in the medical records of our institution.

To our knowledge, this is the first study using the classification system for BCIS proposed by Donaldson and colleagues, to describe the incidence of BCIS and its risk factors and impact on early and late mortality in a large population of patients undergoing cemented hemiarthroplasty for hip fracture. The strength of the study includes our efforts to obtain clinical signs of BCIS from the anaesthesia chart of each individual of the included population of more than a thousand patients.

After the publication of **Paper I**, a single study from the Netherlands has confirmed our findings on the incidence of BCIS[164]. Thus, Rassir and co-workers found similar rates of BCIS, where 31% (282/915) of the patients developed BCIS I and 9% (78/915) developed the more

severe grades II and III. We had similar study populations regarding age, ASA-grade and rates of neuraxial vs general anaesthesia. Previous to our registry study, no data on the incidence of BCIS were available and only case reports and registry studies describing early mortality after cemented hemiarthroplasty were available.

Our findings strengthen the assumption of BCIS being an embolic driven event causing a reactive pulmonary vasoconstriction. Based on our results, it seems appropriate to state that BCIS is a common complication in cemented hemiarthroplasty and the severe forms are prevalent enough to warrant diligence in the management of our hip fracture population. We believe that we have shown a plausible incidence for BCIS as defined by Donaldson et al.

5.3 HAEMODYNAMICS, MORBIDITY AND MORTALITY IN CEMENTED VS UNCEMENTED HEMIARTHROPLASTY

Compared to the patients presented in **Paper I**, uncemented hemiarthroplasty, as studied in **Paper II**, was not associated with significant haemodynamic deterioration or hypoxia during surgery. Hazard ratio (HR) for one year mortality was 1.9 for the cemented group compared to the uncemented group.

Paper II is limited by its retrospective design. Therefore, we were bound by the quality of data presented in the medical records from

both hospitals. The study groups varied in size by a factor of 10. A post-hoc power analysis revealed, however, that the smaller study group having uncemented hemiarthroplasty was adequate to reach our desired endpoints. Furthermore, we have no information on the cause of death. In addition, although we have adjusted for several known confounders, confounding may persist. A number of possible confounders are not accounted for in our model and these include surgeon and anaesthesiologist seniority, time of admission, BMI, and smoking history amongst others. Delay of surgery is a known factor for mortality, data on this was not available for retrieval at the time of data collection.[165]

It is our belief that the evidence of association between bone cementation and 1-year mortality seems robust to residual confounding, as a sizeable unmeasured confounding factor is needed to negate the observed association (E-value ≥ 3).[159] We are unaware of any potential confounder with such a strong risk (HR ≥ 3), above those already in the model. Another strength of the study is that we have analysed individual anaesthesia charts of more than 1,000 patients undergoing hemiarthroplasty for femoral neck fractures with or without bone cementation. This method allowed us to identify cases experiencing hemodynamic and pulmonary instability at the time around prosthesis insertion, insights that are not captured by registry data.

Alingsås Hospital, where the uncemented hemiarthroplasties were performed, have fewer junior doctors. There is a well-established elective arthroplasty service with a cohort of experienced orthopaedic surgeons who manage the emergency list. Finally, Alingsås Hospital, as not being a university hospital, does not have resident anaesthesiologists on a regular, eventually influencing the perioperative care. We have no data on these factors, but we assume that some measures of the standard of care could be a part of the residual confounding effect (E-value). Alingsås Hospital emergency department is closed during night-time (22-07) and suspected hip fractures are, during these hours, transported to other hospitals, not included in this study. We have no basis of determining if there are any significant demographic differences between these latter patients and those admitted to Alingsås during daytime.

Our results diverge from larger registry based studies where the mortality difference is equal or in favour of the cemented technique after one year.[166–172] An increased mortality rate during the first days after surgery for cemented hemiarthroplasty with no difference between cemented and uncemented after one year is the dominating finding in those studies.

5.4 PREOPERATIVE RISK FACTORS AS QUANTIFIED BY NHFS

Due to the high postoperative mortality rates (8-12%) after hip fracture surgery[173], the identification of "at-risk-individuals" should be a priority. A large patient population and a high mortality rate strengthens the argument to use all possible tools to identify and minimize risk peri-operatively, as the absolute numbers of patients benefitting is quite large.

Nottingham Hip Fracture Score failed to discriminate 30-day mortality convincingly in our patient cohort, with an AUC of 0.64. Nottingham Hip Fracture Score also underestimated the observed 30-day mortality rate using the formula from the Moppett et al 2012 revision. By replicating the last step in the conversion from NHFS points to a risk estimate, we were able to recalibrate the formula in a subset of our cohort. This recalibration was then tested against the remainder of the cohort showing excellent validation.

Discrimination was also assessed for ASA score, showing a similar AUC to that of NHFS. In fact, the NHFS is not better than the clinical judgement of the anaesthesiologist, when it comes to predicting mortality.

Internal validation is, even after data splitting, bound to be a good fit in a large population such as ours. Regardless of calibration, discrimination is still poor.

A strength of our study is that it is a single centre study where all surgical procedures and anaesthetic technique are similar over the investigated period. Patient factors were collected from manual chart reviews and not from automated registry queries, enabling us to include information in free text. Further, 30-day mortality was easily assessed in Swedish Taxation Registry.

In comparison to other scores outlined previously, NHFS has similar or poorer performance. All risk prediction scores discussed earlier, as well as NHFS, are based virtually on the same factors; age, sex, comorbidities, mobility and some sort of classification of living status. The different scores weight the different factors variably. Basically, all scores can only assign weight to factors reliably measured in their cohort. This implies that factors such as age, sex and ASA are readily available for inclusion in large registry-based prediction scores. For NHFS, a number of predefined co-morbidities are used. In our study data were primarily extracted from admission notes or from recent admission or discharge notes. One strength of NHFS is its simplicity and that it allows us to document the score early in the admission process, in comparison to some of the more complicated scores that are designed to query large databases for specific diagnose codes in retrospect.

There has been attempts to validate Nottingham Hip Fracture Score in several European and Asian cohorts with mixed results. In Greece the

factor institutional living was removed as this was uncommon in this country.[174] In our and in several of the studies from the Netherlands, we replace the MMTS factor with a dichotomized dementia yes/no, based on admission charts.[175] A comparison with validation attempts from Singapore[176] is difficult as they report good discrimination (AUC 0,80), but also present a rate of surgical repair of only around 70%, whereas close to 100% of all geriatric hip fractures are surgically treated in Sweden.[7,176]

NHFS is comparable to ASA but available earlier in the clinical pathway. There is not surprisingly a large degree of covariance with ASA classification and the similar performance in prediction was expected.[6] The formula for translating score to risk percentage of 30-day mortality needs to be continuously calibrated, both over time and in different regions. With a 30-day mortality around 10%, hip fracture surgery is a major undertaking and any instrument helping us make better informed decisions is a welcome addition. As illustrated in the introduction, there are a great many different risk prediction scores for hip fracture patients. In order to have meaningful comparisons of results between regions and centres, it is of interest to have common scoring system to quantify pre-existing comorbidity. The use of NHFS as a tool to communicate risk to patients and their family could be of value

5.5 SYSTEMIC HAEMODYNAMICS DURING CONTINUOUS SPINAL ANAESTHESIA IN ELDERLY HIP FRACTURE PATIENTS

In this study on 15 patients with a median age of 89 years, with hip fracture surgery, only 5/15 required NE support. MAP and CI both fell significantly by 10% and 17%, respectively, after the first dose and were unaltered after the second spinal anaesthesia dose. SVRI showed a minor drop after the first dose and was unaltered after the second dose. Based on our observations we conclude that, in our population, the fall in MAP was due to a fall in CI and not in SVRI, leading us to believe that our spinal doses induced a vasodilation of mainly the venous capacitance vessels, decreasing venous return and preload, as reflected by the fall in SVI and a stable HR. Arterial elastance was unchanged in our cohort, further strengthening the argument that it is the venous side of the circulation that is most susceptible to vasodilation in low-dose spinal anaesthesia.[177]

With only 15 included patients, the generalizability of our findings is difficult. We were limited by running an invasive haemodynamic study alongside a busy emergency operating list. Anticoagulation therapy was a limiting factor to the use of neuraxial anaesthesia in general and indwelling spinal catheter in particular.

