



RESEARCH ARTICLE

REVISED Fractional spinal anesthesia and systemic hemodynamics in frail elderly hip fracture patients [version 3; peer review: 1 approved, 2 approved with reservations]

Fredrik Olsen , Mathias Hård af Segerstad, Ketii Dalla, Sven-Erik Ricksten, Bengt Nellgård

Anesthesia and Critical Care, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden

V3 First published: 24 Feb 2023, 12:210
<https://doi.org/10.12688/f1000research.130387.1>
 Second version: 04 May 2023, 12:210
<https://doi.org/10.12688/f1000research.130387.2>
 Latest published: 31 Jul 2023, 12:210
<https://doi.org/10.12688/f1000research.130387.3>

Abstract

Background: Systemic haemodynamic effects of intrathecal anaesthesia in an aging and frail population has not been well investigated. We examined the systemic haemodynamics of fractional spinal anaesthesia following intermittent microdosing of a local anaesthetic and an opioid.

Methods: We included 15 patients aged over 65 with significant comorbidities, planned for hip fracture repair. Patients received a spinal catheter and cardiac output monitoring using the LiDCOplus system. All measurements were performed prior to start of surgery. Invasive mean arterial pressure (MAP), cardiac index (CI), systemic vascular resistance index (SVRI), heart rate and stroke volume index (SVI) were registered. Two doses of bupivacaine 2.25 mg and fentanyl 15 µg were administered with 25-minute intervals. Hypotension was defined as a fall in MAP by >30% or a MAP <65 mmHg.

Results: The incidence of hypotension was 30%. Hypotensive patients (n=5) were treated with low doses of norepinephrine (0.01-0.12 µg/kg/min). MAP showed a maximum reduction of 17% at 10 minutes following the first dose. CI, systemic vascular resistance index and stroke volume index decreased by 10%, 6%, and 7%, respectively, while heart rate was unchanged over time. After the second dose, none of the systemic haemodynamic variables were affected.

Conclusions: Fractional spinal anaesthesia administered prior to surgery induced a minor to moderate fall in MAP, mainly caused by a reduction in cardiac output, induced by systemic venodilation, causing a fall in venous return. Our results are contrary to the widely held belief that hypotension is mainly the result of a reduction of systemic vascular resistance.

Open Peer Review

Approval Status

	1	2	3
version 3 (revision) 31 Jul 2023	 view		
version 2 (revision) 04 May 2023	 view	 view	 view
version 1 24 Feb 2023	 view		

- Luigi La Via** , "Policlinico-San Marco" University Hospital, Catania, Italy
- Michael Irwin** , The University of Hong Kong, Hong Kong, Hong Kong
- Tony Kwun-Tung Ng** , The University of Hong Kong, Hong Kong, Hong Kong
 Frankston Pain Management, Melbourne, Australia
 Tuen Mun Hospital, Hong Kong, Hong Kong
 The Chinese University of Hong Kong, Hong Kong, Hong Kong
 The Hong Kong Polytechnic University, Hong Kong

Keywords

Spinal Anesthesia, hip fracture surgery, cardiac output, hypotension, elderly patients

Kong, Hong Kong

Any reports and responses or comments on the article can be found at the end of the article.

Corresponding author: Fredrik Olsen (fredrik.olsen@vgregion.se)

Author roles: **Olsen F:** Conceptualization, Data Curation, Formal Analysis, Investigation, Visualization, Writing – Original Draft Preparation; **Hård af Segerstad M:** Conceptualization, Methodology, Writing – Review & Editing; **Dalla K:** Writing – Review & Editing; **Ricksten SE:** Conceptualization, Methodology, Writing – Review & Editing; **Nellgård B:** Project Administration, Writing – Review & Editing

Competing interests: No competing interests were disclosed.

Grant information: This study was supported by Swedish State Support for Clinical Research (LUA-ALF).

Copyright: © 2023 Olsen F *et al.* This is an open access article distributed under the terms of the [Creative Commons Attribution License](#), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

How to cite this article: Olsen F, Hård af Segerstad M, Dalla K *et al.* **Fractional spinal anesthesia and systemic hemodynamics in frail elderly hip fracture patients [version 3; peer review: 1 approved, 2 approved with reservations]** F1000Research 2023, 12:210 <https://doi.org/10.12688/f1000research.130387.3>

First published: 24 Feb 2023, 12:210 <https://doi.org/10.12688/f1000research.130387.1>

REVISED Amendments from Version 2

Minor changes in wording of the discussion paragraph as per reviewers suggestion.

Any further responses from the reviewers can be found at the end of the article

Introduction

A hip fracture in a frail elderly patient poses a major challenge in anesthesiology as these patients are mostly presented off-hours and many have comorbidities.¹ The 30-day mortality among hip fracture patients is as high as 6-10%.² Many factors have been associated with mortality, including time to start-of-surgery,³ cementation of hemi- or total arthroplasty,⁴ male sex,⁵ and preoperative morbidity assessed by the American Society of Anaesthesiologist (ASA) risk score and Nottingham Hip Fracture Score (NHFS).^{6,7} Preoperative cardiology consulting, however, rarely affects surgical management, but could alter anesthesiologic management.⁸

The peri-operative anaesthesia strategy for the management of the frail hip fracture patient differs worldwide: where many centers give general anaesthesia, while particularly in northern Europe, neuraxial anaesthesia is the preferred technique.⁹ However, both techniques frequently induce hypotension, requiring fluid resuscitation and/or the need for vasopressors.¹⁰ Perioperative hypotension is a problem predisposing patients to organ hypoperfusion with consequences such as myocardial injury, delirium and renal failure.^{10,11} The physiological origin of the hypotension is unclear, but many anesthesiologists believe that the decrease of systemic vascular resistance (SVR) is the main cause of hypotension,¹² while others believe that hypotension is caused by a fall in cardiac output¹³ or a combination of both.

In our hospital, we routinely administer neuraxial anaesthesia for hip fracture surgery. We have a vast experience with this technique and in the present study we utilized the continuous spinal anaesthesia (CSA) technique to elucidate the hemodynamic response to fractional dosing without the influence of surgical manipulation. The use of CSA is well recognized to have a limited effect on hypotension.¹⁴ It also allows us to study the hemodynamics in a prolonged period prior to surgery, minimizing the potential for other factors such as positioning, sedation and surgical stress to influence the measurements in a way a single shot spinal does not. The hemodynamics were monitored with LiDCOplus. LiDCOplus is a validated system in which a lithium dilution technique is used to calibrate the arterial pulse contour analysis.¹⁵ The LiDCO system has previously been used in hip fracture patients in the perioperative setting.¹⁶⁻¹⁸ The advantage of LiDCO compared to other invasive hemodynamic devices is that lithium can be injected in a peripheral venous cannula and then lithium concentration is captured through a standard 20G arterial cannula. Thus, we could avoid more invasive monitoring using central venous catheters, femoral arterial cannula, or the Swan-Ganz catheter.

The aim of the present study was to investigate the systemic haemodynamic response to fractional spinal anaesthesia, in a group of elderly and comorbid patients with hip fracture, using the LiDCOplus system to monitor pre-surgical haemodynamic changes over time.

Methods

Ethical approval was granted by the Gothenburg Regional Ethical Review Board (Dnr 2020-05684). During the study period we screened daily for patients planned for hip fracture surgery and these were identified through the theatre planning software (Orbit, TietoEVERY, Espoo, Finland). Inclusion criteria were: 1) patient with hip fracture, 2) >65 years of age, 3) ASA ≥ 2 , 4) scheduled for neuraxial anaesthesia and 5) mentally fit to give written informed consent or permission by next-of-kin in cognitive impaired patients. Exclusion criteria were: a) lithium or anticoagulation medication, b) planned for general anaesthesia, c) ongoing atrial fibrillation, d) if surgery was delayed >72 hours, e) lack of informed consent and f) patient agitation requiring intermittent sedation. The study was carried out in accordance with the Declaration of Helsinki (2000). Finally, inclusion rate was dependent and affected by the primary investigator's availability and the operative capacity, by recruiting consecutive cases within these limitations we aspired to recruit a representative selection of patients with regards to self-reported gender and level of comorbidity. NHFS was calculated, the scale going from 1-10 with higher numbers correlated to a higher 30-day mortality.^{6,19} ASA grade along with defined laboratory values, demographic data and chronic disease were also recorded after study inclusion.

