The relationship between preoperative hypertension and intraoperative haemodynamic changes known to be associated with postoperative morbidity

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CRWMAR006

A dissertation submitted to the Faculty of Health Sciences, University of Cape Town, in partial fulfilment for the degree of Master of Medicine in Anaesthesiology

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University of Cape Town, Department of Anaesthesia and Perioperative Medicine

Cape Town, 10 October 2018
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1. Declaration

I, Marcelle Crowther, hereby declare that the work on which this dissertation is based is my original work (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or any other university.

I empower the university to reproduce for the purpose of research either the whole or any portion of the contents in any manner whatsoever.

Signature: [Signed by candidate]

Date: 10 October 2018
2. Publications and presentations arising from thesis

This work or parts thereof has been presented or published on the following platforms:

- South African Society of Anaesthesiologists National Congress on 23rd of March 2017 held at the Sandton Convention Centre Johannesburg, South Africa
- Department of Anaesthesia and Perioperative Medicine, Research Day on the 17th of November 2017 at D23 Groote Schuur Hospital, Cape Town, South Africa
- Reply published in response to a letter received pertaining to the above article: Crowther M, Rood F, Biccard BM. Pre-operative hypertension and intra-operative hypotension: a reply. Anaesthesia. 2018;73(11): 1438-1439
3. Abstract

*The relationship between preoperative hypertension and intraoperative haemodynamic changes known to be associated with postoperative morbidity*

Hypertension is not consistently associated with postoperative cardiovascular morbidity and therefore not considered a major peri-operative risk factor. However, hypertension may predispose to peri-operative haemodynamic changes known to be associated with peri-operative morbidity and mortality, such as intra-operative hypotension and tachycardia. The objective of this study was to determine whether pre-operative hypertension was independently associated with haemodynamic changes known to be associated with adverse peri-operative outcomes. We performed a five-day multicentre, prospective, observational cohort study which included all adult inpatients undergoing elective, non-cardiac, non-obstetric surgery. We recruited 343 patients of whom 164 (47.8%) were hypertensive. An intra-operative mean arterial pressure of <55 mmHg occurred in 59 (18.2%) patients, of which 25 (42.4%) were hypertensive. Intra-operative tachycardia (heart rate>100 beats per minute) occurred in 126 (38.9%) patients, of which 61 (48.4%) were hypertensive. Multivariable logistic regression did not show an independent association between the stage of hypertension and either clinically significant hypotension or tachycardia, when controlled for ASA physical status, functional status, major surgery, the duration of surgery or blood transfusion. There was no association between pre-operative hypertension and peri-operative haemodynamic changes known to be associated with major morbidity and mortality. These data therefore support the recommendation of the Joint Guidelines of the Association of Anaesthetists of Great Britain and Ireland (AAGBI) and the British Hypertension Society to proceed with elective surgery if a patient’s blood pressure is <180/110 mmHg.
4. Acknowledgements

I would like to acknowledge the Department of Anaesthesia and Perioperative Medicine of the University of Cape Town; the Provincial Government of the Western Cape; and the seven participating provincial hospitals namely Groote Schuur Hospital, New Somerset Hospital, Paarl Hospital, Victoria Hospital, Mitchell’s Plain Hospital, Worcester Hospital and George Hospital that all supported and facilitated this multicentre research collaboration. The contributions of co-authors of the manuscript is listed below.

This manuscript has 14 authors from a multicenter, prospective, observational study of seven hospitals in the Western Cape (South Africa). All 14 authors listed below meet the following criteria of the International Committee of Medical Journal Editors (ICMJE). We have itemised their contributions according to the ICMJE criteria below:

- **M Crowther**
  - Overall conception and design of the study, the acquisition of data at Groote Schuur Hospital, interpretation
  - Drafting and critical revising of the work
  - Final approval of the version to be published
  - Agree to be accountable for all aspects, accuracy and integrity of the work

- **K van der Spuy**
  - Overall conception and design of the study, the acquisition of data at Groote Schuur Hospital, interpretation
  - Critical revising of the work
  - Final approval of the version to be published
  - Agree to be accountable for all aspects, accuracy and integrity of the work

- **F Roodt**
  - Overall conception and design of the study, the acquisition of data at Mitchell’s Plain Hospital, analysis, interpretation
  - Drafting and critical revising of the work
  - Final approval of the version to be published
  - Agree to be accountable for all aspects, accuracy and integrity of the work

- **MB Nejthardt**
  - Overall conception and design of the study
  - Critical revising of the work
  - Final approval of the version to be published
• JG Davids
  o The acquisition of data at George Provincial Hospital
  o Critical revising of the work
  o Final approval of the version to be published
  o Agree to be accountable for all aspects, accuracy and integrity of the work
• J Roos
  o The acquisition of data at Mitchell’s Plain Hospital
  o Critical revising of the work
  o Final approval of the version to be published
  o Agree to be accountable for all aspects, accuracy and integrity of the work
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  o The acquisition of data at New Somerset Hospital
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  o Final approval of the version to be published
  o Agree to be accountable for all aspects, accuracy and integrity of the work
• JG van der Walt
  o The acquisition of data at Victoria Hospital
  o Critical revising of the work
  o Final approval of the version to be published
  o Agree to be accountable for all aspects, accuracy and integrity of the work
• C van der Westhuizen
  o The acquisition of data at Worcester Provincial Hospital
  o Critical revising of the work
  o Final approval of the version to be published
  o Agree to be accountable for all aspects, accuracy and integrity of the work
• M Flint
  o The acquisition of data at Groote Schuur Hospital
  o Drafting and critical revising of the work
  o Final approval of the version to be published
  o Agree to be accountable for all aspects, accuracy and integrity of the work