Our study cohort was homogenous with the similar age and fracture type in a single tertiary orthopaedic centre. Demographically our

patients were older (89 years median) with associated risk of higher mortality and morbidity *versus* the average hip fracture population.

Our findings are in line with Jakobsson et al (2017)[153],while other studies argue that a fall in SVRI, reflecting vasodilation on the arterial side, is the major contributor to the fall in MAP in spinal anaesthesia.[152,154,178]

Results from the present study implicate that since most of the haemodynamic changes occur in post capillary circulation, special care should be taken to achieve normovolemia or at a minimum avoid hypovolemia prior to spinal anaesthesia. Volume status may be hard to assess as both the duration of fasting periods pre-operatively and fluid status prior to arrival to the OR can be unclear.

The low doses of bupivacaine in our protocol may at first seem insufficient in providing an adequate surgical anaesthesia. The doses are a part of our clinical routine and the amount of bupivacaine is equivalent to what Szucs et al recommend after a systematic dose finding study in 2015.[157] Their recommendation was a dose of 0.4 ml 5 mg/ml (2 mg) isobaric bupivacaine for hip fracture repair. The intact motor function in some of our patients could be explained by the dilution of bupivacaine to 1.5 mg/ml. None of the patients experienced neurological sequala and all patients had uneventful postoperative care.

The use of low-dose continuous spinal anaesthesia (CAS) is a viable option in patients with small cardiorespiratory reserves for surgery in the lower extremities. Titration allows us to use the smallest possible dose to achieve adequate anaesthesia during surgery without severe haemodynamic deterioration, who are particularly sensitive to an intraoperative hypotension. This is especially important in patients with severe aortic stenosis. Our findings of stable haemodynamics are in line with earlier studies in the field.[148,179–181] Aortic stenosis is an increasing problem in the aging population. With an incidence rising with age and a prevalence of 7-10% in octogenarians.[182–184]

6 CONCLUSIONS

The major findings of the present thesis were:

- The incidence of the BCIS was 27% in patients undergoing cemented hemiarthroplasty for femoral neck fracture. Early mortality in BCIS increased with increasing BCIS grade from 5.2 (Grade 0) to 88% Grade 3. Severe BCIS was associated with a 16-fold increase in mortality. Independent risk factors for severe BCIS were: ASA grade III-IV, chronic obstructive lung disease and medication with warfarin or diuretics.

- The incidence of severe hypoxia/hypotension was 6.9% in the cemented group but not observed in the uncemented patients. When adjusted for confounders, the use of bone cement was an independent risk factor for increased one-year mortality.

- Nottingham hip fracture score (NHFS) is an easily accessible scoring system, that after local recalibration, can be a useful tool in quantifying risk of 30-day mortality in patients after hip fracture surgery. However, it is difficult to use as a comparison between

different countries and over time. NHFS should routinely be assessed pre-operatively to early quantify the presence of high-risk patients on the surgical schedule and to communicate a level of risk to the patient, their family and involved staff.

- Fractional spinal anaesthesia causes a low incidence of hypotension, induced mainly by a systemic venodilation, causing a decrease in venous return and a fall in cardiac output. Our results show that fractional spinal anaesthesia is safe technique from a haemodynamic point of view.

7 FUTURE PERSPECTIVES

Future studies should target the exploration of the intravascular biochemistry following BCIS, such as key vasoconstrictory triggers that can be targeted. Further research into the current incidence and prevention of BCIS is needed. An appropriate animal model could make this research logistically easier.

However, a fall in SBP > 20% from baseline did not influence 30-day mortality. This raises the question whether relative blood pressure thresholds are meaningful? Should we use absolute pressures instead?

What is the implication for your current patient of having their NHFS score registered? Will a high or a low score make any difference regarding the treatment? All factors included in the NHFS are hopefully part of an admission exam and history and one would expect these factors to be integrated in the decision-making regardless of what acronym they are a part of?

7.1 BONE CEMENT IMPLANTATION SYNDROME

BCIS, as defined in Donaldson et al 2009 is an arbitrary grading, AJ Donaldson has not published reports related to BCIS before or after 2009. In a study of over 11000 surgeries, there was a clear correlation between intraoperative hypotension defined as SBP lower than

80mmHg and/or MAP below 60mmHg.[185] However, a relative fall in SBP of more than 20% from baseline did not have a statistical significance regarding risk of 30-day mortality post-surgery. This cohort was not limited to hip fracture surgery. It does however raise questions as to whether the BCIS definition from 2009 is the best it could be? Are the blood pressure thresholds meaningful? Should we use absolute pressures instead. At the same time the definition includes absolute values for oxygen saturation, would it be more clinically relevant to have relative or an absolute difference compared to a baseline value instead?

Non-thrombotic pulmonary embolism (NTPE) is a collective term for PE of non-thrombotic origin. NTPE includes fat embolism, amniotic fluid embolism, tumour embolism, gas emboli and particulate matter emboli amongst others.[186] Fat embolism, as seen in histopathology is common in pelvic fractures, following intramedullary reaming and in long-bone fractures.[187] Presence of fat emboli in the pulmonary vasculature is a hallmark finding in severe BCIS. Findings from animal experiments also find the same composition of the fat retrieved from the lungs and in the bone-marrow.[188]

We know that the fat found in the lung vasculature comes from the bone marrow. We know from clinical experience and ultrasound findings that there is temporal association with certain stages in cemented hemiarthroplasty and the passage of emboli as well as symptoms. It is also established by pulmonary artery sampling that fat

emboli are bloodborne as globules. All these findings argue that BCIS is a variation of fat emboli with a hyperacute presentation, and not prolonged as Fat Embolism Syndrome (FES) which usually occurs after 24-48h and includes paradoxical embolization.[187]

Future studies should target the exploration of the intravascular biochemistry following BCIS. Are there common pathological pathways with other forms of NTPE´s such as amniotic fluid embolism? If so, are there key vasoconstrictory triggers that can be targeted?

Further research into the current incidence of BCIS in our own and in other centres would be of value. In order to bring clarity to the pathophysiology, studies focusing on molecular factors and signalling in the pulmonary vasculature is needed. An appropriate animal model would make this research logistically easier.

7.2 NOTTINGHAM HIP FRACTURE SCORE

Prediction scores will most certainly play a role in the future management of hip fracture patients. No one single model will accurately predict mortality on a patient-to-patient basis. A scoring system with good discrimination and validation might be a useful tool on a population level for comparison between centres. There are several factors that appear to be pivotal in predicting risk after hip fracture surgery; age, male sex, cardiovascular disease and cognitive

impairment. With standardized databases and robust population data, the possibility of a continuously updated model, based on updated outcome measures is a possibility.

In the development of risk scores, retrospective data is the most prevalent source. The model is by implication limited to the data that is available for analysis. The result being that risk factors or combinations of risk factors may not be included in the models. Again, leading us back to the same factors that most scoring systems use. By selecting factors based on univariate analysis and using logistic regression to assign weight as is the case with NHFS, interactions between variables might be lost.

For other types of emergency surgery, such as emergency laparotomy, studies have shown that there was a lower mortality rate in those patients where risk was quantified compared to those who were not assessed.[14,15] These findings were independent of the actual risk score. Assessing risk in a structured manner, forces clinicians to actively relate to the risk quantification and may affect decision-making.
30-day mortality is an outcome metric commonly used to quantify mortality connected to surgery. NHFS is one among many of the tools that help us quantify risk of 30-day mortality. The question of to whom this information is important arises. In hip fracture surgery one can easily imagine that return to pre-operative functional status is paramount for the patient.[189] Regarding the use of mortality as an outcome measure, a review article from 2013 by dr. JB Carlisle argues

to take in to account remaining life expectancy in our risk prediction models, quantifying risk over time. ; "*If the function of a hospital were to kill the sick, statistical comparisons of this nature would be admissible"*[190] In effect, presenting a formula to adjust risk to the patients biological age with mortality risk over time as an outcome measure instead of the dichotomized alive or dead at day 30 after surgery.[191]

As a British-developed score, NHFS is based on that context. Institutionalization criteria and what it implies varies in different regions of the world. As the expected life-span increases there will be need to adjust the cut off values for age periodically. Is a malignant disease, remission free, in your medical history of the same prognostic value as a current cancer? Could we use NHFS in conjunction with scores based on current physiological status such as National Early warning Score-2 (NEWS-2)?[192]

7.3 CONTINUOUS SPINAL ANAESTHESIA

Continuous or intermittent intrathecal dosing of anaesthesia is an option to manage a subset of patients with cardiovascular disease. The technique is a variation of epidural anaesthesia and should be well known to anaesthesiologists. Our experience is that it is an underutilized method.