After arriving to the preoperative area, patients were given 5 liters of oxygen on a face mask and ECG and pulse-oximetry monitoring was started. Oral premedication with standardized doses of paracetamol (1 g) and oxycodone (5 mg) was given orally, followed by the placement of a venous 18G cannula in an antecubital vein and a radial arterial catheter (20G). The patient was also given a fascia iliaca compartment (FIC) block, or an ultrasound guided femoral nerve block with ropivacaine 3.5 mg/mL 20-40mL, to minimize discomfort and to avoid sedation or systematic

analgesia when positioning for the neuraxial block. In addition, the LiDCOplus (LiDCO Group Plc, London, England) system was set up and calibrated according to manufacturer's instructions. Calibration was performed with 0.3-0.45 mmol lithium chloride injection based on body weight. After calibration and baseline parameter registration, the LiDCOplus system provided cardiac output variables and based on these and the invasive blood pressure, haemodynamic variables could be derived.

Following aseptic skin preparation of the lumbar area, a subarachnoid puncture by a 18G Tuohy needle was performed either between the L2 - L3 or the L3 - L4 interspaces, preferably using a mid-line approach. An intrathecal catheter 20G was then inserted 4-5 cm into the intrathecal space. This technique of a continuous spinal anaesthesia (CSA) was performed on all patients by a dedicated physician (FO).

An intrathecal mixture (10 mL) containing 1.5 mg/mL bupivacaine and 10 µg/mL fentanyl was prepared. Intrathecal anaesthesia was induced by giving 1.5 mL (2.25 mg of bupivacaine and 15 µg of fentanyl) of the mixture, followed by a second 1.5 mL injection after 25 min (*i.e.*, a total intrathecal dose of 4.5 mg of bupivacaine and 30 µg of fentanyl). Sensory level was monitored by "cold spray". Hemodynamic recordings were documented every five minutes up until 45 minutes after initial intrathecal dose when research monitoring was also terminated. The patient was then operated upon in the pre-planned time slot and was further managed at the discretion of the attending anesthetist.

Mean arterial blood pressure (MAP) was maintained, when needed, with a norepinephrine infusion to target a MAP >65 mmHg or to avoid more than 30% decline in MAP from baseline. In addition to SaO₂ and ECG, the following parameters were recorded: cardiac index (CI), stroke volume index (SVI), systemic vascular resistance index (SVRI), systolic arterial pressure, (SAP), diastolic arterial pressure (DAP) and nor-epinephrine doses over time. Finally, effective arterial elastance (EA) was calculated by the formula; $0.9 \times \text{SAP} / \text{SV}$.²⁰ For indexing parameters, the Du Bois and Du Bois formula for body surface area (BSA) was used.²¹

Statistics

Statistical analysis was performed with RStudio for Mac (version 1.2.5033) and GPower version 3.1.9.6 (Franz Faul, Universität Kiel, Germany) to determine sample size. Normality was assessed with Shapiro-Wilk test prior to deciding appropriate variation testing, one-way repeated measures ANOVA for normally distributed and Friedmann test for non-normal distributions. For repeated measures, ANOVA was utilized to study changes in haemodynamic variables over time. A p-value <0.05 was considered statistically significant. A sample size of n=13 patients for the repeated measured ANOVA was needed to have an 80% power ($\beta=0.20$) for detection the effect size $F=0.25$ ($\alpha=0.05$).

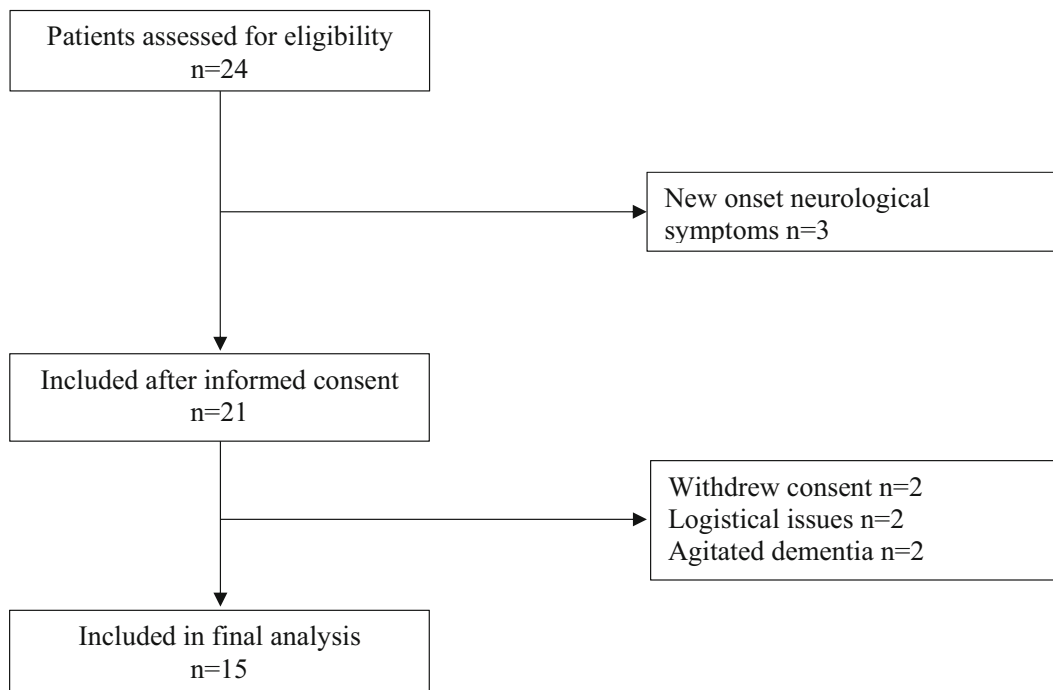


Figure 1. Consort diagram.

Results

The clinical trial profile is shown in [Figure 1](#). A total of 24 patients were eligible for the study inclusion, of whom 15 were finally included. Two patients withdrew consent, two patients were excluded due to logistical issues, two patients were excluded for agitated dementia and finally, three patients were excluded due to having new onset of neurological symptoms. Hypertension was the dominant comorbidity present in 73% of patients, while dementia was found in 47%. Prior or present malignancy was found in 33% of patients. Further demographic data of the studied patients are summarized in [Table 1](#). The study population had a median age of 89 years and consisted primarily of women (12/15). The median ASA grade was 3 (range 2-4) and the median NHFS score was 5 (range 4-7). None of the patients had significant arrhythmias during the experimental procedure and none required vasopressor support prior to the first intrathecal dose of the bupivacaine/fentanyl mixture was given.

Sensory and motor functions were assessed, revealing that all patients had satisfactory levels of sensory block at minimum (>Th 12) documented with sensation to cold or painful reaction to flexion of the hip, which is the same assessment used for the single shot spinal prior to surgery. In mentally intact patients, all had a temperature discrimination demonstrated by a sensory block <Th 8 level. Further, we noticed a high incidence of retained motor function after the initial neuraxial 1.5 mL dose (2.25 mg bupivacaine and 15 µg fentanyl), possibly due to a less dense blockade.

Data on systemic haemodynamics are shown in [Figures 2–7](#). MAP, CI, SVRI, SVI and arterial elastance were all found to have normal distribution at each point of measurement according to Shapiro-Wilk's test. After applying the one-way repeated measures ANOVA test, MAP, SVRI, SVI and CI all showed significant variance over time. Thus, MAP decreased by 17% from baseline with the lowest mean noted at 10 min after the first intrathecal dose was given. CI was reduced by 10% also after 10 minutes. SVRI showed a 6% reduction from baseline found directly after the intrathecal dose was given. SVI dropped by 7% with a lowest mean value at 10 minutes after anaesthesia induction and, finally, heart rate decreased non-significantly by 3% from baseline. Elastance did not show significant variation over time as measured

Table 1. Demographic data.

	Overall (N=15)
Gender, n (%)	
Female	12 (80%)
Male	3 (20%)
Age, (y; range)	89 (69-94)
ASA, n (%)	
2	4 (27%)
3	10 (67%)
4	1 (7%)
NHFS, n (%)	
4	6 (40%)
5	3 (20%)
6	4 (27%)
7	2 (13%)
Body mass index (kg/m²)	22.0 (3.71)
Body surface area (m²)	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%)

ASA: American Society of Anesthesiologists risk score, NHFS: Nottingham Hip Fracture Score, COPD; chronic obstructive pulmonary disease. Values are mean±SD, Age is median (range).