• JLC Swanevelder
  o Overall conception and design of the study
  o Critical revising of the work
  o Final approval of the version to be published
  o Agree to be accountable for all aspects, accuracy and integrity of the work

• BM Biccard
  o Overall conception and design of the study, and analysis
  o Drafting and critical revising of the work
  o Final approval of the version to be published
  o Agree to be accountable for all aspects, accuracy and integrity of the work
5. List of figures

- Figure 1: Study flow diagram including participant recruitment rate
  - Footnote: MAP: mean arterial pressure, HR: heart rate, bpm: beats per minute
- Figure 2: Pre-operative ward measurements compared with pre-induction measurements of blood pressure and heart rate of patients included in the study.
  - Footnote: bpm: beats per minute, MAP: mean arterial pressure, SBP: systolic blood pressure, DBP: diastolic blood pressure, HR: heart rate, ◆ p<0.01, □ p= 0.022

6. List of tables

- Table 1: Hypertensive participants classified according to stage of hypertension and described as number (proportions). Stages of hypertension as recommended by the Joint Guidelines from the Association of Anaesthetists of Great Britain and Ireland (AAGBI) and the British Hypertension Society [3] Values are number (proportion).
- Table 2: Baseline characteristics of the study population. Values are mean (SD) or number (proportion).
- Table 3: Univariable and multivariable associations with a mean arterial pressure (MAP) < 55 mmHg.
- Table 4: Univariable and multivariable associations with a heart rate > 100 beats per minute.
7. Publication ready manuscript

7.a) Original article

*The relationship between pre-operative hypertension and intra-operative haemodynamic changes known to be associated with postoperative morbidity*

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7.b) Summary

Hypertension is not consistently associated with postoperative cardiovascular morbidity and therefore not considered a major peri-operative risk factor. However, hypertension may predispose to peri-operative haemodynamic changes known to be associated with peri-operative morbidity and mortality, such as intra-operative hypotension and tachycardia. The objective of this study was to determine whether pre-operative hypertension was independently associated with haemodynamic changes known to be associated with adverse peri-operative outcomes. We performed a five-day multicentre, prospective, observational cohort study which included all adult inpatients undergoing elective, non-cardiac, non-obstetric surgery. We recruited 343 patients of whom 164 (47.8%) were hypertensive. An intra-operative mean arterial pressure of <55 mmHg occurred in 59 (18.2%) patients, of which 25 (42.4%) were hypertensive. Intra-operative tachycardia (heart rate>100 beats per minute) occurred in 126 (38.9%) patients, of which 61 (48.4%) were hypertensive. Multivariable logistic regression did not show an independent association between the stage of hypertension and either clinically significant hypotension or tachycardia, when controlled for ASA physical status, functional status, major surgery, the duration of surgery or blood transfusion. There was no association between pre-operative hypertension and peri-operative haemodynamic changes known to be associated with major morbidity and mortality. These data therefore support the recommendation of the Joint Guidelines of the Association of Anaesthetists of Great Britain and Ireland (AAGBI) and the British Hypertension Society to proceed with elective surgery if a patient’s blood pressure is <180/110 mmHg.
7.c) Introduction

Hypertension is a common global health problem with an estimated prevalence of 30% [1] and is a preventable cause of premature morbidity and mortality [2]. The current Joint Guidelines of the Association of Anaesthetists of Great Britain and Ireland (AAGBI) and the British Hypertension Society recommend proceeding with elective surgery if the blood pressure (BP) is <180/110 mmHg [3], although the evidence for this recommendation remains limited [4, 5, 6].

Hypertension alone is not considered a major peri-operative risk factor, because it is not consistently associated with postoperative morbidity [4, 6, 7, 8, 9]. However, the complications associated with hypertension are known to increase peri-operative risk, and these include coronary artery disease, congestive cardiac failure, renal failure, cerebrovascular disease and diabetes mellitus [10, 11]. Patients with known cardiovascular disease or established risk factors for cardiovascular disease have a 6-7% risk of a major adverse cardiac event (MACE) within 30 days of surgery [12, 13, 14].

Pre-operative hypertension may predispose to intra-operative haemodynamic instability known to be associated with adverse peri-operative outcomes [3, 15, 16], although the current evidence supporting this is limited. Peri-operative haemodynamic responses that have been associated with major adverse outcomes in non-cardiac surgical patients include intra-operative hypotension [17, 18]. Walsh et al. defined intra-operative hypotension as a mean arterial pressure (MAP) of < 55 mmHg. A MAP of <55 mmHg for more than one minute was independently associated with myocardial injury and acute kidney injury following surgery. A MAP of <55 mmHg for more than twenty minutes was independently associated with increased mortality [18]. Tachycardia has also been associated with myocardial ischaemia and adverse cardiac events [19, 20]. Beattie at al. showed that a heart rate (HR) > 100 beats per minute (bpm) was associated with an adverse outcome [21].

If pre-operative hypertension independently predisposes to haemodynamic changes known to be associated with adverse outcomes in the peri-operative period, then it is possible that this may be an important risk predictor. It is possible that poor pre-operative control of BP, or a higher hypertensive stage (Table 1) may be associated with an increased risk of haemodynamic instability in the peri-operative period [16].