The method has been surrounded by some controversy regarding the risk of local anaesthetic neurotoxicity, leading to the FDA in USA banning the use of CSA with microcatheters.

Despite being home to one of northern Europe's largest orthopaedic centres, the use of CSA is limited to a handful of colleagues confident in the technique and its indications. It is thus easy to imagine the threshold against using CSA in smaller centres. Risk of post puncture dural headache is, however, not greater than single shot spinal or epidural.[193]

Future studies further examining the haemodynamics of spinal anaesthesia are needed in the geriatric population. Variations on the single shot spinal such as injection time should also be assessed for haemodynamic response.

7.4 PULSE CONTOUR ANALYSIS

As the technology behind the interpretation of pulse contour improves and the cost of use falls, the technology will be more available for routine use. Now pulse contour analysis is a third-tier monitoring modality after non-invasive and invasive blood pressure monitoring. New software also has the possibility of predicting risk of hypotension before it even occurs through the Hypotension Prediction Index (HPI).[194–196] More and more information will be available to the clinician without the need for more invasive monitoring systems.

Combined with the increasing use of ultrasound by anaesthesiologists in the perioperative setting, more extensive monitoring of high-risk patients will be possible without an increase in procedure-related complications. The pulse contour analysis method of CO monitoring is only as good as the algorithm it is based on, all other haemodynamic variables are derived from CO and are therefore subject to the same measurement errors.

Initializing LiDCO monitoring was quick and without major difficulties. Once the arterial catheter is established and the equipment is prepared, the calibration process is done in 5-10 minutes for at least 2 calibrations. The Pulsepower™ algorithm can also be calibrated by a recent cardiac ultrasound, eliminating the need for lithium calibration. LiDCO monitoring does not require more invasive monitoring than what is already needed in the patient group. The drawback of the system is the need for calibration which is a process with several steps and the cost per calibration/measurement kit (1700 SEK/case)

More values on the screen are not necessarily associated with improved outcome by itself. Clinical judgement and proper interpretation are pivotal in caring for this complicated group of patients.

7.5 INTRAOPERATIVE HYPOTENSION

End organ damage after hypotension is commonly measured by dynamic changes in biomarkers such as troponin, creatinine and NTproBNP.[128] Studies have shown an association between hypotension and biomarker change as opposed to reaction inflicted by the surgical trauma itself.[128,197] The same studies also associate biomarker dynamics with functional end-organ outcomes.

The prevention of hypotension has the potential to mitigate end-organ damage. Every tool possible should be used to achieve this. Primary prevention with identification of at-risk patients, continuous blood-pressure monitoring, prophylactic vasopressor administration, judicious evaluation of fluid status and possibly the use of predictive monitoring. Manifest hypotension should be treated promptly, as time with hypotension also seems to be associated with negative outcome.

Major adverse cardiac or cerebrovascular events (MACCE) following intraoperative hypotension seems to be associated not only with blood pressure. In patients not experiencing IOH but with hypotension in the postoperative period there was no significant difference in the occurrence of MACCE. Hypotension seems to have a more damaging effect in the intraoperative period.[198]

8 FINAL REMARKS

Bone Cement implantation syndrome is a devastating complication in cemented hip arthroplasty. We believe that peering deeper into the pathophysiological pathways might reveal treatment targets. The possibility of finding common pathways with other forms of non-thrombotic pulmonary embolism is exciting and opens up new avenues of research.

Mortality is easily defined and measured. The opposite of mortality is remaining alive. The "remaining alive" state can be quantified by other instruments assessing functional outcome, mobility, quality of life etc. It is in the diversity of “remaining alive” that patients experience some level of satisfaction. Unfortunately, we seem to be stuck in using 30-day mortality as a sign of success of the care we deliver.

With an increasing lifespan, more diseases of old age will pose challenges to us in the perioperative setting. For the patient with marginal cardiac or respiratory reserves, continuous spinal anaesthesia for lower extremity surgery might be a relatively safe and predictable method. Its use allows for stable anaesthesia in our patient category. A major challenge to its use is the widespread use of anticoagulant treatment. New pharmacological developments for the reversal and better laboratory tests may provide some guidance.

Intraoperative monitoring will probably advance at the same or a faster rate the next 10 years than in the previous decade. More information will become available and more treatment options will be at our disposal. Prediction models will likely become a part of standard monitoring but cannot predict external events such as BCIS. There will always be a role for the keen-eyed clinician in monitoring and assessing risk.

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REFERENCES

1. Rikshöft. Rikshöft 2018. *Rikshöft Årsrapport 2018* https://04e8d8b0-c67b-4aa0-a7e7-d272a37c2285.filesusr.com/ugd/3ac01b_c34a4c9991404c0595ee861991c37ea8.pdf.
2. White, S. & Griffiths, R. Projected incidence of proximal femoral fracture in England: a report from the NHS Hip Fracture Anaesthesia Network (HIPFAN). *Injury* **42**, 1230–1233 (2011).
3. White, S., Moppett, I. & Griffiths, R. Outcome by mode of anaesthesia for hip fracture surgery. An observational audit of 65 535 patients in a national dataset. *Anaesthesia* **69**, 224–230 (2014).
4. Baker, P. N. *et al.* Evolution of the hip fracture population: time to consider the future? A retrospective observational analysis. *BMJ Open* **4**, (2014).
5. Kristiansson, J., Hagberg, E. & Nellgård, B. The influence of time-to-surgery on mortality after a hip fracture. *Acta Anaesthesiol. Scand.* **64**, 347–353 (2020).
6. Johansen, A., Tsang, C., Boulton, C., Wakeman, R. & Moppett, I. Understanding mortality rates after hip fracture repair using ASA physical status in the National Hip Fracture Database. *Anaesthesia* **72**, 961–966 (2017).
7. Rikshöft (The Swedish Registry for Hip Fracture Care) Annual Report 2020.
8. Boulton, C. & Wakeman, R. Lessons from the national hip fracture database. *Orthop. Trauma* **30**, 123–127 (2016).
9. Olsen, F., Hård Af Segerstad, M., Nellgård, B., Houltz, E. & Ricksten, S.-E. The role of bone cement for the development of intraoperative hypotension and hypoxia and its impact on mortality in hemiarthroplasty for femoral neck fractures. *Acta Orthop.* **91**, 293–298 (2020).
10. Maxwell, M. J., Moran, C. G. & Moppett, I. K. Development and

validation of a preoperative scoring system to predict 30 day mortality in patients undergoing hip fracture surgery. *Br. J. Anaesth.* **101**, 511–517 (2008).
11. Marufu, T. C., White, S. M., Griffiths, R., Moonesinghe, S. R. & Moppett, I. K. Prediction of 30-day mortality after hip fracture surgery by the Nottingham Hip Fracture Score and the Surgical Outcome Risk Tool. *Anaesthesia* **71**, 515–521 (2016).
12. Gundel, O., Thygesen, L. C., Gögenur, I. & Ekeloef, S. Postoperative mortality after a hip fracture over a 15-year period in Denmark: a national register study. *Acta Orthop.* **91**, 58–62 (2020).
13. Rapp, K. *et al.* The association between orthogeriatric co-management and mortality following hip fracture: an observational study of 58 000 patients from 828 hospitals. *Dtsch. Ärztebl. Int.* **117**, 53 (2020).
14. *The First Ptient Report of the Ntional EMERGENCY Laparatomy Audit (NELA)*. https://www.nela.org.uk/downloads/Executive%20Summary%20-%20The%20First%20Patient%20Report%20of%20the%20National%20Ememrgency%20Laparotomy%20Audit%202015.pdf.
15. Poulton, T., Murray, D., & the National Emergency Laparotomy Audit (NELA) project team. Pre-optimisation of patients undergoing emergency laparotomy: a review of best practice. *Anaesthesia* **74**, 100–107 (2019).
16. Bhandari, M. & Swiontkowski, M. Management of acute hip fracture. *N. Engl. J. Med.* **377**, 2053–2062 (2017).
17. Garden, R. Reduction and fixation of subcapital fractures of the femur. *Orthop. Clin. North Am.* **5**, 683–712 (1974).
18. Garden, R. S. Low-angle fixation in fractures of the femoral neck. *J. Bone Jt. Surg. B* 647–661 (1961).
19. Harty, M. Blood supply of the femoral head. *Br. Med. J.* **2**, 1236 (1953).
20. Arora, M., Chan, E. K., Gupta, S. & Diwan, A. D.