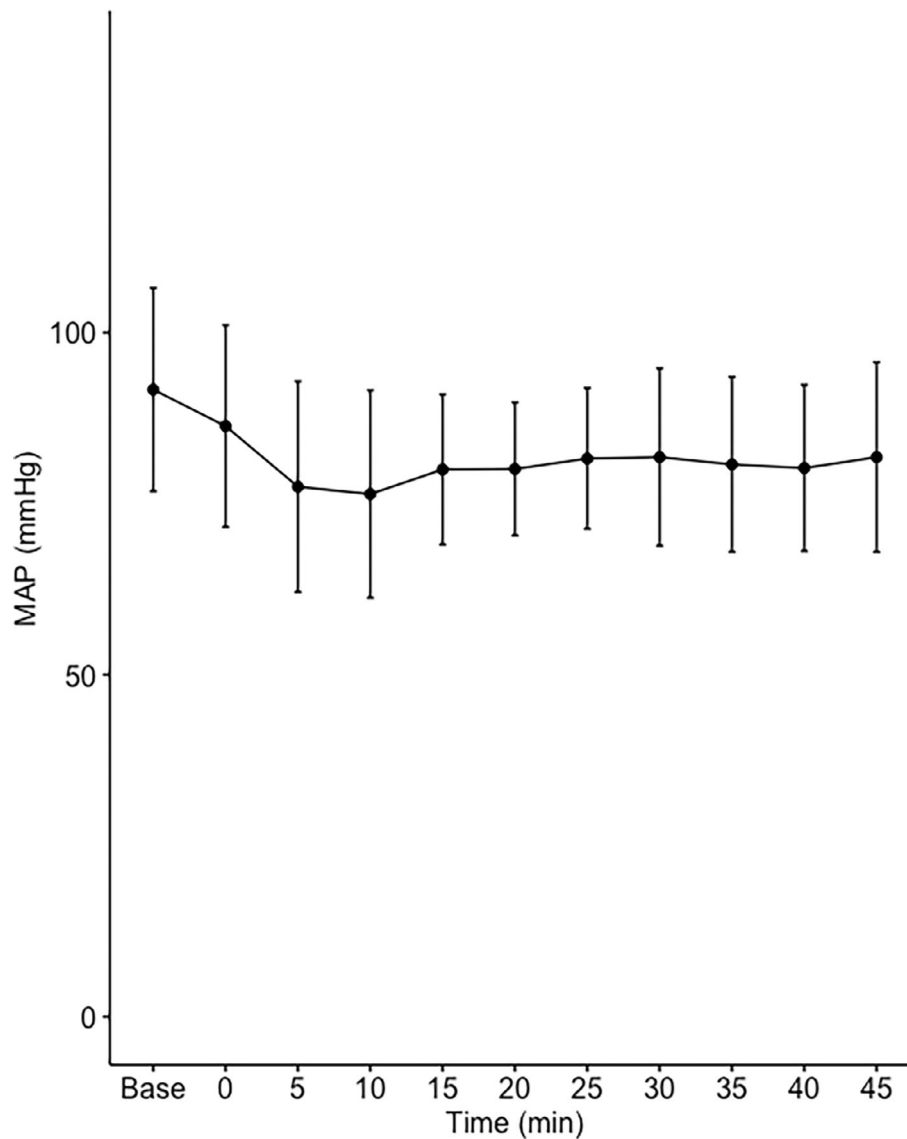


Figure 2. Changes in mean arterial pressure over time (mean±1SD).

by ANOVA. The largest reduction from the baseline value was -10% at 5 min after the initial spinal dose. One third (5/15) of the patients required norepinephrine infusion either to maintain a MAP>65 mmHg or to avoid a decrease by >30% from the baseline. The largest dose used was 0.12 µg/kg/min (Table 2).

Discussion

The main findings of the present study were that the hemodynamic aberrations after induction of fractional spinal anesthesia were minor to moderate, with a maximal fall in CI and MAP of 10-17%, 10 minutes following the first dose. After the second dose, no further changes in hemodynamics were seen arguing for a hemodynamic stability using CSA.

Interestingly, the maximal fall in SVRI was 6% and appeared early after the first dose with no further fall after the second dose. Thus, the MAP reduction was less than expected and the major contributor to the fall in MAP was a fall in CI, which explained almost 60% of the MAP reduction. This leads us to the conclusion that fractional spinal anaesthesia, as described in the present study, induces a vasodilation more prominent in systemic venous capacitance vessels, which decreases venous return and cardiac preload, as reflected by a decrease in SVI.

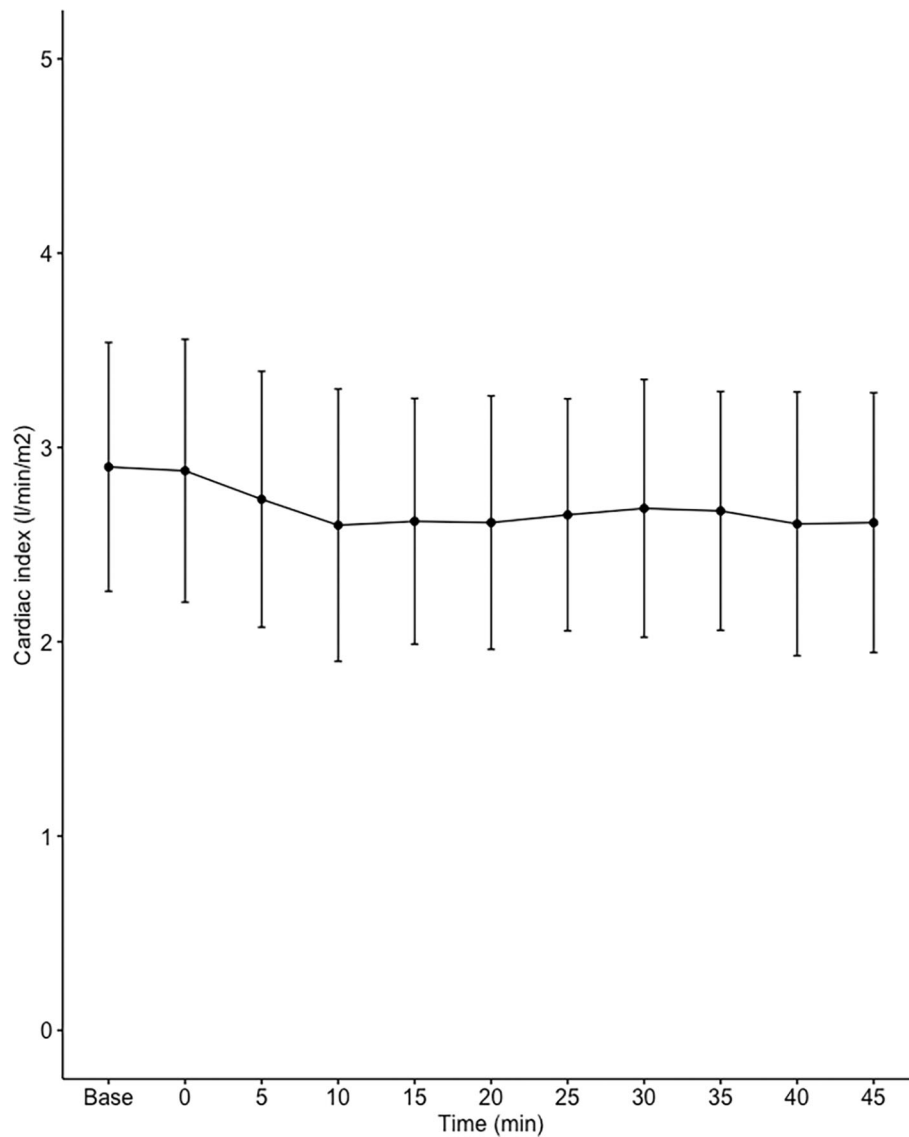


Figure 3. Changes in cardiac index over time (mean±1SD).

In this study, we defined hypotension as having a MAP <65 mmHg or a decrease of MAP >30% from the baseline level, a definition previously used in other studies.^{22–24} Using this definition, the incidence of hypotension following single-shot spinal anaesthesia, has previously been described as being 28–69%, which is considerably higher than noted in the present study.^{25,26} Hypotension from a spinal anaesthesia has been described by Butterworth²⁷ as a decrease in systemic vascular resistance and central venous pressure as a result of the sympathetic block, with vasodilation of both systemic resistance vessels as well as venous capacitance vessels, the latter causing redistribution of central blood volume to the lower extremities and splanchnic beds and thus impaired venous return. In the present study, MAP decreased by 17%, CI by 10%, SVRI by 6% and SVI by 7% at 10 minutes after the initial intrathecal injection. Our data imply that the MAP reduction can not be explained by a reduction in SVRI alone. The proportionally larger fall in CI implicates vasodilation more on the venous capacitance vessels, leading to reduced venous return and subsequently a fall in CI and MAP. These findings are in line with the findings of Jakobsson *et al.*, showing that a single shot of spinal anaesthesia (15 mg bupivacaine) induced hypotension in 50% of the patients, mainly caused by a fall in CI (20%) and SVI (15%).¹³ Nakasuji *et al.*, on the other hand, found that the hypotension seen after a single-shot spinal anaesthesia (10 mg bupivacaine), in elderly patients, was mainly caused by systemic vasodilation and a fall in SVRI.¹² Our data exhibited a significantly smaller fall in SVRI than described by Salinas *et al.*,²⁸ possibly due to lower dosing achieved with intermittent dosing and subsequently lower levels of sympathetic block. Effective arterial elastance (Ea) incorporates all elements of total LV