Previous peri-operative hypertension studies of haemodynamic instability have not adequately controlled for other known risk factors independently associated with MACE [16], which include the American Society of Anesthesiologists (ASA) physical status [22], functional status [23], major surgery [8, 22], duration of surgery [24] and blood transfusion [25]. We decided to determine whether pre-operative hypertension was independently
associated with peri-operative haemodynamic instability known to be associated with adverse peri-operative outcomes.
7. d) Methods

Study approval was obtained from the University of Cape Town Faculty of Health Sciences Human Research Ethics Committee, the Western Cape Department of Health, as well as institutional approval from all participating centres. All patients provided written informed consent and we followed the STROBE statement [26]. This was a five-day, multicentre, prospective, observational cohort study at seven public sector, government funded, hospitals in the Western Cape of South Africa. Eligible participants included all adult inpatients undergoing elective, non-cardiac, non-obstetric surgery. Exclusion criteria were day case patients, cardiac, obstetric or emergency surgery, paediatric patients and patients having radiological or local ophthalmology procedures.

Pre-operative and intra-operative data collection was performed by the attending anaesthetist on a paper case report form. The pre-operative data included: patient baseline characteristics (age, weight, height and sex); ASA physical status; functional status; type of surgery; anti-hypertensive therapy; any chronic diseases and pre-operative creatinine value (within 30 days of surgery). Functional status assessment was based on history in accordance with the Gupta et al Cardiovascular Risk Calculator and the ACS NSQIP risk calculator [28]. Pre-operative BP measurements and baseline HR were recorded on the day before surgery. The BP measurements were conducted in accordance with recommendations in the Joint Guidelines from the Association of Anaesthetists of Great Britain and Ireland (AAGBI) and the British Hypertension Society [3]. Three BP measurements were taken and recorded the day before surgery for the accurate diagnosis of pre-existing or undiagnosed hypertension [27]. In addition, we determined whether the pre-operative electrocardiogram (ECG), performed within six months of surgery, demonstrated left ventricular hypertrophy or an irregular rhythm. During the intra-operative period, the data recorded included pre-induction BP and HR, the duration of observed intra-operative hypotension (MAP <55 mmHg) and tachycardia (HR >100 bpm), type of anaesthesia, minor, intermediate or major surgery [28], the duration of surgery, intra-operative fluid administration (type and volume) and intra-operative vasopressor requirements. Data recorded on the paper case report forms were captured electronically onto the Research Electronic Data Capture (REDCap) application by local investigators. Access to the data entry system was username and password protected. Patient confidentiality and anonymity was ensured through the generation of a unique numerical code during the electronic data transcription.

The primary aim of the study was to determine whether the stage of pre-operative hypertension was independently associated with an intra-operative MAP of <55 mmHg for
more than one minute i.e whether preoperative hypertension is associated with intraoperative hypotension. The secondary aims were to determine whether the stage of preoperative hypertension was independently associated with a MAP <55 mmHg for >20 minutes and/or a HR >100 bpm. In the multivariable model, a priori we planned to include the pre-operative hypertension stage and the following five peri-operative risk factors known to be independently associated with MACE: ASA physical status ≥3, functional status, duration of surgery, need for blood transfusion and major surgery. Based on the need for six risk predictors to be included in a multivariable model, we required approximately 60 primary outcome events, to ensure that we had 10 events per variable [29]. Based on previous work in our surgical population, we estimated that we would require a sample size of approximately 500 participants, as we anticipated that approximately 150 (30%) patients [27] would be hypertensive and that 44% of these would experience intra-operative hypotension [18]. Based on our expected elective surgical volume at the participating hospitals, we believed that we could recruit this number of participants in five days.

For statistical analysis, the categorical independent binary variables in Table 2 were described as proportions and analysed using Fisher exact and Chi square testing. The continuous numerical data in Table 2 were described as mean (central tendency) and standard deviation (dispersion). A MAP < 55 mmHg and HR >100 bpm were risk adjusted for ASA physical status [22], functional status [23], duration of surgery [24], blood transfusion [25] and major surgery [8, 22]. An HR >100 bpm was also risk-adjusted for β-adrenergic antagonist therapy. Multivariable logistic regression was performed for the primary and secondary objectives, using Statistical Package for the Social Sciences (SPSS) version 21 (SPSS Inc., Chicago, IL, USA) software.
7.e) Results

The study flow diagram is shown in Figure 1. Three hundred and twenty-four patients were included in the multivariable analysis. Table 2 shows the characteristics of the study population. Hypertension occurred in 164 (47.8%) of elective surgical participants of which 133 (81.1%) were known to have hypertension and 31 (18.9%) had undiagnosed hypertension. Hypertensive patients were older, had a higher BMI and ASA physical status and were more likely to have diabetes mellitus, renal failure, retinopathy or partial functional dependence. Surgery was longer in hypertensive patients, with increased blood loss, when compared with normotensive patients. The distribution of hypertension stages in the study population is shown in Table 1. Of the known hypertensive patients, 83 (51%) were controlled and 50 (37.6%) were inadequately controlled on existing anti-hypertensive treatment. The anti-hypertensive medications included diuretics in 62.2%, angiotensin converting enzyme inhibitors in 48.2% and β adrenergic antagonists in 32.9%. The Revised Cardiac Risk Index (RCRI) scoring system was completed on the entire patient population presenting for elective surgery including healthy ASA 1 patients who do not routinely require creatinine measurement. The RCRI score incorporates an elevated creatinine as a risk factor and therefore 20 patients lack RCRI data.

**Table 1:** Hypertensive participants classified according to stage of hypertension and described as number (proportions). Stages of hypertension as recommended by the Joint Guidelines from the Association of Anaesthetists of Great Britain and Ireland (AAGBI) and the British Hypertension Society [3].