Polymethylmethacrylate bone cements and additives: A review of the literature. *World J. Orthop.* **4**, 67 (2013).
21. Vaishya, R., Chauhan, M. & Vaish, A. Bone cement. *J. Clin. Orthop. Trauma* **4**, 157–163 (2013).
22. Apple, D. J. & Sims, J. Harold Ridley and the invention of the intraocular lens. *Surv. Ophthalmol.* **40**, 279–292 (1996).
23. Ridley, H. Intra-Ocular Acrylic Lenses : A Recent Development in the Surgery of Cataract. *Br. J. Ophthalmol.* **36**, 113–122 (1952).
24. Elson, R., Jephcott, A., McGechie, D. al & Verettas, D. Antibiotic-loaded acrylic cement. *J. Bone Joint Surg. Br.* **59**, 200–205 (1977).
25. Webb, J. & Spencer, R. The role of polymethylmethacrylate bone cement in modern orthopaedic surgery. *J. Bone Joint Surg. Br.* **89**, 851–857 (2007).
26. Lewis, G. Properties of acrylic bone cement: State of the art review. *J. Biomed. Mater. Res.* **38**, 155–182 (1997).
27. Charnley, J. Anchorage of the femoral head prosthesis to the shaft of the femur. *J. Bone Joint Surg. Br.* **42**, 28–30 (1960).
28. Charnley, J. THE BONDING OF PROSTHESES TO BONE BY CEMENT. *J. Bone Joint Surg. Br.* **46-B**, 518–529 (1964).
29. Nottrott, M. Acrylic bone cements: influence of time and environment on physical properties. *Acta Orthop.* **81**, 1–27 (2010).
30. Rogmark, C. & Leonardsson, O. Hip arthroplasty for the treatment of displaced fractures of the femoral neck in elderly patients. *Bone Jt. J.* **98**, 291–297 (2016).
31. Enocson, A., Tidermark, J., Törnkvist, H. & Lapidus, L. J. Dislocation of hemiarthroplasty after femoral neck fracture: better outcome after the anterolateral approach in a prospective cohort study on 739 consecutive hips. *Acta Orthop.* **79**, 211–217 (2008).
32. Sköldenberg, O., Ekman, A., Salemyr, M. & Bodén, H. Reduced dislocation rate after hip arthroplasty for femoral neck fractures

when changing from posterolateral to anterolateral approach: a prospective study of 372 hips. *Acta Orthop.* **81**, 583–587 (2010).
33. Moerman, S. *et al.* More complications in uncemented compared to cemented hemiarthroplasty for displaced femoral neck fractures: a randomized controlled trial of 201 patients, with one year follow-up. *BMC Musculoskelet. Disord.* **18**, 169 (2017).
34. Mäkelä, K. T. *et al.* Failure rate of cemented and uncemented total hip replacements: register study of combined Nordic database of four nations. *Bmj* **348**, (2014).
35. Springer, B. D. *et al.* Perioperative periprosthetic femur fractures are strongly correlated with fixation method: an analysis from the American Joint Replacement Registry. *J. Arthroplasty* **34**, S352–S354 (2019).
36. Okike, K., Chan, P. H., Prentice, H. A., Paxton, E. W. & Burri, R. A. Association between uncemented vs cemented hemiarthroplasty and revision surgery among patients with hip fracture. *Jama* **323**, 1077–1084 (2020).
37. Gebhard, J. S., Amstutz, H. C., Zinar, D. M. & Dorey, F. J. A comparison of total hip arthroplasty and hemiarthroplasty for treatment of acute fracture of the femoral neck. *Clin. Orthop.* 123–131 (1992).
38. Donaldson, A. J., Thomson, H. E., Harper, N. J. & Kenny, N. W. Bone cement implantation syndrome. *Br. J. Anaesth.* **102**, 12–22 (2009).
39. Kotyra, M., Houltz, E. & Ricksten, S.-E. Pulmonary haemodynamics and right ventricular function during cemented hemiarthroplasty for femoral neck fracture: Pulmonary haemodynamics and right ventricular function. *Acta Anaesthesiol. Scand.* **54**, 1210–1216 (2010).
40. Hård af Segerstad, M. *et al.* Pulmonary haemodynamics and right ventricular function in cemented vs uncemented total hip arthroplasty—A randomized trial. *Acta Anaesthesiol. Scand.* **63**, 298–305 (2019).
41. Hård af Segerstad, M., Olsen, F., Houltz, E., Nellgård, B. &

Ricksten, S. Inhaled prostacyclin for the prevention of increased pulmonary vascular resistance in cemented hip hemiarthroplasty—A randomised trial. *Acta Anaesthesiol. Scand.* **63**, 1152–1161 (2019).
42. McIntyre, K. M. & Sasahara, A. A. The hemodynamic response to pulmonary embolism in patients without prior cardiopulmonary disease. *Am. J. Cardiol.* **28**, 288–294 (1971).
43. Wood, K. E. Major Pulmonary Embolism. *Chest* **121**, 877–905 (2002).
44. Weingärtner, K. *et al.* Bone cement implantation syndrome in cemented hip hemiarthroplasty—a persistent risk. *Eur. J. Trauma Emerg. Surg.* 1–9 (2021).
45. Jain, S., Pal, A., Jain, M. & Ajmera, A. Incidence and risk for Cement Implantation Syndrome after hemiarthroplasty. *Orthop. J. MP Chapter* **25**, 77–81 (2019).
46. Chulsomlee, K. *et al.* Predictive factor for bone cement implantation syndrome in osteoporotic femoral neck fracture undergoing cemented hip arthroplasty: a retrospective review of 142 cases. (2020).
47. Schwarzkopf, E. *et al.* Occurrence, risk factors, and outcomes of bone cement implantation syndrome after hemi and total hip arthroplasty in cancer patients. *J. Surg. Oncol.* **120**, 1008–1015 (2019).
48. Willeumier, J. J., van der Linden, Y. M., van de Sande, M. A. & Dijkstra, P. S. Treatment of pathological fractures of the long bones. *EFORT Open Rev.* **1**, 136–145 (2016).
49. Thomas, T. A., Sutherland, I. C. & Waterhouse, T. D. Cold curing acrylic bone cement.: A clinical study of the cardiovascular side effects during hip joint replacement. *Anaesthesia* **26**, 298–303 (1971).
50. Dahl, O. E. *et al.* Fatal vascular outcomes following major orthopedic surgery. *Thromb. Haemost.* **93**, 860–866 (2005).
51. Mir, G. N., Lawrence, W. H. & Autian, J. Toxicological and pharmacological actions of methacrylate monomers I: Effects on

isolated, perfused rabbit heart. *J. Pharm. Sci.* **62**, 778–782 (1973).
52. Peebles, D. J., Ellis, R. H., Stride, S. D. K. & Simpson, B. R. J. Cardiovascular Effects of Methylmethacrylate Cement. *BMJ* **1**, 349–351 (1972).
53. Modig, J., Busch, C. & Waernbaum, G. Effects of graded infusions of monomethylmethacrylate on coagulation, blood lipids, respiration and circulation. An experimental study in dogs. *Clin. Orthop.* 187–197 (1975).
54. Kallos, T & Enis, J. Intramedullary Embolism in Dogs during Pressure Insertion and Pulmonary Medullary of Bone Contents Cement of Femoral Medullary Contents in Dogs during Insertion of Bone Cement and a Prosthesis. *J. Bone Jt. Surg.* **56**, (1974).
55. McLAUGHLIN, R. E. *et al.* Blood clearance and acute pulmonary toxicity of methylmethacrylate in dogs after simulated arthroplasty and intravenous injection. *JBJS* **55**, 1621–1628 (1973).
56. Tryba, M., Linde, I., Voshage, G. & Zenz, M. Histamine release and cardiovascular reactions to implantation of bone cement during total hip replacement. *Anaesthesist* **40**, 25–32 (1991).
57. Mitsuhata, H. *et al.* Methylmethacrylate bone cement does not release histamine in patients undergoing prosthetic replacement of the femoral head. *Br. J. Anaesth.* **73**, 779–781 (1994).
58. Lamad, W. R., Friedl, W., Schmid, B. & Meeder, P. J. Bone cement implantation syndrome. 5.
59. Bengtson, A., Larsson, M., Gammer, W. & Heideman, M. Anaphylatoxin release in association with methylmethacrylate fixation of hip prostheses.: *J. Bone Jt. Surg.* **69**, 46–49 (1987).
60. Dahl, O. E. *et al.* Studies on coagulation, fibrinolysis, kallikrein-kinin and complement activation in systemic and pulmonary circulation during hip arthroplasty with acrylic cement. *Thromb. Res.* **50**, 875–884 (1988).
61. Thordardottir, S., Vikingsdottir, T., Bjarnadottir, H., Jonsson Jr, H. & Gudbjornsson, B. Activation of complement following total