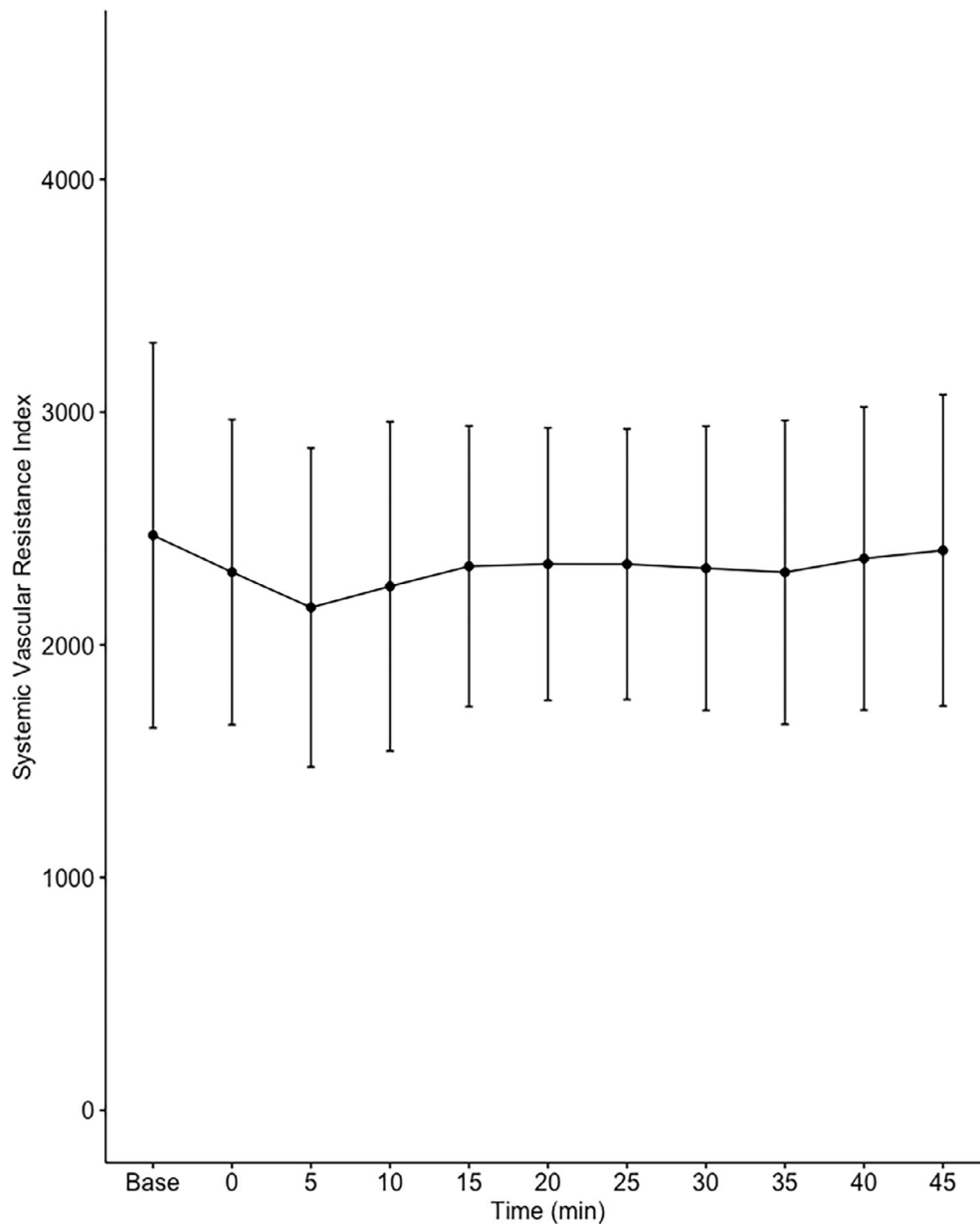


Figure 4. Changes in systemic vascular resistance index over time (mean \pm 1SD).

afterload, including vascular resistance, arterial compliance and characteristic impedance.²⁹ The finding that E_a was not affected by fractional spinal anaesthesia also indicates that the driving force of hypotension in the present study was systemic venodilation.

Single-shot neuraxial anaesthesia is predominantly used around the world in in this population of patients. Dosages have decreased over time and in our clinical routine, we rarely administer more than 2.5 mL of mixtures of local anesthetics and opioids. The injection time the mixture is given may have an effect on the hypotension severity and we await studies addressing this topic. In an interesting study by Szucs *et al.*³⁰ they used the “up-and-down” method described by Dixon and Massey in 1969 to find the lowest intrathecal dose of local anesthetic to provide adequate anaesthesia for a hip fracture operation.³¹ They concluded that 0.24 mL of 5 mg/mL isobaric bupivacaine was enough as a single dose but still recommended a dose of 0.4 mL or more *i.e.* 2 mg. A more recent meta-analysis concluded that 6.5 mg of bupivacaine seems sufficient for hemodynamic stability, patient comfort and adequate motor block.³² This is in concert with the present investigation where we gave dosages of 2.25 mg of isobaric bupivacaine although diluted to 1.5 mg/mL with

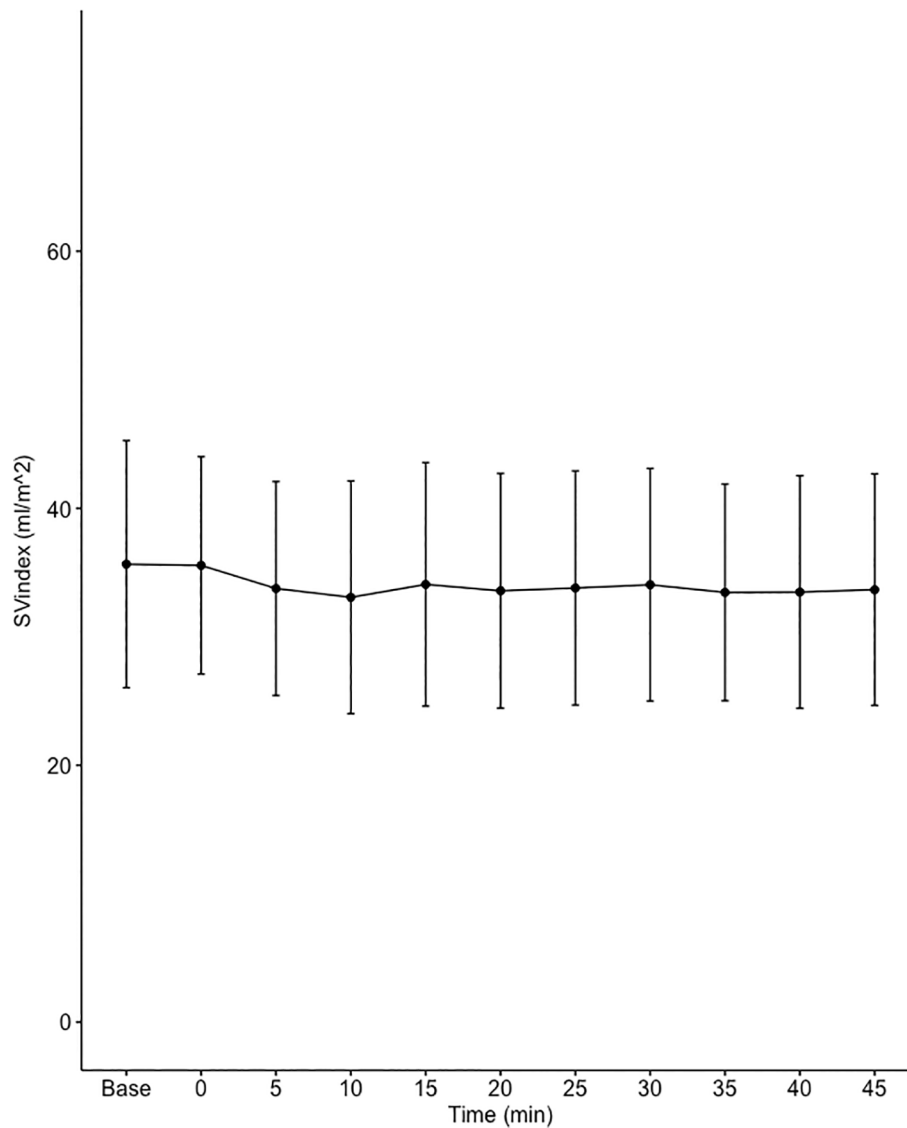


Figure 5. Changes in stroke volume index (SVI) over time (mean \pm 1SD).

sodium chloride and fentanyl. The volume in this study was larger, being 1.5 mL of the above-stated-mixture. However, most clinicians would not consider administering such low doses with the eminent risk of blockade failure and forcing the attending anaesthesiologist to give general anaesthesia, an alternative considered worse at the preoperative evaluation.