<table>
<thead>
<tr>
<th>Hypertension stage</th>
<th>Systolic BP (mmHg)</th>
<th>Diastolic BP (mmHg)</th>
<th>BP</th>
<th>Study population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normotensive</td>
<td>&lt;140</td>
<td>&lt;90</td>
<td>83 (51%)</td>
<td></td>
</tr>
<tr>
<td>Hypertension stage</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>140-159</td>
<td>90-99</td>
<td>55 (34%)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>160-179</td>
<td>100-109</td>
<td>19 (12%)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>≥180</td>
<td>≥110</td>
<td>7 (3%)</td>
<td></td>
</tr>
</tbody>
</table>

BP: Blood pressure
Our expected elective surgical volume at the participating centers was 500 participants. The 5 days our study was conducted only 397 patients presented for elective surgery. We did not feel we had to extend the data collection period as we had obtained enough primary outcome variables to include in the multivariable model. We anticipated that approximately 150 (30%) patients would be hypertensive [27], but our study revealed a hypertension rate of 48.7% instead with a 20% intraoperative hypertension rate. This resulted in a smaller sample size, but it did not affect the power of the study.

MAP: mean arterial pressure, HR: heart rate, bpm: beats per minute
Table 2: Baseline characteristics of the study population. Values are mean (SD) or number (proportion).

<table>
<thead>
<tr>
<th>Baseline characteristics</th>
<th>Study population</th>
<th>Hypertensive population</th>
<th>Normotensive population</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age; years</td>
<td>49 (16)</td>
<td>57 (13)</td>
<td>41 (14)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Sex; male</td>
<td>130 (38%)</td>
<td>58 (35%)</td>
<td>72 (40%)</td>
<td>0.37</td>
</tr>
<tr>
<td>BMI</td>
<td>28 (7)</td>
<td>30 (7)</td>
<td>27 (7)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>ASA physical status</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>121/340 (36%)</td>
<td>18/164 (11%)</td>
<td>103/176 (59%)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>2</td>
<td>159/340 (47%)</td>
<td>98/164 (60%)</td>
<td>61/176 (35%)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>54/340 (16%)</td>
<td>43/164 (26%)</td>
<td>11/176 (6%)</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>6/340 (2%)</td>
<td>5/164 (3%)</td>
<td>1/176 (1%)</td>
<td></td>
</tr>
<tr>
<td>Functional status</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Totally independent</td>
<td>296/335 (88%)</td>
<td>133/159 (84%)</td>
<td>163/176 (93%)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Partially dependent</td>
<td>33/335 (10%)</td>
<td>26/159 (16%)</td>
<td>7/176 (4%)</td>
<td></td>
</tr>
<tr>
<td>Totally dependent</td>
<td>6/335 (2%)</td>
<td>0/159 (0%)</td>
<td>6/176 (3%)</td>
<td></td>
</tr>
<tr>
<td>Hypertension-associated target organ damage</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LVH on ECG</td>
<td>33/343 (10%)</td>
<td>29/164 (18%)</td>
<td>4/179 (2%)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>CRF and low eGFR</td>
<td>22/247 (9%)</td>
<td>20/147 (14%)</td>
<td>2/100 (2%)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Complications of hypertension</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CAD</td>
<td>11/343 (3%)</td>
<td>9/164 (6%)</td>
<td>2/179 (1%)</td>
<td>0.03</td>
</tr>
<tr>
<td>Heart failure</td>
<td>5/343 (2%)</td>
<td>4/164 (2%)</td>
<td>1/179 (1%)</td>
<td>0.20</td>
</tr>
<tr>
<td>Stroke</td>
<td>6/343 (2%)</td>
<td>5/164 (3%)</td>
<td>1/179 (1%)</td>
<td>0.11</td>
</tr>
</tbody>
</table>
Pre-induction BP>140/90 mmHg occurred in 81 (23.6%) of participants. All undiagnosed hypertensive patients had a pre-induction BP>140/90 mmHg and none of the normotensive participants had pre-induction hypertension. There was a significant increase in BP and HR prior to induction when compared with the ward recordings on the day prior to surgery (Figure 2).
The primary outcome, a MAP<55 mmHg for >1 minute intra-operatively, occurred in 59 (18.2%) patients. Twenty-five (42.4%) were hypertensive, and this constituted 15.2% of the hypertensive cohort. A MAP<55 mmHg for >20 minutes intra-operatively, occurred in 4 (1.2%) patients, of which none were known hypertensives. An intra-operative HR of >100 bpm occurred in 126 (38.9%) patients, of which 61 (48.4%) were hypertensive. This constituted 39.1% of the hypertensive cohort. None of the patients with stage 3 hypertension developed clinically significant intra-operative hypotension, so we collapsed hypertensive stages 2 and 3 into a single variable for the purposes of logistic regression. After risk adjustment for a MAP <55 mmHg and a HR of >100 bpm with ASA physical status, functional status, major surgery, hypertensive stages, blood transfusion and duration of surgery (and adrenergic antagonist therapy for HR), pre-existing hypertension was not independently associated with clinically important intra-operative hypotension or tachycardia. The univariable and multivariable associations with the primary and secondary outcomes are shown in Tables 3 and 4 respectively. None of the predictors were independently associated with the primary or secondary outcomes.
Hypertensive participants received more intra-operative vasopressors (p=0.04) and total fluid therapy (p=0.04) when compared with normotensive patients. Blood was administered to 8 (2.3%) patients.