hip replacement. *Scand. J. Immunol.* **83**, 219–224 (2016).
62. Smulders, Y. M. Pathophysiology and treatment of haemodynamic instability in acute pulmonary embolism: the pivotal role of pulmonary vasoconstriction. *Cardiovasc. Res.* **48**, 23–33 (2000).
63. Furchgott, R. F. & Vanhoutte, P. M. Endothelium-derived relaxing and contracting factors. *FASEB J.* **3**, 2007–2018 (1989).
64. Ferlinz, J. Right ventricular function in adult cardiovascular disease. *Prog. Cardiovasc. Dis.* **25**, 225–267 (1982).
65. Voga, G. Right ventricular function in critically ill patients. *Signa Vitae- J. Intensive Care Emerg. Med.* **13**, 24–26 (2017).
66. Krüger, W. Acute right heart failure. in *Acute Heart Failure* 209–271 (Springer, 2017).
67. Jung, J. & Bonde, P. Surgical Management of Pulmonary Embolism. *Curr. Manag. Venous Dis.* 405–418 (2018).
68. Memtsoudis, S. G. *et al.* Perioperative mortality in patients with pulmonary hypertension undergoing major joint replacement. *Anesth. Analg.* **111**, 1110–1116 (2010).
69. Christie, J., Robinson, C. M., Pell, A. C., McBirnie, J. & Burnett, R. Transcardiac echocardiography during invasive intramedullary procedures. *J. Bone Joint Surg. Br.* **77**, 450–455 (1995).
70. Pitto, R., Schramm, M., Hohmann, D. & Kössler, M. Relevance of the drainage along the linea aspera for the reduction of fat embolism during cemented total hip arthroplasty. *Arch. Orthop. Trauma Surg.* **119**, 146–150 (1999).
71. Ulrich, C., Burri, C., Wörsdörfert, O. & Heinrich, H. Intraoperative transesophageal two-dimensional echocardiography in total hip replacement. *Arch. Orthop. Trauma. Surg.* **105**, 274–278 (1986).
72. Wenda, K., Runkel, M., Degreif, J. & Ritter, G. Pathogenesis and clinical relevance of bone marrow embolism in medullary nailing—demonstrated by intraoperative echocardiography. *Injury* **24**, S73–S81 (1993).
73. Modig, J., Olerud, S., Malmberg, P. & Busch, C. Medullary fat

embolization during total hip replacement surgery: a preliminary report. *Injury* **5**, 161–164 (1973).
74. Oates, J. A. *et al.* Clinical implications of prostaglandin and thromboxane A2 formation. *N. Engl. J. Med.* **319**, 689–698 (1988).
75. Goncharova, N. *et al.* Pulmonary arterial hypertension modeling with synthetic stable thromboxane A2 analogue (U46619) in porcine: dose adjustment and acute hemodynamic reactions. *Eur. Heart J.* **41**, ehaa946-3812 (2020).
76. Lyhne, M. D., Kline, J. A., Nielsen-Kudsk, J. E. & Andersen, A. Pulmonary vasodilation in acute pulmonary embolism–a systematic review. *Pulm. Circ.* **10**, 2045894019899775 (2020).
77. Barst, R. J. PDGF signaling in pulmonary arterial hypertension. *J. Clin. Invest.* **115**, 2691–2694 (2005).
78. Hood, K. Y. *et al.* Serotonin signaling through the 5-HT1B receptor and NADPH oxidase 1 in pulmonary arterial hypertension. *Arterioscler. Thromb. Vasc. Biol.* **37**, 1361–1370 (2017).
79. MacLean, M. R. & Dempsie, Y. Serotonin and pulmonary hypertension—from bench to bedside? *Curr. Opin. Pharmacol.* **9**, 281–286 (2009).
80. Griffiths, R. *et al.* Guideline for the management of hip fractures 2020: Guideline by the Association of Anaesthetists. *Anaesthesia* **76**, 225–237 (2021).
81. Membership of the Working Party *et al.* Safety guideline: reducing the risk from cemented hemiarthroplasty for hip fracture 2015: Association of Anaesthetists of Great Britain and Ireland British Orthopaedic Association British Geriatric Society. *Anaesthesia* **70**, 623–626 (2015).
82. Engesaeter, L. B., Strand, T., Raugstad, T. S., Husebø, S. & Langeland, N. Effects of a distal venting hole in the femur during total hip replacement. *Arch. Orthop. Trauma. Surg.* **103**, 328–331 (1984).
83. Singh, V. A., Sarrafan, S. & Veriah, R. S. Distal Medullary Canal

Decompression in Long Stem Hip Replacement in Long Bone Metastasis: Does it Reduce Cardiopulmonary Complications? *Indian J. Orthop.* **52**, 15–21 (2018).
84. Stephen, D. The technique of venting the femoral canal. *Tech. Orthop.* **19**, 45–48 (2004).
85. Özcan, A. T. D. *et al.* Comparison between colloid preload and coload in bone cement implantation syndrome under spinal anesthesia: A randomized controlled trial. *Anesth. Essays Res.* **12**, 879 (2018).
86. Rothberg, D. L., Kubiak, E. N., Peters, C. L., Randall, R. L. & Aoki, S. K. Reducing the Risk of Bone Cement Implantation Syndrome During Femoral Arthroplasty. *Orthopedics* **36**, e463–e467 (2013).
87. Dahl, O. E. Cardiorespiratory and vascular dysfunction related to major reconstructive orthopedic surgery. *Acta Orthop. Scand.* **68**, 607–614 (1997).
88. Kaufmann, K. B. *et al.* Evaluation of hemodynamic goal-directed therapy to reduce the incidence of bone cement implantation syndrome in patients undergoing cemented hip arthroplasty–a randomized parallel-arm trial. *BMC Anesthesiol.* **18**, 63 (2018).
89. Krebs, J. *et al.* Cardiovascular Changes after Pulmonary Cement Embolism: An Experimental Study in Sheep. *Am. J. Neuroradiol.* **28**, 1046–1050 (2007).
90. Neto-Neves, E. M. *et al.* Sildenafil improves the beneficial hemodynamic effects exerted by atorvastatin during acute pulmonary thromboembolism. *Eur. J. Pharmacol.* **670**, 554–560 (2011).
91. Figueiredo, L. B. *et al.* Bone Cement Implantation Syndrome in Cemented Hip Arthroplasty: Hypothetization of a New Therapeutic Approach and Proposition of a Treatment Algorithm. *Ann. Med. Health Sci. Res.* **8**, (2018).
92. Yingchoncharoen, T. & Srimachai, S. ROLE OF ECMO IN BONE CEMENT IMPLANTATION SYNDROME. *J. Am. Coll. Cardiol.* **73**, 2953–2953 (2019).