An attractive alternative to single-shot spinal is the continuous spinal anaesthesia (CSA) a technique described in the 1940's³³ and improved by catheter insertion.³⁴ CSA has been associated with fewer incidents of hypotension *per se* and less severe episodes of hypotension.³⁵ This led us to revisit the technique at our clinic, as we have many hip fracture patients and many of them with variable severity of aortic stenosis.^{36–38} We confirm the result of Minville *et al.* that by carefully giving a CSA we can avoid severe hypotensive incidents even in frail patients.³⁵ A side effect of this lower dosing was a less prominent motor blockage, also noted in the present investigation.

LiDCOplus is a semi-invasive, (needing an arterial catheter), validated method enabling us to register haemodynamic variables without the need for central venous- and/or Swan-Ganz catheters. The LiDCO system is therefore less invasive and does not require a higher degree of invasiveness than is routinely included in the normal clinical management of hip fracture patients at our hospital. To our knowledge, the golden standard technique for measuring cardiac output is the use of a Swan-Ganz catheter with thermodilution, but this technique is hardly doable in a cohort of frail elderly hip fracture

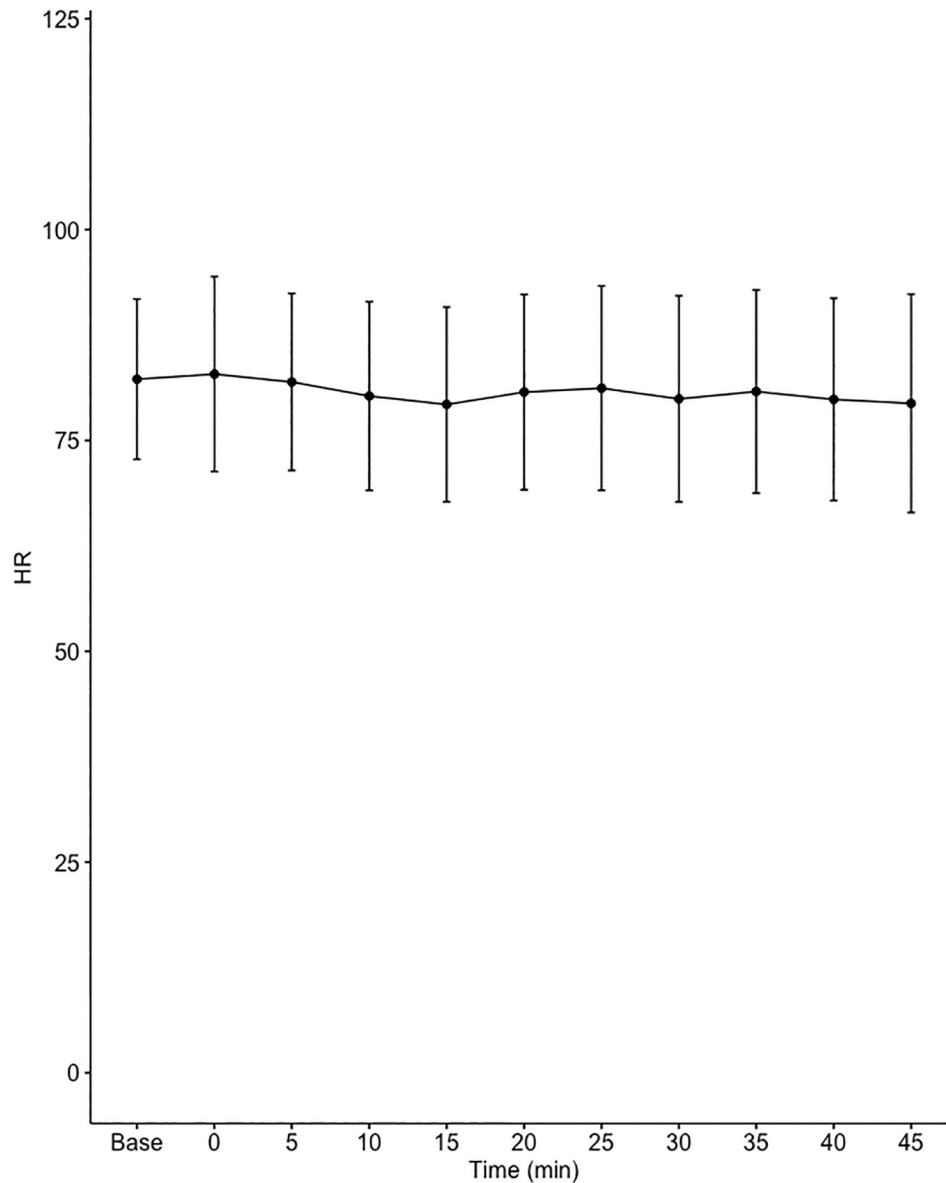


Figure 6. Changes in heart rate (HR) over time (mean \pm 1SD).

patients. Calibrated cardiac output (CO) using LiDCO monitoring is relatively easy and quick to start in patients already in need of arterial cannulation and provides a deeper insight into perioperative haemodynamic changes.

Limitation and strengths

With only 15 included patients the generalizability of our findings may be limited. We were restricted by the dynamic nature of running an effective emergency operating list, but also by the prevalence of patient anticoagulation therapy limiting the use of neuraxial anaesthesia in general and indwelling spinal catheter in particular. Haemodynamic monitoring with LiDCOplus gives us estimations of cardiac output after calibration where all other haemodynamic variables are derived from CO from the pulse power analysis and invasive blood pressure together with the heart rate. A strength of our study is that the cohort was very homogenous with similar age, fracture type, sex and surgical procedure in a single tertiary orthopedic center. Demographically our patients were older with an elevated risk of higher mortality and morbidity versus the average hip fracture population (Table 1). All patients were included from the acute list and were operated upon during office hours.

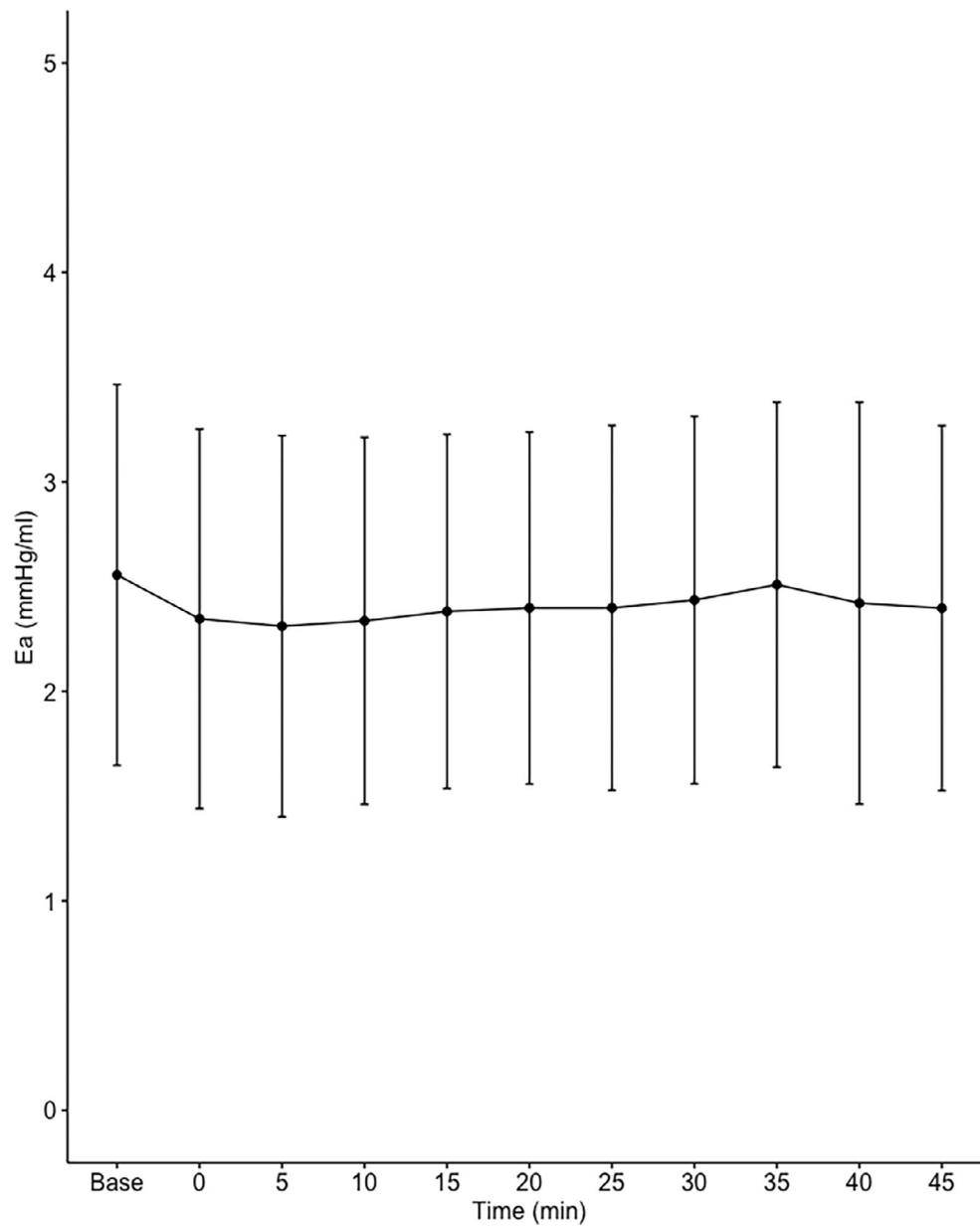


Figure 7. Changes in effective arterial elastance over time (mean \pm 1SD).