**Table 3: Univariable and multivariable associations with a mean arterial pressure (MAP) <55mmHg.**

<table>
<thead>
<tr>
<th></th>
<th>Univariable</th>
<th>Multivariable</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR</td>
<td>95% CI</td>
</tr>
<tr>
<td>Functionally dependent</td>
<td>1.7</td>
<td>0.8-3.9</td>
</tr>
<tr>
<td>ASA physical status ≥ 3</td>
<td>0.9</td>
<td>0.4-1.8</td>
</tr>
<tr>
<td>Major surgery</td>
<td>1.5</td>
<td>0.7-3.2</td>
</tr>
<tr>
<td>Duration of surgery per minute</td>
<td>1.005</td>
<td>1.001-1.009</td>
</tr>
<tr>
<td>Blood transfusion</td>
<td>4.8</td>
<td>1.2-19.6</td>
</tr>
<tr>
<td>Hypertension ≥ stage 2</td>
<td>0.9</td>
<td>0.3-2.7</td>
</tr>
</tbody>
</table>

OR: odds ratio, CI: confidence interval

**Table 4: Univariable and multivariable associations with a heart rate >100 beats per minute.**

<table>
<thead>
<tr>
<th></th>
<th>Univariable</th>
<th>Multivariable</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR</td>
<td>95% CI</td>
</tr>
<tr>
<td>Functionally dependent</td>
<td>1.2</td>
<td>0.59-2.33</td>
</tr>
<tr>
<td>ASA physical status ≥ 3</td>
<td>1.4</td>
<td>0.76-2.5</td>
</tr>
<tr>
<td>Major surgery</td>
<td>2.3</td>
<td>1.2-4.4</td>
</tr>
<tr>
<td>Duration of surgery per minute</td>
<td>1.005</td>
<td>1.001-1.009</td>
</tr>
<tr>
<td>Blood transfusion</td>
<td>2.7</td>
<td>0.63-11</td>
</tr>
<tr>
<td>Hypertension ≥ stage 2</td>
<td>1.1</td>
<td>0.49-2.6</td>
</tr>
</tbody>
</table>

OR: odds ratio, CI: confidence interval
Hypertension is common amongst elective surgical patients, with a prevalence of 47.8% in our patient population, which is higher than the estimated 30% worldwide prevalence. Hypertension was associated with higher ASA physical status, decreased functional status, older age and obesity, all of which increase the risk for cardiovascular disease and adverse peri-operative outcomes. However, our data failed to find an association between pre-existing hypertension and clinically important haemodynamic instability in the peri-operative period.

Intra-operative hypotension was common, with 18.2% of elective surgical patients developing a MAP <55 mmHg for at least a minute, and 1.2% for more than 20 minutes. However, our data failed to show a significant association between any of the known peri-operative cardiovascular risk predictors and intra-operative hypotension. In addition, pre-operative hypertension was not independently associated with an intra-operative tachycardia. We did not investigate whether hypotension and tachycardia occurred simultaneously. There is however good evidence that shows that hypotension and tachycardia is associated with adverse outcomes individually [18, 21].

Our results suggest that pre-operative hypertension is not an independent predictor of haemodynamic instability and lend support to the recommendation of the Joint Guidelines from the Association of Anaesthetists of Great Britain and Ireland (AAGBI) and the British Hypertension Society as well as the South African recommendation by James et al [30], that if a patient’s BP is <180/110 mmHg it is safe to proceed with elective surgery.

No patients with stage 3 hypertension developed clinically significant intra-operative hypotension, so we cannot provide data on the risk for haemodynamic instability in this subgroup but we do advocate caution. A pre-induction systolic BP of ≥140 mmHg or diastolic BP≥90 mmHg should consider possible referral of the patient to an appropriate primary healthcare facility for further screening and management following surgery.

One strength of this study is that it was adequately powered to determine the association between pre-existing hypertension and other known independent predictors of major adverse cardiac events, with clinically important intra-operative hypotension. We believe our findings provide some support to the recommendation to proceed with surgery when the pre-operative BP is <180/110 mmHg. Furthermore, it did not find any compelling reasons not to follow the proposed guidelines.

Our study has some limitations. Firstly, due to the limited number of events of MAP<55 mmHg for >20minutes, and the limited number of participants with stage 3 hypertension, we
are unable to explore the relationship between pre-existing hypertension and prolonged intra-operative hypotension. Further work is necessary to address this area. Secondly, because our data collection was not electronically captured and the attending anaesthetists were required to document the duration of hypotension in minutes, we expect that there may well have been a Hawthorne effect as a result. Thirdly, although this study was conducted in a middle-income country, we believe that the findings are generalisable to high-income countries, but recommend external validation of these data. Intra-operative hypotension is common and is associated with major morbidity and mortality. However, the determinants of intra-operative hypotension remain unclear. Further work is necessary to determine independent risk predictors for clinically important intra-operative hypotension. Furthermore, it is important to establish whether treating intra-operative hypotension will improve postoperative outcomes. Finally, this study only addressed a surrogate outcome (intraoperative hypotension), and not hard outcomes, such as myocardial injury or death.

In conclusion, hypertension is common amongst elective, non-cardiac, non-obstetric patients. Pre-existing hypertension up to stage 2 is not independently associated with intra-operative hypotension or tachycardia known to be associated with adverse peri-operative outcomes. Therefore we believe that the Joint Guidelines from the Association of Anaesthetists of Great Britain and Ireland (AAGBI) and the British Hypertension Society as well as the South African recommendation as per James et al [30], which recommend proceeding with elective surgery if blood pressure is <180/110 mmHg, are appropriate. We would advise caution in patients with stage 3 hypertension, as our study contained insufficient numbers to determine whether there was an association between stage 3 hypertension and clinically important intra-operative haemodynamic changes. It would appear that hypertension is a public health issues rather than a peri-operative problem [9].