93. Eldor, J. & Kotlovker, V. Intralipid treatment: Is it only the tip of an iceberg? A new suggestion: Bone cement implantation syndrome (BCIS). *J Anesth. Clin Sci* **1**, 1–7 (2012).
94. Faxon, H. H., Flynn, J. H. & Anderson, R. M. Stellate block as an adjunct to the treatment of pulmonary embolism. *N. Engl. J. Med.* **244**, 586–590 (1951).
95. Stratmann, G. & Gregory, G. A. Neurogenic and humoral vasoconstriction in acute pulmonary thromboembolism. *Anesth. Analg.* **97**, 341–354 (2003).
96. Joffe, A. M., Wood, K. E. & Coursin, D. B. Sympathetic blockade for pulmonary embolus: Novel therapy or novelty? *Crit. Care Med.* **35**, 2653–2654 (2007).
97. Garneau, S. Y. *et al.* Preliminary experience in the use of preoperative echo-guided left stellate ganglion block in patients undergoing cardiac surgery. *J. Cardiothorac. Vasc. Anesth.* **25**, 78–84 (2011).
98. Jannaway, M., Torrens, C., Warner, J. A. & Sampson, A. P. Resolvin E1, resolvin D1 and resolvin D2 inhibit constriction of rat thoracic aorta and human pulmonary artery induced by the thromboxane mimetic U46619. *Br. J. Pharmacol.* **175**, 1100–1108 (2018).
99. Parvizi, J., Holiday, A. D., Ereth, M. H. & Lewallen, D. G. Sudden Death During Primary Hip Arthroplasty: *Clin. Orthop.* **369**, 39–48 (1999).
100. de Froidmont, S., Bonetti, L. R., Villaverde, R. V., del Mar Lesta, M. & Palmiere, C. Postmortem Findings in Bone Cement Implantation Syndrome–Related Deaths: *Am. J. Forensic Med. Pathol.* **35**, 206–211 (2014).
101. Sevitt, S. Fat embolism in patients with fractured hips. *Br Med J* **2**, 257–262 (1972).
102. Neri, M. *et al.* CD61 and fibrinogen immunohistochemical study to improve the post-mortem diagnosis in a fat embolism syndrome clinically demonstrated by transesophageal echocardiography. *Forensic Sci. Int.* **202**, e13–e17 (2010).

103. Razuin, R., Effat, O., Shahidan, M. N., Shama, D. V. & Miswan, M. F. M. Bone cement implantation syndrome. *Malays. J. Pathol.* **35**, 87–90 (2013).
104. Moppett, I. K. *et al.* Nottingham Hip Fracture Score: longitudinal and multi-centre assessment. *Br. J. Anaesth.* **109**, 546–550 (2012).
105. Karres, J., Heesakkers, N. A., Ultee, J. M. & Vrouenraets, B. C. Predicting 30-day mortality following hip fracture surgery: Evaluation of six risk prediction models. *Injury* **46**, 371–377 (2015).
106. Donati, A. *et al.* A new and feasible model for predicting operative risk. *Br. J. Anaesth.* **93**, 393–399 (2004).
107. Nijmeijer, W. S., Folbert, E. C., Vermeer, M., Slaets, J. P. & Hegeman, J. H. Prediction of early mortality following hip fracture surgery in frail elderly: The Almelo Hip Fracture Score (AHFS). *Injury* **47**, 2138–2143 (2016).
108. van de Ree, C. L. *et al.* Development and validation of the Brabant Hip Fracture Score for 30-day and 1-year mortality. *HIP Int.* 112070001983696 (2019) doi:10.1177/1120700019836962.
109. Protopapa, K. L., Simpson, J. C., Smith, N. C. E. & Moonesinghe, S. R. Development and validation of the surgical outcome risk tool (SORT). *Br. J. Surg.* **101**, 1774 (2014).
110. Jonsson, M. H., Bentzer, P., Turkiewicz, A. & Hommel, A. Accuracy of the Physiological and Operative Severity Score for the enUmeration of Mortality and morbidity score and the Nottingham risk score in hip fracture patients in Sweden - A prospective observational study. *Acta Anaesthesiol. Scand.* **62**, 1057–1063 (2018).
111. Ramanathan, T. S., Moppett, I. K., Wenn, R. & Moran, C. G. POSSUM scoring for patients with fractured neck of femur † †An abstract of part of the study was presented at the Anaesthetic Research Society meeting, Aberdeen, April 2004 and published in British Journal of Anaesthesia 2004; 93: 161. *Br. J. Anaesth.* **94**, 430–433 (2005).

112. Elixhauser, A., Steiner, C., Harris, D. R. & Coffey, R. M. Comorbidity measures for use with administrative data. *Med. Care* 8–27 (1998).
113. Ondeck, N. T. *et al.* Discriminative ability for adverse outcomes after surgical Management of hip Fractures: a comparison of the Charlson comorbidity index, Elixhauser comorbidity measure, and modified frailty index. *J. Orthop. Trauma* **32**, 231–237 (2018).
114. Charlson, M. E., Pompei, P., Ales, K. L. & MacKenzie, C. R. A new method of classifying prognostic comorbidity in longitudinal studies: Development and validation. *J. Chronic Dis.* **40**, 373–383 (1987).
115. Kirkland, L. L., Kashiwagi, D. T., Burton, M. C., Cha, S. & Varkey, P. The Charlson Comorbidity Index Score as a Predictor of 30-Day Mortality After Hip Fracture Surgery. *Am. J. Med. Qual.* **26**, 461–467 (2011).
116. Toson, B., Harvey, L. A. & Close, J. C. T. The ICD-10 Charlson Comorbidity Index predicted mortality but not resource utilization following hip fracture. *J. Clin. Epidemiol.* **68**, 44–51 (2015).
117. Hirose, J., Mizuta, H., Ide, J. & Nomura, K. Evaluation of estimation of physiologic ability and surgical stress (E-PASS) to predict the postoperative risk for hip fracture in elder patients. *Arch. Orthop. Trauma Surg.* **128**, 1447–1452 (2008).
118. Tsang, C. & Cromwell, D. Statistical methods developed for the National Hip Fracture Database annual report, 2014. *Lond. R. Coll. Surg. Engl.* (2014).
119. Rockwood, K. *et al.* A global clinical measure of fitness and frailty in elderly people. *Can. Med. Assoc. J.* **173**, 489 (2005).
120. Patel, K. V. *et al.* Association of a modified frailty index with mortality after femoral neck fracture in patients aged 60 years and older. *Clin. Orthop. Relat. Res.* **472**, 1010–1017 (2014).
121. Traven, S. A., Reeves, R. A., Althoff, A. D., Slone, H. S. & Walton, Z. J. New five-factor modified frailty index predicts

morbidity and mortality in geriatric hip fractures. *J. Orthop. Trauma* **33**, 319–323 (2019).
122. Dawe, E. J. C., Lindisfarne, E., Singh, T., McFadyen, I. & Stott, P. Sernbo score predicts survival after intracapsular hip fracture in the elderly. *Ann. R. Coll. Surg. Engl.* **95**, 29–33 (2013).
123. Mellner, C. *et al.* The Sernbo score as a predictor of 1-year mortality after hip fracture: a registry study on 55,716 patients. *Eur. J. Trauma Emerg. Surg.* 1–6 (2020).
124. Anaesthesia Sprint Audit of Practice. Falls and Fragility Fracture Audit Programme National Hip Fracture Database: (2014).
125. Beecham, G., Cusack, R., Vencken, S., Crilly, G. & Buggy, D. J. Hypotension during hip fracture surgery and postoperative morbidity. *Ir. J. Med. Sci. 1971-* 1–10 (2020).
126. Kristiansson, J., Olsen, F., Hagberg, E., Dutkiewicz, R. & Nellgård, B. Prolonged vasopressor support during hip-fracture surgery is a risk factor for enhanced mortality. *Acta Anaesthesiol. Scand.* **63**, 46–54 (2019).
127. Sessler, D. I. & Khanna, A. K. Perioperative myocardial injury and the contribution of hypotension. *Intensive Care Med.* **44**, 811–822 (2018).
128. Wesselink, E. M., Kappen, T. H., Torn, H. M., Slooter, A. J. C. & van Klei, W. A. Intraoperative hypotension and the risk of postoperative adverse outcomes: a systematic review. *Br. J. Anaesth.* **121**, 706–721 (2018).
129. Salmasi, V. *et al.* Relationship between intraoperative hypotension, defined by either reduction from baseline or absolute thresholds, and acute kidney and myocardial injury after noncardiac surgery: a retrospective cohort analysis. *Anesthesiology* **126**, 47–65 (2017).
130. Jang, W. Y., Jung, J.-K., Lee, D. K. & Han, S.-B. Intraoperative hypotension is a risk factor for postoperative acute kidney injury after femoral neck fracture surgery: a retrospective study. *BMC Musculoskelet. Disord.* **20**, 1–5 (2019).
131. Radinovic, K. *et al.* Impact of intraoperative blood pressure,