Registry data of the Swedish hip fracture population demonstrates an average age of 82 and around 2/3 being female.² Thus, our patient cohort was seven years older and thereby probably frailer than the average hip fracture patient. A surrogate marker for frailty in this investigation was ASA grading (mean value 3) and the NHFS score (mean value 5), both slightly elevated *versus* the Swedish average.² Both scales assess comorbidity in various ways and are further used as prognostic scores for mortality risk in the perioperative and postoperative phase, like 30-day mortality.^{4,7} Therefore, we claim to have succeeded in finding a patient population with high comorbidity, speculatively having a higher risk for intraoperative hypotension than the average hip fracture population.

Table 2. Changes in hemodynamic variables over time.

	Baseline	0 min Dose 1	5 min	10 min	15 min	20 min	25 min Dose 2	30 min	35 min	40 min	45 min	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/m ²)	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/cm ⁵ /m ²)	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/m ²)	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

MAP: mean arterial pressure, CI: cardiac index, SVRI: systemic vascular resistance index, SVI: stroke volume index, HR: heart rate, Ea: arterial elastance.

Conclusions

Our results confirm that spinal anaesthesia-induced hypotension is not solely a result of a fall in SVRI but mainly by systemic venodilation, reducing venous return to the heart and followed by a consequent fall in CO and MAP. The incidence of hypotension was low and only one third of the patients needed nor-epinephrine infusions all at modest doses, highest infusion rate was 0.12 µg/kg/min nor-epinephrine. Our results contradict the idea of spinal anaesthesia-induced hypotension as being solely a result of a fall in SVRI due to loss of sympathetic vascular tone.

Authors contributions

FO: Planned and designed the study. Established intrathecal catheter and set up LidCO monitoring, collected and analyzed data. Wrote the first draft.

MHaS: Planned and designed the study and revised the manuscript

KD: Revised the manuscript

SER: Planned and designed the study and revised the manuscript

BN: Planned and designed the study and revised the manuscript

Data availability

Underlying data

Open Science Framework: Fractional anesthesia lidco, <https://doi.org/10.17605/OSF.IO/XAGBY>.³⁹

This project contains the following underlying data:

- fractionspinalidcoFO.csv

Data are available under the terms of the [Creative Commons Zero “No rights reserved” data waiver](#) (CC0 1.0 Public domain dedication).

Reporting guidelines

Open Science Framework: TREND checklist for “Fractional spinal anesthesia and systemic hemodynamics in frail elderly hip fracture patients”, <https://doi.org/10.17605/OSF.IO/D98VG>.⁴⁰

Data are available under the terms of the [Creative Commons Zero “No rights reserved” data waiver](#) (CC0 1.0 Public domain dedication).

Acknowledgements

We are grateful for the assistance and support of the nursing staff at the Department of Anaesthesia and Intensive Care at Sahlgrenska University Hospital/Mölndal. This study was supported by Swedish State Support for Clinical Research (LUA-ALF).

A version of this manuscript is available as a preprint on ResearchSquare (<https://doi.org/10.21203/rs.3.rs-1053831/v1>).

References

1. Lunde A, Tell GS, Pedersen AB, *et al.*: **The Role of Comorbidity in Mortality After Hip Fracture: A Nationwide Norwegian Study of 38,126 Women With Hip Fracture Matched to a General-Population Comparison Cohort.** *Am. J. Epidemiol.* 2019; **188**: 398–407.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
2. Rikshöft: **Rikshöft 2018. Rikshöft Årsrapport.** 2018. Accessed December 16, 2020.
[Reference Source](#)
3. Kristiansson J, Hagberg E, Nellgård B: **The influence of time-to-surgery on mortality after a hip fracture.** *Acta Anaesthesiol. Scand.* 2020; **64**: 347–353.
[PubMed Abstract](#) | [Publisher Full Text](#)
4. Olsen F, Hård Af Segerstad M, Nellgård B, *et al.*: **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.* 2020; **91**: 293–298.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
5. Aslan A, Atay T, Aydoğan NH: **Risk factors for mortality and survival rates in elderly patients undergoing hemiarthroplasty for hip fracture.** *Acta Orthop. Traumatol. Turc.*