7.g) Acknowledgements

The study was registered at ClinicalTrials.gov (NCT03157661). The authors acknowledge the co-operation of the Provincial Government of the Western Cape in the performance of this multicentre research study and the enthusiasm and co-operation of the theatre staff from all 7 public sector, government funded hospitals. Participating centres were Groote Schuur Hospital, New Somerset Hospital, Paarl Hospital, Victoria Hospital, Mitchell’s Plain Hospital, Worcester Hospital and George Hospital. No other external funding or competing interests declared.
7.h) References


8. Appendices

a. Protocol as submitted to University of Cape Town Faculty of Health Sciences Human Research Ethics Committee
b. Ethics approval documents
c. Case report form
d. Informed consent document
e. *Anaesthesia* author guidelines
8.a) Protocol as submitted to the University of Cape Town Faculty of Health Sciences Human Research Ethics Committee
Is there a relationship between pre-operative blood pressure measurement and intra-operative haemodynamic changes that are known to be associated with postoperative morbidity?

Substudy justification for ethics review

Supervisor: Dr Francois Roodt
Co-supervisors: Prof B Biccard
Dr Marcin Netjhardt
Author: Marcelle Crowther

MP number: MP 0729248
Student number: CRWMAR006

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Synopsis

This is a proposal for a substudy of 'An Audit of the Prevalence of Hypertensive Disease in Patients Presenting for Elective Surgery' by Dr Karen van der Spuy.

Hypertension is a major public health problem in the Western Cape, and is the 15th leading cause of years of life lost in Southern Sub-Saharan Africa [1], and between 40 and 50% of patients in middle-income countries have hypertension [2]. The anaesthetist is therefore often responsible for administering anaesthesia to hypertensive surgical patients.

Pre-operative hypertension has been associated with physiological derangements such as intra-operative hypotension, hypertension and arrhythmia, but the association between these haemodynamic fluctuations and significant postoperative clinical morbidity is unclear [3, 4]. Furthermore, it is unclear whether pre-operative in hospital blood pressure measurements are the correct measurements to use as an indicators of peri-operative risk [5]. Therefore, the effects of elevated pre-operative blood pressure measurements and its impact on perioperative and long term morbidity remain unclear in elective surgical patients [3].

The hypothesis of this substudy is that pre-operative hypertension may be associated with peri-operative morbidity. This substudy will therefore evaluate the relationship between the pre-operative in hospital blood pressure and intra-operative haemodynamic changes which are known to be associated with postoperative morbidity.

This is a prospective observational study of adult, non-cardiac, non-obstetric elective surgery patients conducted over a period of one week.

The primary objective is to categorize patients into the following groups based on their pre-operative in hospital blood pressure measurement:

- SBP<140mmHg and DBP <90mmHg
- SBP<160mmHg and DBP<100mmHg
- SBP<180mmHg and DBP<110mmHg without end organ damage
- SBP<180mmHg and DBP<110mmHg with end organ damage
These patients will be risk adjusted for duration of surgery, the need for intra-operative blood transfusion, pre-operative anaemia, ASA status, functional status, major surgery as well as type of anaesthesia.

Pre-operative in hospital blood pressure as described above and its association with intra-operative hypotension i.e. MAP < 55mmHg for >1 minute as defined by Walsh et al [6] will be evaluated.

The secondary objectives are to determine the relationship between preoperative in hospital blood pressure measurement and MAP<55mmHg for >20min [6], HR>100 beats per minute [7], volume and type of fluid administered as well as the use of perioperative vasopressors.

If a relationship can be demonstrated between pre-operative hypertension and significant hypotension, it will allow for identification of patients at risk of perioperative morbidity who could be identified pre-operatively during routine clinical examination and blood pressure measurement. This will allow the anaesthetist to better anticipate these haemodynamic changes and intervene appropriately to prevent adverse outcomes. It will also encourage further research with regards to management of the pre-operative elevated blood pressure and hopefully the development of a standard approach or evidence based guideline with the ultimate goal to improve the peri-operative management and outcomes in this patient group.
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>SBP</td>
<td>Systolic Blood Pressure</td>
</tr>
<tr>
<td>DBP</td>
<td>Diastolic Blood Pressure</td>
</tr>
<tr>
<td>BP</td>
<td>Blood Pressure</td>
</tr>
<tr>
<td>MAP</td>
<td>Mean Arterial Pressure</td>
</tr>
<tr>
<td>HR</td>
<td>Heart Rate</td>
</tr>
<tr>
<td>GSH</td>
<td>Groote Schuur Hospital</td>
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<td>NICE</td>
<td>National Institute for Health and Care Excellence</td>
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<td>AAGBI</td>
<td>Association of Anaesthetists of Great Britain and Ireland</td>
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<tr>
<td>UCT</td>
<td>University of Cape Town</td>
</tr>
<tr>
<td>IOH</td>
<td>Intra-operative Hypotension</td>
</tr>
<tr>
<td>LVH</td>
<td>Left Ventricular Hypertrophy</td>
</tr>
<tr>
<td>AKI</td>
<td>Acute Kidney Injury</td>
</tr>
<tr>
<td>MINS</td>
<td>Myocardial Injury after Non-cardiac Surgery</td>
</tr>
<tr>
<td>MI</td>
<td>Myocardial infarction</td>
</tr>
<tr>
<td>SPSS</td>
<td>Statistical Package for Social Sciences</td>
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mmHg: Millimetres of Mercury
ASA: American Society of Anesthesiologist; Physical classification system
Introduction:
Hypertension is an important disease of our time and has been described by NICE as ‘one of the most important preventable causes of premature morbidity and mortality in the United Kingdom’[8] [3]. Hypertension is a major public health problem in the Western Cape, and is the 15th leading cause of years of life lost in Southern Sub-Saharan Africa [1], and between 40 and 50% of patients in middle-income countries have hypertension[2].