blood pressure fluctuation, and pulse pressure on postoperative delirium in elderly patients with hip fracture: a prospective cohort study. *Injury* **50**, 1558–1564 (2019).
132. Khanna, G. & Cernovsky, J. Bone cement and the implications for anaesthesia. *Contin. Educ. Anaesth. Crit. Care Pain* **12**, 213–216 (2012).
133. Byrick, R. J. Cement implantation syndrome: a time limited embolic phenomenon. *Can. J. Anaesth.* **44**, 107–111 (1997).
134. Linton, R. A. F., Band, D. M. & Haire, K. M. A new method of measuring cardiac output in man using lithium dilution. *Br. J. Anaesth.* **71**, 262–266 (1993).
135. Valentinuzzi, M., Geddes, L. & Baker, L. A simple mathematical derivation of the Stewart-Hamilton formula for the determination of cardiac output. *Med. Biol. Eng.* **7**, 277–282 (1969).
136. Cecconi, M., Dawson, D., Grounds, R. & Rhodes, A. Lithium dilution cardiac output measurement in the critically ill patient: determination of precision of the technique. *Intensive Care Med.* **35**, 498–504 (2009).
137. Zuzan, O. Cardiac output monitoring. *Anesth Analg* (2010).
138. Verbraecken, J., Van de Heyning, P., De Backer, W. & Van Gaal, L. Body surface area in normal-weight, overweight, and obese adults. A comparison study. *Metabolism* **55**, 515–524 (2006).
139. Jonas, M. M. *et al.* A comparison of lithium dilution cardiac output measurements made using central and antecubital venous injection of lithium chloride. *J. Clin. Monit. Comput.* **15**, 525–528 (1999).
140. Pearse, R. M., Ikram, K. & Barry, J. Equipment review: An appraisal of the LiDCO^{TM} plus method of measuring cardiac output. *Crit. Care* **8**, 1–6 (2004).
141. Guay, J., Parker, M. J., Gajendragadkar, P. R. & Kopp, S. Anaesthesia for hip fracture surgery in adults. *Cochrane Database Syst. Rev.* **2**, CD000521–CD000521 (2016).
142. Morgan, L., McKeever, T., Nightingale, J., Deakin, D. & Moppett, I. Spinal or general anaesthesia for surgical repair of hip

fracture and subsequent risk of mortality and morbidity: a database analysis using propensity score-matching. *Anaesthesia* **75**, 1173–1179 (2020).
143. Dean, H. Discussion on the relative value of inhalation and injection methods of inducing anaesthesia. *Br. Med. J.* 869–877 (1907).
144. Denny, N. & Selander, D. Continuous spinal anaesthesia. *Br. J. Anaesth.* **81**, 590–597 (1998).
145. Schneider, M. *et al.* Transient neurologic toxicity after hyperbaric subarachnoid anesthesia with 5% lidocaine. *Anesth. Analg.* **76**, 1154–1157 (1993).
146. Palmer, C. M. Continuous spinal anesthesia and analgesia in obstetrics. *Anesth. Analg.* **111**, 1476–1479 (2010).
147. Moore, J. M. Continuous spinal anesthesia. *Am. J. Ther.* **16**, 289–294 (2009).
148. Minville, V. *et al.* Spinal anesthesia using single injection small-dose bupivacaine versus continuous catheter injection techniques for surgical repair of hip fracture in elderly patients. *Anesth. Analg.* **102**, 1559–1563 (2006).
149. Ye, M., Seet, E. & Kumar, C. M. Myths and mysteries surrounding continuous spinal anaesthesia. *Trends Anaesth. Crit. Care* **17**, 5–10 (2017).
150. Messina, A. *et al.* Hemodynamic changes associated with spinal and general anesthesia for hip fracture surgery in severe ASA III elderly population: a pilot trial. *Minerva Anestesiol* **79**, 1021–9 (2013).
151. Meyhoff, C. S., Hesselbjerg, L., Koscielniak-Nielsen, Z. & Rasmussen, L. S. Biphasic cardiac output changes during onset of spinal anaesthesia in elderly patients. *Eur. J. Anaesthesiol. EJA* **24**, 770–775 (2007).
152. Critchley, L. A. H. Hypotension, subarachnoid block and the elderly patient. *Anaesthesia* **51**, 1139–1143 (1996).
153. Jakobsson, J., Kalman, S. H., Lindeberg-Lindvet, M. & Bartha, E. Is postspinal hypotension a sign of impaired cardiac

performance in the elderly? An observational mechanistic study. *Br. J. Anaesth.* **119**, 1178–1185 (2017).
154. Nakasuji, M. *et al.* Hypotension from spinal anesthesia in patients aged greater than 80 years is due to a decrease in systemic vascular resistance. *J. Clin. Anesth.* **24**, 201–206 (2012).
155. Hofhuizen, C., Lemson, J., Snoeck, M. & Scheffer, G.-J. Spinal anesthesia-induced hypotension is caused by a decrease in stroke volume in elderly patients. *Local Reg. Anesth.* **12**, 19 (2019).
156. White, S. M. *et al.* Secondary analysis of outcomes after 11,085 hip fracture operations from the prospective UK Anaesthesia Sprint Audit of Practice (ASAP-2). *Anaesthesia* **71**, 506–514 (2016).
157. Szucs, S., Rauf, J., Iohom, G. & Shorten, G. D. Determination of the minimum initial intrathecal dose of isobaric 0.5% bupivacaine for the surgical repair of a proximal femoral fracture: a prospective, observational trial. *Eur. J. Anaesthesiol. EJA* **32**, 759–763 (2015).
158. Ben-David, B., Frankel, R., Arzumonov, T., Marchevsky, Y. & Volpin, G. Minidose bupivacaine–fentanyl spinal anesthesia for surgical repair of hip fracture in the aged. *J. Am. Soc. Anesthesiol.* **92**, 6–6 (2000).
159. VanderWeele, T. J. & Ding, P. Sensitivity Analysis in Observational Research: Introducing the E-Value. *Ann. Intern. Med.* **167**, 268 (2017).
160. Nattino, G., Lemeshow, S., Phillips, G., Finazzi, S. & Bertolini, G. Assessing the calibration of dichotomous outcome models with the calibration belt. *Stata J.* **17**, 1003–1014 (2017).
161. Rutter, P. D., Panesar, S. S., Darzi, A. & Donaldson, L. J. What is the risk of death or severe harm due to bone cement implantation syndrome among patients undergoing hip hemiarthroplasty for fractured neck of femur? A patient safety surveillance study. *BMJ Open* **4**, (2014).
162. Guazzi Marco & Naeije Robert. Pulmonary Hypertension in Heart Failure. *J. Am. Coll. Cardiol.* **69**, 1718–1734 (2017).

163. Caravita, S. *et al.* Haemodynamics to predict outcome in pulmonary hypertension due to left heart disease: a meta-analysis. *Eur. Respir. J.* **51**, (2018).
164. Rassir, R., Schuiling, M., Sierevelt, I. N., van der Hoeven, C. W. & Nolte, P. A. What Are the Frequency, Related Mortality, and Factors Associated with Bone Cement Implantation Syndrome in Arthroplasty Surgery? *Clin. Orthop. Relat. Res.* 10.1097 (2020).
165. Sheehan, K. J., Sobolev, B., Chudyk, A., Stephens, T. & Guy, P. Patient and system factors of mortality after hip fracture: a scoping review. *BMC Musculoskelet. Disord.* **17**, 166 (2016).
166. Ekman, E. *et al.* Cementing does not increase the immediate postoperative risk of death after total hip arthroplasty or hemiarthroplasty: a hospital-based study of 10,677 patients. *Acta Orthop.* 1–8 (2019) doi:10.1080/17453674.2019.1596576.
167. Duijnisveld, B. J., Koenraadt, K. L., Van Steenbergen, L. N. & Bolder, S. B. Mortality and revision rate of cemented and uncemented hemiarthroplasty after hip fracture: an analysis of the Dutch Arthroplasty Register (LROI). *Acta Orthop.* **91**, 408–413 (2020).
168. Imam, M. *et al.* The Effect of Type of Femoral Component Fixation on Mortality and Morbidity after Hip Hemiarthroplasty: A Systematic Review and Meta-Analysis. *HSS Journal*® 1–11 (2020).
169. Aslan, A., Atay, T. & Aydoğan, N. H. Risk factors for mortality and survival rates in elderly patients undergoing hemiarthroplasty for hip fracture. *Acta Orthop. Traumatol. Turc.* **54**, 138 (2020).
170. Costain, D. J. *et al.* Perioperative mortality after hemiarthroplasty related to fixation method: A study based on the Australian Orthopaedic Association National Joint Replacement Registry. *Acta Orthop.* **82**, 275–281 (2011).
171. Fenelon, C. *et al.* Perioperative Mortality After Cemented or Uncemented Hemiarthroplasty for Displaced Femoral Neck Fractures—A Systematic Review and Meta-analysis. *J. Arthroplasty* **36**, 777–787 (2021).