- 2020; **54**: 138–143.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
6. Moppett IK, Parker M, Griffiths R, *et al.*: **Nottingham Hip Fracture Score: longitudinal and multi-centre assessment.** *Br. J. Anaesth.* 2012; **109**: 546–550.
[PubMed Abstract](#) | [Publisher Full Text](#)
 7. Johansen A, Tsang C, Boulton C, *et al.*: **Understanding mortality rates after hip fracture repair using ASA physical status in the National Hip Fracture Database.** *Anaesthesia.* 2017; **72**: 961–966.
[PubMed Abstract](#) | [Publisher Full Text](#)
 8. Smeets SJM, van Wunnik BPW, Poeze M, *et al.*: **Cardiac overscreening hip fracture patients.** *Arch. Orthop. Trauma Surg.* 2020; **140**: 33–41.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 9. Neuman MD, Feng R, Carson JL, *et al.*: **Spinal Anesthesia or General Anesthesia for Hip Surgery in Older Adults.** *N. Engl. J. Med.* 2021; **385**(22): 2025–2035.
[PubMed Abstract](#) | [Publisher Full Text](#)
 10. Beecham G, Cusack R, Vencken S, *et al.*: **Hypotension during hip fracture surgery and postoperative morbidity.** *Ir. J. Med. Sci. (1971-).* 2020; 1–10.
[PubMed Abstract](#) | [Publisher Full Text](#)
 11. Jang WY, Jung J-K, Lee DK, *et al.*: **Intraoperative hypotension is a risk factor for postoperative acute kidney injury after femoral neck fracture surgery: a retrospective study.** *BMC Musculoskelet. Disord.* 2019; **20**: 1–5.
[PubMed Abstract](#) | [Publisher Full Text](#)
 12. Nakasuji M, Suh SH, Nomura 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.* 2012; **24**: 201–206.
[PubMed Abstract](#) | [Publisher Full Text](#)
 13. Jakobsson J, Kalman SH, Lindeberg-Lindvet M, *et al.*: **Is postspinal hypotension a sign of impaired cardiac performance in the elderly? An observational mechanistic study.** *Br. J. Anaesth.* 2017; **119**: 1178–1185.
[PubMed Abstract](#) | [Publisher Full Text](#)
 14. Almeida CR, Cunha P, Vieira L, *et al.*: **Low-dose spinal block for hip surgery: A systematic review.** *Trends Anaesth. Crit. Care.* 2022; **45**: 5–20.
[Publisher Full Text](#)
 15. Pearce RM, Ikram K, Barry J: **Equipment review: An appraisal of the LiDCO™ plus method of measuring cardiac output.** *Crit. Care.* 2004; **8**: 1–6.
[PubMed Abstract](#) | [Publisher Full Text](#)
 16. Wiles MD, Whiteley WJ, Moran CG, *et al.*: **The use of LiDCO based fluid management in patients undergoing hip fracture surgery under spinal anaesthesia: neck of femur optimisation therapy-targeted stroke volume (NOTTS): study protocol for a randomized controlled trial.** *Trials.* 2011; **12**: 1–8.
[PubMed Abstract](#) | [Publisher Full Text](#)
 17. Moppett IK, Rowlands M, Mannings A, *et al.*: **LiDCO-based fluid management in patients undergoing hip fracture surgery under spinal anaesthesia: a randomized trial and systematic review.** *Br. J. Anaesth.* 2015; **114**: 444–459.
[PubMed Abstract](#) | [Publisher Full Text](#)
 18. Bartha E, Arfwedson C, Imnell A, *et al.*: **Towards individualized perioperative, goal-directed haemodynamic algorithms for patients of advanced age: observations during a randomized controlled trial (NCT01141894).** *Br. J. Anaesth.* 2016; **116**: 486–492.
[PubMed Abstract](#) | [Publisher Full Text](#)
 19. Maxwell MJ, Moran CG, Moppett IK: **Development and validation of a preoperative scoring system to predict 30 day mortality in patients undergoing hip fracture surgery.** *Br. J. Anaesth.* 2008; **101**: 511–517.
[PubMed Abstract](#) | [Publisher Full Text](#)
 20. Jozwiak M, Millasseau S, Richard C, *et al.*: **Validation and critical evaluation of the effective arterial elastance in critically ill patients.** *Crit. Care Med.* 2019; **47**: e317–e324.
[PubMed Abstract](#) | [Publisher Full Text](#)
 21. Burton RF: **Estimating body surface area from mass and height: theory and the formula of Du Bois and Du Bois.** *Ann. Hum. Biol.* 2008; **35**: 170–184.
[PubMed Abstract](#) | [Publisher Full Text](#)
 22. Kouz K, Hoppe P, Briesenick L, *et al.*: **Intraoperative hypotension: Pathophysiology, clinical relevance, and therapeutic approaches.** *Indian J. Anaesth.* 2020; **64**: 90.
[PubMed Abstract](#) | [Publisher Full Text](#)
 23. Sessler DI, Khanna AK: **Perioperative myocardial injury and the contribution of hypotension.** *Intensive Care Med.* 2018; **44**: 811–822.
[PubMed Abstract](#) | [Publisher Full Text](#)
 24. Sessler DI, Bloomstone JA, Aronson S, *et al.*: **Perioperative quality initiative consensus statement on intraoperative blood pressure, risk and outcomes for elective surgery.** *Br. J. Anaesth.* 2019; **122**: 563–574.
[PubMed Abstract](#) | [Publisher Full Text](#)
 25. Wood R, White S: **Anaesthesia for 1131 patients undergoing proximal femoral fracture repair: a retrospective, observational study of effects on blood pressure, fluid administration and perioperative anaemia.** *Anaesthesia.* 2011; **66**: 1017–1022.
[PubMed Abstract](#) | [Publisher Full Text](#)
 26. Critchley LAH: **Hypotension, subarachnoid block and the elderly patient.** *Anaesthesia.* 1996; **51**: 1139–1143.
[Publisher Full Text](#)
 27. Butterworth J: **Physiology of spinal anesthesia: what are the implications for management?** *Reg. Anesth. Pain Med.* 1998; **23**: 370–373.
[PubMed Abstract](#) | [Publisher Full Text](#)
 28. Salinas FV, Sueda LA, Liu SS: **Physiology of spinal anaesthesia and practical suggestions for successful spinal anaesthesia.** *Best Pract. Res. Clin. Anaesthesiol.* 2003; **17**: 289–303.
[PubMed Abstract](#) | [Publisher Full Text](#)
 29. Segers P, Stergiopoulos N, Westerhof N: **Relation of effective arterial elastance to arterial system properties.** *Am. J. Phys. Heart Circ. Phys.* 2002; **282**: H1041–H1046.
[Publisher Full Text](#)
 30. Szucs S, Rauf J, Iohom G, *et al.*: **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.* 2015; **32**: 759–763.
[PubMed Abstract](#) | [Publisher Full Text](#)
 31. Dixon WJ, Massey FJ Jr: **Introduction to statistical analysis.** 1951.
 32. Messina A, La Via L, Milani A, *et al.*: **Spinal anesthesia and hypotensive events in hip fracture surgical repair in elderly patients: a meta-analysis.** *J. Anesth. Analg. Crit. Care.* 2022; **2**: 19.
[Publisher Full Text](#)
 33. Lemmon WT: **A method for continuous spinal anesthesia: A preliminary report.** *Ann. Surg.* 1940; **111**: 141–144.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 34. Tuohy EB: **The use of continuous spinal anesthesia: utilizing the ureteral catheter technic.** *J. Am. Med. Assoc.* 1945; **128**: 262–264.
[Publisher Full Text](#)
 35. Minville V, Fourcade O, Grousset D, *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.* 2006; **102**: 1559–1563.
[PubMed Abstract](#) | [Publisher Full Text](#)
 36. Collard CD, Eappen S, Lynch EP, *et al.*: **Continuous spinal anesthesia with invasive hemodynamic monitoring for surgical repair of the hip in two patients with severe aortic stenosis.** *Anesth. Analg.* 1995; **81**: 195–198.
[PubMed Abstract](#)
 37. Fuzier R, Murat O, Gilbert M, *et al.*: **Continuous spinal anesthesia for femoral fracture in two patients with severe aortic stenosis.** Vol 25. 2006; pp. 528–531.
 38. López MM, Guasch E, Schiraldi R, *et al.*: **Continuous spinal anaesthesia with minimally invasive haemodynamic monitoring for surgical hip repair in two patients with severe aortic stenosis.** *Rev. Bras. Anesthesiol.* 2016; **66**: 82–85.
[Publisher Full Text](#)
 39. Olsen F: **Fractional anesthesia lidco.** 2023, January 11.
[Publisher Full Text](#)
 40. Olsen F: **Fractional anesthesia lidco.** 2023, January 27.
[Publisher Full Text](#)

Open Peer Review

Current Peer Review Status:   

Version 3

Reviewer Report 01 August 2023

<https://doi.org/10.5256/f1000research.153803.r192515>

© 2023 La Via L. This is an open access peer review report distributed under the terms of the [Creative Commons Attribution License](#), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.



Luigi La Via 

Department of Anesthesia and Intensive Care, "Policlinico-San Marco" University Hospital, Catania, Italy

After the revision, I have no more comments to make.

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Anesthesia; Critical Care

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Version 2

Reviewer Report 24 July 2023

<https://doi.org/10.5256/f1000research.147676.r184709>

© 2023 Ng T. This is an open access peer review report distributed under the terms of the [Creative Commons Attribution License](#), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.



Tony Kwun-Tung Ng 

¹ Anaesthesiology, The University of Hong Kong, Hong Kong, Hong Kong

² Frankston Pain Management, Melbourne, Victoria, Australia

³ Anaesthesia and Operating Theatre Services, Tuen Mun Hospital, Hong Kong, Hong Kong

⁴ Anaesthesia and Intensive Care, The Chinese University of Hong Kong, Hong Kong, Hong Kong

⁵ Rehabilitation Sciences, The Hong Kong Polytechnic University, Hong Kong, Hong Kong

Thank you for giving me an opportunity to review this article. I am personally a big fan of CSA in fracture hip patients although my regime is a bit different from your study regime.

Here are my comments:

1. Did you measure the preoperative hydration status which is a crucial factor to affect the hemodynamic response after CSA?
2. What is the fluid management in conjunction of this technique?
3. Can you share with us the incidence of urinary retention after a total of 30mcg intrathecal fentanyl? I understand it is used to improve the quality of the CSA despite some retained motor function. Yet, it is a rather big dose to me.
4. Methodology wise, is there any reason to use 2 intrathecal boluses instead of a bolus followed by infusion? Infusion can supposedly provide an even more stable hemodynamic.
5. Is there any evaluation of the timing to commence norepinephrine infusions for those 5 patients?
6. Concerning the FIC and Femoral nerve block, it is written down as 20-40ml diluted ropivacaine. Can you clarify which LA volume is used for which block? 40ml ropivacaine for femoral nerve block doesn't make sense to me in the presence of ultrasound guidance.

Is the work clearly and accurately presented and does it cite the current literature?

Yes

Is the study design appropriate and is the work technically sound?

Partly

Are sufficient details of methods and analysis provided to allow replication by others?

Yes

If applicable, is the statistical analysis and its interpretation appropriate?

I cannot comment. A qualified statistician is required.

Are all the source data underlying the results available to ensure full reproducibility?

Yes

Are the conclusions drawn adequately supported by the results?

Partly

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Regional anaesthesia in hip surgery. Neurolysis in inoperable fracture hip. Use of opioid in pain management. Peripheral joint denervation.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Author Response 27 Jul 2023

Fredrik Olsen

Thank you for taking the time and effort to review our work.

I have attempted to answer your questions point for point below. We see the shortcomings in not having a robust fluid protocol in place, a major limitation was conducting the study without disrupting the logistics of the department as a whole and some concessions needed to be made to the protocol.