The anaesthetist is therefore often responsible for administering anaesthesia to hypertensive surgical patients. Elective surgery is often postponed due to elevated pre-operative blood pressure, although the evidence for this is currently lacking [9]. Hypertension is a major burden to both the patient and public health system resources. The lack of evidence and guidelines with regards to postponement of surgery due to elevated blood pressure leads to variable anaesthetic practices that cause confusion amongst patients, surgeons and referral centres [10]. It is therefore imperative to establish the relationship between pre-operative hypertension and peri-operative outcomes. To this end, it is important that an emphasis should be placed on directing management and interventions based on the cardiovascular risk associated with hypertension rather than simply targeting a numerical blood pressure value peri-operatively.

Peri-operative hypertension:

Hypertension will be defined as per main study[11]:

<table>
<thead>
<tr>
<th>Category</th>
<th>Systolic arterial blood pressure (SBP)</th>
<th>Diastolic arterial blood pressure (DBP)</th>
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<tr>
<td>Optimal</td>
<td>&lt; 120</td>
<td>&lt; 80</td>
</tr>
<tr>
<td>Normal</td>
<td>&lt; 130</td>
<td>&lt; 85</td>
</tr>
<tr>
<td>High normal</td>
<td>130-139</td>
<td>85-89</td>
</tr>
<tr>
<td>Hypertension</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage 1: Mild</td>
<td>140-159</td>
<td>90-99</td>
</tr>
<tr>
<td>Stage 2: Moderate</td>
<td>160-179</td>
<td>100-109</td>
</tr>
<tr>
<td>Stage 3: Severe</td>
<td>180-209</td>
<td>110-119</td>
</tr>
<tr>
<td>Stage 4: Very severe</td>
<td>&gt; 210</td>
<td>&gt; 120</td>
</tr>
<tr>
<td>Isolated systolic hypertension</td>
<td>&gt; 140</td>
<td>&lt; 90</td>
</tr>
<tr>
<td>Pulse pressure hypertension</td>
<td>&gt; 80</td>
<td></td>
</tr>
</tbody>
</table>

Note: The South African Hypertension Society only recognises up to Stage 3, but the other grades are useful for perioperative decisions.
Patients may present with peri-operative hypertension due to several factors, including [3]:

- **Pre-operative**
  - False hypertension measurements (e.g. white coat)
  - Undiagnosed hypertension
  - Poorly controlled hypertension in known chronic hypertensive patients

- **Intra-operative and postoperative**
  - Induction of anaesthesia
  - Airway manipulation
  - Acute pain
  - Hypothermia
  - Hypoxia
  - Consequences of fluid therapy

Although, hypertension is an established risk factor for cardiovascular disease [5] with good evidence-based guidelines for the diagnosis and management of adult hypertension in the community, there remains poor guidance on ‘safe’ blood pressures for elective surgery [3]. It is for this reason that the AAGBI (Association of Anaesthetists of Great Britain and Ireland) and the British Hypertension Society have made the following recommendations in their joint guidelines with regards to elective surgery patients:

- **Primary care objectives**
  - Diagnosing and obtaining control of blood pressures below 160 mmHg systolic and 100 mmHg diastolic over a period of 12 months before referral for elective surgery [3]

- **Secondary care objectives**
  - Avoid false hypertensive measurements [3].
  - Do not attempt to diagnose hypertension in patients who are normotensive in primary care [3]. This has been criticized due to the occurrence of mask hypertension that is associated with high cardiovascular risk and consequently diagnostic opportunities should not be missed [10].

- **Patients with no documented primary care blood pressures**
  - Proceed with elective surgery if blood pressures are below 180 mmHg systolic and 110 mmHg diastolic[3].
In stage 1 or 2 hypertension (SBP <180mmHg and DBP < 110mmHg) in the absence of target organ damage there is currently no clear evidence of increased peri-operative cardiovascular risk and surgery should not be postponed [3] [12]. However, in known hypertensive patients with resultant target organ damage, there is an increased incidence of peri-operative major adverse cardiovascular events [3, 13]. It remains unclear however, whether postponing elective surgery for adequate blood pressure control in these patients decreases the rate or occurrence of adverse cardiovascular events [1, 6][12]. The risk benefit of delaying surgery to establish hypertension control should always be considered in patients with severe hypertension[12]

Target organ damage as described in the South African hypertension guidelines practice guidelines 2014 includes[14]:

- Left Ventricular Hypertrophy (LVH) on ECG
  - Sokolow-Lyons > 35 mm
  - R in aVL > 11 mm
  - Cornel > 2 440 (mm/ms)
- Microalbuminuria
  - Spot Albumin: Creatinin ratio 3–30 mg/mmol
  - eGFR > 60 ml/min

Hypertensive patients are known to have a labile intra-operative haemodynamic course fluctuating between hypertension and hypotension [3]. Hypotension occurs as a result of decreased systemic vascular resistance which is exaggerated during deep anaesthesia and in fluid-depleted patients. Hypertensive patients also tend to have exaggerated haemodynamic responses to surgery, pain and emergence [3, 15]. It is possible that these haemodynamic responses may be associated with postoperative morbidity.