172. Talsnes, O. *et al.* Perioperative mortality in hip fracture patients treated with cemented and uncemented hemiprosthesis: a register study of 11,210 patients. *Int. Orthop.* **37**, 1135–1140 (2013).
173. Eamer, G. *et al.* Review of risk assessment tools to predict morbidity and mortality in elderly surgical patients. *Am. J. Surg.* **216**, 585–594 (2018).
174. Tilkeridis, K. *et al.* Validity of Nottingham Hip Fracture Score in Different Health Systems and a New Modified Version Validated to the Greek Population. *Med. Sci. Monit.* **24**, 7665–7672 (2018).
175. de Jong, L., Mal Klem, T., Kuijper, T. M. & Roukema, G. R. Validation of the Nottingham Hip Fracture Score (NHFS) to predict 30-day mortality in patients with an intracapsular hip fracture. *Orthop. Traumatol. Surg. Res.* **105**, 485–489 (2019).
176. Kau, C. Y. & Kwek, E. Can preoperative scoring systems be applied to Asian hip fracture populations? Validation of the Nottingham Hip Fracture Score (NHFS) and identification of preoperative risk factors in hip fractures. *Ann Acad Med Singap.* **43**, 448–53 (2014).
177. Segers, P., Stergiopulos, N. & Westerhof, N. Relation of effective arterial elastance to arterial system properties. *Am. J. Physiol.-Heart Circ. Physiol.* **282**, H1041–H1046 (2002).
178. Critchley, L., Stuart, J., Short, T. & Gin, T. Haemodynamic effects of subarachnoid block in elderly patients. *Br. J. Anaesth.* **73**, 464–470 (1994).
179. Collard, C. D., Eappen, S., Lynch, E. P. & Concepcion, M. Continuous spinal anesthesia with invasive hemodynamic monitoring for surgical repair of the hip in two patients with severe aortic stenosis. *Anesth. Analg.* **81**, 195–198 (1995).
180. Fuzier, R., Murat, O., Gilbert, M., Magues, J. & Fourcade, O. Continuous spinal anesthesia for femoral fracture in two patients with severe aortic stenosis. in vol. 25 528–531 (2006).
181. López, M. M. *et al.* Continuous spinal anaesthesia with minimally invasive haemodynamic monitoring for surgical hip repair in two patients with severe aortic stenosis. *Rev. Bras.*

Anestesiol. **66**, 82–85 (2016).
182. Rostagno, C. *et al.* Outcome in elderly patients with aortic stenosis undergoing hip fracture surgery. Results may suggest a different postoperative strategy? *Trauma Surg. Acute Care Open* **4**, e000218 (2019).
183. Iung, B. *et al.* A prospective survey of patients with valvular heart disease in Europe: The Euro Heart Survey on Valvular Heart Disease. *Eur. Heart J.* **24**, 1231–1243 (2003).
184. Kim, J. *et al.* 481: Severe Aortic Stenosis in Older Patients With Hip Fractures Is Not a Contraindication to Surgery. *Crit. Care Med.* **49**, 231 (2021).
185. Dony, P., Seidel, L., Pirson, M. & Haller, G. Common clinical thresholds of intraoperative hypotension and 30-day mortality following surgery: A retrospective cohort study. *Acta Anaesthesiol. Scand.* **64**, 1388–1396 (2020).
186. Montagnana, M., Cervellin, G., Franchini, M. & Lippi, G. Pathophysiology, clinics and diagnostics of non-thrombotic pulmonary embolism. *J. Thromb. Thrombolysis* **31**, 436–444 (2011).
187. Rothberg, D. L. & Makarewich, C. A. Fat embolism and fat embolism syndrome. *JAAOS-J. Am. Acad. Orthop. Surg.* **27**, e346–e355 (2019).
188. Kerstell, J. Pathogenesis of post-traumatic fat embolism. *Am. J. Surg.* **121**, 712–715 (1971).
189. National Confidential Enquiry into Patient Outcome and Death & Findley, G. *Knowing the risk: a review of the peri-operative care of surgical patients: summary*. (NCEPOD, 2011).
190. Nightingale, F. *Notes on hospitals*. (Longman, Green, Longman, Roberts, and Green, 1863).
191. Carlisle, J. B. Risk prediction models for major surgery: composing a new tune. *Anaesthesia* **74**, 7–12 (2019).
192. Pimentel, M. A. *et al.* A comparison of the ability of the National Early Warning Score and the National Early Warning Score 2 to identify patients at risk of in-hospital mortality: a multi-centre

database study. *Resuscitation* **134**, 147–156 (2019).
193. Elfeky, M. A., Al Sayed, M. S., Sabra, M. M., Mahareak, A. A. & Alkumity, A. A. Randomized comparison of continuous spinal anesthesia versus continuous epidural anesthesia in high-risk elderly patients undergoing major orthopedic lower limb surgeries. *Res. Opin. Anesth. Intensive Care* **6**, 72 (2019).
194. Hatib, F. *et al.* Machine-learning Algorithm to Predict Hypotension Based on High-fidelity Arterial Pressure Waveform Analysis: *Anesthesiology* **129**, 663–674 (2018).
195. Davies, S. J., Vistisen, S. T., Jian, Z., Hatib, F. & Scheeren, T. W. L. Ability of an Arterial Waveform Analysis–Derived Hypotension Prediction Index to Predict Future Hypotensive Events in Surgical Patients: *Anesth. Analg.* **130**, 352–359 (2020).
196. Maheshwari, K. *et al.* Hypotension Prediction Index software for management of hypotension during moderate-to high-risk noncardiac surgery: protocol for a randomized trial. *Trials* **20**, 1–7 (2019).
197. Talsnes, O., Hjelmstedt, F., Dahl, O. E., Pripp, A. H. & Reikerås, O. Clinical and biochemical prediction of early fatal outcome following hip fracture in the elderly. *Int. Orthop.* **35**, 903–907 (2011).
198. Khanna, A. K. *et al.* Postoperative Hypotension and Adverse Clinical Outcomes in Patients Without Intraoperative Hypotension, After Noncardiac Surgery. *Anesth. Analg.* 10–1213 (2021).

APPENDIX

Parameter	Formula	Normal range	Unit
Systolic arterial pressure (SAP)		90-140	mmHg
Diastolic arterial pressure (DAP)		60-90	mmHg
Mean arterial pressure (MAP)	$\frac{SAP + (DAPx2)}{3}$ or measured directly	70-105	mmHg
Central venous pressure (CVP)	Measured directly	2-7	mmHg
Body surface area (BSA) Du Bois and du Bois	$0{,}024265 * cm^{0{,}3964} * kg^{0{,}5378}$		m^2
Cardiac Output (CO)	HR x SV/1000	4-8	l/min
Cardiac Index (CI)	$^{CO}/_{BSA}$	2,5-4	l/min/m^2
Stroke Volume (SV)	$\frac{CO}{HR} x\ 1000$	60-100	ml
Stroke volume Index (SVI)	$\frac{SV}{BSA}$	33-47	ml/m^2
Systemic vascular resistance (SVR)	$\frac{MAP - CVP}{CO} x80$	1000-1500	dynes·sec·cm^{-5}
Systemic vascular resistance index (SVRI)	$\frac{MAP - CVP}{CI} x80$	1970-2390	dynes·sec·cm^{-5}/m^2
Pulmonary vascular resistance index (PVRI)	$\frac{MPAP - PAWP}{CI} x80$	255-285	dynes·sec·cm^{-5}/m^2
Effective arterial elastance	0,9 SAP/SV		mmHg/ml

Table 11 Formula for haemodynamic parameters, MPAP; Mean Pulmonary artery pressure, PAWP; Pulmonary artery wedge pressure.