1. We did not quantify preoperative fluid status prior to inclusion.
2. Fluid management prior to surgery is managed initially by the ambulance service/emergency department and then by the geriatric department. Patients were assessed by the study team on an individual basis with regards to time from hospital admission, assessed delay from fracture to hospital arrival and delivered fluids prior to arrival at the operating department.
3. No data on postoperative urinary retention was collected. Patients followed the ordinary postoperative routine after surgery. Through informal follow-up no reports of retention needing intervention was brought to our attention. This does not imply that it could have been an issue though.
4. Regarding the use of bolus instead of continuous infusion; we attempted to mimic the use of low dose single shot spinal anaesthesia without our measurements being obscured by ongoing surgery. A spinal catheter enabled us to do that with out the need of administering a second single shot spinal for surgical anaesthesia.
5. Regarding timing of norepinephrine start; Those patients requiring NE infusion received in conjunction with the first dose. The second dose did not seem to trigger the need for a higher dose or the start of NE in patients not requiring it prior.
6. The higher volume of LA volume (40ml) was used with a landmark based FIC block when ultrasound guidance was not available. With ultrasound guidance, 20ml was used for a targeted femoral block.

Competing Interests: No competing interests were disclosed.

Reviewer Report 19 July 2023

<https://doi.org/10.5256/f1000research.147676.r184705>

© 2023 Irwin M. This is an open access peer review report distributed under the terms of the [Creative Commons Attribution License](#), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.



Michael Irwin 

The University of Hong Kong, Hong Kong, Hong Kong

An interesting and well conducted study. I think it is fairly well known that SA induced hypotension is multifactorial and that venodilation is an important factor¹. I would, therefore, describe this as confirmatory.

Ref 12 is over 10 years old. Using LiDCO is a strength as is the use of plain bupivacaine (hyperbaric solutions should not be used in these frail elderly hip fracture cases in my opinion). The trial design was done to actually minimise the risk of hypotension and the results show that it will occur even with a meticulous technique (not CSA per se but use of a modest dose of plain local anaesthetic - cited refs 25 and 26 were not using plain bupivacaine).

I suggest the conclusion should be "*Our results confirm that spinal anaesthesia-induced hypotension is not solely a result of a fall in SVRI but mainly by systemic venodilation, reducing venous return to the heart and followed by a consequent fall in CO and MAP. Using isobaric bupivacaine and CSA, the incidence of hypotension was low and only one third of the patients needed nor-epinephrine infusions all at modest doses*".

Minor: line 1 'Anaesthesiologic' is not an accepted term. 'A major challenge in anaesthesiology' is better.

A follow up study with single shot isobaric bupivacaine / fentanyl would be interesting as it is a simpler and quicker technique than CSA

References

1. Ferré F, Martin C, Bosch L, Kurrek M, et al.: Control of Spinal Anesthesia-Induced Hypotension in Adults. *Local Reg Anesth.* 2020; **13**: 39-46 [PubMed Abstract](#) | [Publisher Full Text](#)

Is the work clearly and accurately presented and does it cite the current literature?

Partly

Is the study design appropriate and is the work technically sound?

Yes

Are sufficient details of methods and analysis provided to allow replication by others?

Yes

If applicable, is the statistical analysis and its interpretation appropriate?

Yes

Are all the source data underlying the results available to ensure full reproducibility?

Yes

Are the conclusions drawn adequately supported by the results?

Partly

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Perioperative medicine; TIVA

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Author Response 27 Jul 2023

Fredrik Olsen

Thank you for taking the time to read and review our work.

Your comments are to the point and relevant to the study. I have implemented parts of the text you suggested in the conclusion section and rewritten the line that contained the phrase "Anaesthesiologic" a per your recommendation.

Competing Interests: No competing interests were disclosed.

Reviewer Report 05 May 2023

<https://doi.org/10.5256/f1000research.147676.r171947>

© 2023 La Via L. This is an open access peer review report distributed under the terms of the [Creative Commons Attribution License](#), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.



Luigi La Via 

Department of Anesthesia and Intensive Care, "Policlinico-San Marco" University Hospital, Catania, Italy

I have no more comments to add.

Is the work clearly and accurately presented and does it cite the current literature?

Partly

Is the study design appropriate and is the work technically sound?

Partly

Are sufficient details of methods and analysis provided to allow replication by others?

Partly

If applicable, is the statistical analysis and its interpretation appropriate?

Partly

Are all the source data underlying the results available to ensure full reproducibility?

Partly

Are the conclusions drawn adequately supported by the results?

Partly

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Anesthesia; Critical Care

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Version 1

Reviewer Report 11 April 2023

<https://doi.org/10.5256/f1000research.143142.r164674>

© 2023 La Via L. This is an open access peer review report distributed under the terms of the [Creative Commons Attribution License](#), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.



Luigi La Via

Department of Anesthesia and Intensive Care, "Policlinico-San Marco" University Hospital, Catania, Italy

I read with great interest the manuscript by Olsen *et al.* on the effect of fractional spinal anesthesia on systemic hemodynamics in frail elderly hip fracture patients. The authors investigated the changes in haemodynamic variables caused by two doses of intrathecal bupivacaine 2.25 mg and fentanyl 15 µg in 15 patients aged over 65. The paper is sound and well written. However, there are some minor issues to be addressed.

Introduction

- When you state "where many centers give general anaesthesia, while particularly in northern Europe, neuraxial anaesthesia is the preferred technique" you should add an appropriate reference (for example, Neuman *et al.* (2021)¹).
- Spinal anesthesia is also the preferred technique for other kind of surgeries^{2,3}. Please briefly discuss and add these 2 references.

Results

- Please explain why "two patients were excluded due to logistical issues".

Discussion

- Please discuss the results of the recently published meta-analysis on the investigated topic⁴.

Conclusion

- Considering the limitations of this study, I would state "The initial blood pressure decline after fractional spinal anaesthesia MIGHT BE caused mainly by systemic venodilation".

References

1. Neuman MD, Feng R, Carson JL, Gaskins LJ, et al.: Spinal Anesthesia or General Anesthesia for Hip Surgery in Older Adults. *N Engl J Med*. 2021; **385** (22): 2025-2035 [PubMed Abstract](#) | [Publisher Full Text](#)
2. Çilesiz NC, Özkan A, Kalkanlı A, Gezmiş CT, et al.: Spinal Anesthesia Provides Longer Administration Time for Postoperative Intravesical Chemotherapy after TUR-B Operation. *Urol Int*. 2022; **106** (8): 768-774 [PubMed Abstract](#) | [Publisher Full Text](#)
3. LA Via L, Santonocito C, Bartolotta N, Lanzafame B, et al.: α -2 agonists vs. fentanyl as adjuvants for spinal anesthesia in elective cesarean section: a meta-analysis. *Minerva Anesthesiol*. 2022. [PubMed Abstract](#) | [Publisher Full Text](#)
4. Messina A, La Via L, Milani A, Savi M, et al.: Spinal anesthesia and hypotensive events in hip fracture surgical repair in elderly patients: a meta-analysis. *Journal of Anesthesia, Analgesia and Critical Care*. 2022; **2** (1). [Publisher Full Text](#)

Is the work clearly and accurately presented and does it cite the current literature?

Partly

Is the study design appropriate and is the work technically sound?

Yes

Are sufficient details of methods and analysis provided to allow replication by others?

Yes

If applicable, is the statistical analysis and its interpretation appropriate?

Yes

Are all the source data underlying the results available to ensure full reproducibility?

Yes

Are the conclusions drawn adequately supported by the results?

Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Anesthesia; Critical Care

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have

significant reservations, as outlined above.

Author Response 30 Apr 2023

Fredrik Olsen

Thank you for taking the time and effort to review the paper, your comments are addressed individually in the following text and are reflected in the revisions of the updated draft.

Introduction

- When you state "where many centers give general anaesthesia, while particularly in northern Europe, neuraxial anaesthesia is the preferred technique" you should add an appropriate reference (for example, Neuman *et al.* (2021)¹).
Reference added.
- Spinal anesthesia is also the preferred technique for other kind of surgeries^{2,3}. Please briefly discuss and add these 2 references.
These two references seem only peripherally relevant to this study, and for the sake of brevity will not be included

Results

- Please explain why "two patients were excluded due to logistical issues".
All participants had a preliminary time scheduled for their surgery and we performed the test protocol prior to this. If a slot in the program opened up the protocol stated that surgery would not be delayed to finish the study protocol. This was to keep the departments program flowing as smoothly as possible and to minimise potential harm to our patients.

Discussion

- Please discuss the results of the recently published meta-analysis on the investigated topic⁴.
The reference #31 has been changed to Messina 2022, which I suspect was the reference it was supposed to be all along. Nice observation from the reviewer!

Conclusion

- Considering the limitations of this study, I would state "The initial blood pressure decline after fractional spinal anaesthesia MIGHT BE caused mainly by systemic venodilation".
Edited in the revised draft to reflect reviewers comments

Competing Interests: No competing interests were disclosed.

The benefits of publishing with F1000Research:

- Your article is published within days, with no editorial bias
- You can publish traditional articles, null/negative results, case reports, data notes and more
- The peer review process is transparent and collaborative
- Your article is indexed in PubMed after passing peer review
- Dedicated customer support at every stage

For pre-submission enquiries, contact research@f1000.com

F1000Research