**Intra-operative hypotension:**

Hypertensive patients often have a labile intra-operative haemodynamic course as described above. Hypotension during anaesthesia often requires intervention in the form of vasopressors or fluid administration. We suspect that hypertensive patients receive increased volumes of fluid within this context.
Fluid management remains a controversial topic in the literature with on-going debate concerning type and volume of fluid. Current recommendations with regards to volume of fluid administered suggest avoiding fluid overload and opting for a zero fluid balance approach to fluid therapy which entails the replacement of losses and maintaining normal bodyweight. It is accepted that a liberal fluid strategy with subsequent fluid overload is associated with post-operative complications as a consequence of tissue inflammation and oedema. Avoidance of fluid overload therefore improves outcome.[16, 17]

Short cumulative durations (i.e. < 30 min) of intra-operative hypotension (IOH) during vascular surgery are not associated with myocardial injury [18]. In elderly vascular surgery patients there is however a higher incidence of postoperative myocardial infarction and death within 30 days in patients with mean arterial pressure (MAP) less than 60 mmHg and in patients with a 40% decrease from pre-induction MAP with a cumulative duration of more than 30 min there is an association with postoperative myocardial injury [18]. However, MAP of less than 55mmHg of even a short duration has been associated with increased risk of acute kidney injury (AKI) and myocardial injury postoperatively due to an ischemia–reperfusion injury that leads to organ dysfunction [6].

Intra-operative hypotension remains poorly defined. This substudy will define IOH as per Walsh et al and will take into account the cumulative and not continuous duration of IOH [6].

**Peri-operative tachycardia**

A heart rate of <100 beats per minute has been proven to be associated with cardioprotection whereas heart rates of >100 beats per minute has not demonstrated any cardioprotection [7]. Effective heart rate control has been established to reduce the incidence of postoperative myocardial infarction (MI) and is therefore an important factor in achieving cardioprotection peri-operatively[7].

In general an increase in baseline heart rate is linked with increased cardiovascular risk and mortality. Pertaining non-cardiac surgery an association between pre-operative heart rate of >96 beats per minute and post-operative Myocardial Injury after Non-cardiac Surgery (MINS), MI and mortality has been established by Abbott et al[19].
In conclusion

The current literature suggests that pre-operative hypertension is associated with haemodynamic fluctuations, although their clinical significance is unclear [3, 4]. Furthermore, the clinical risk associated with pre-operative in hospital blood pressure measurements are also unclear [5]. Finally, most perioperative studies that have attempted to illustrate associations between different numerical blood pressure thresholds and peri-operative outcomes are underpowered [5].

We believe that we could address these limitations in the literature, by evaluating the relationship between pre-operative blood pressure measurements and intra-operative haemodynamics which have been specifically associated with post-operative morbidity.

The null hypothesis of this substudy is that in-hospital pre-operative hypertension is not associated with intra-operative haemodynamics known to be associated with postoperative morbidity. The alternate hypothesis is that in-hospital pre-operative hypertension is associated with intra-operative haemodynamics known to be associated with postoperative morbidity. Should this be the case, then those patients at risk could be easily identified pre-operatively through blood pressure measurement, and this would allow the anaesthetist to better anticipate these haemodynamic changes and intervene appropriately to prevent adverse peri-operative outcomes. It will also encourage further research with regards to management of the pre-operative elevated blood pressure and hopefully the development of a standard approach or evidence based guideline to improve the peri-operative management and outcomes of this patient group.
Study Aims and Objectives

Study aim
The aim of this sub study is to determine the relationship between pre-operative blood pressure measurements and intra-operative haemodynamic changes that have been demonstrated in the literature to be associated with peri-operative morbidity.

Objectives

Primary objective
The primary objective is to categorize patients into the following groups based on their pre-operative in hospital blood pressure measurement:

- SBP<140mmHg and DBP<90mmHg
- SBP<160mmHg and DBP<100mmHg
- SBP<180mmHg and DBP<110mmHg without end organ damage
- SBP<180mmHg and DBP<110mmHg with end organ damage

These patients will be risk adjusted for:
- Duration of surgery
- Need for blood transfusion intra-operatively
- Pre-operative anaemia
- ASA status
- Functional status
- Major surgery
- Type of anaesthesia (Dependant on sample size)

Pre-operative in hospital blood pressure as described above and its association with intra-operative hypotension i.e. MAP < 55mmHg for >1minute as defined by Walsh et al [6] will be evaluated.

Secondary objectives:
The secondary objectives are to determine the relationship between preoperative in hospital blood pressure measurement and the following:

i. MAP<55mmHg for >20min [6]
ii. HR>100 beats per minute [7]
iii. Volume and type of fluid administered
iv. Use of perioperative vasopressors
Methodology

Study design

This is a substudy of Dr Karen van der Spuy’s study titled; An Audit of the Prevalence of Hypertensive Disease in Patients Presenting for Elective Surgery’. This will be a prospective observational study of adult, non-cardiac, non-obstetric elective surgical patients conducted over a period of one week.

Study population

The study population comprises all adult non-cardiac, non-obstetric patients presenting for elective surgery at Groote Schuur Hospital, Somerset Hospital, Paarl Hospital, Victoria Hospital, Mitchell’s Plain Hospital, Worcester Hospital and George Hospital over a period of one week.
The study population sample size is estimated at 500 patients. We anticipate that 150 of these patients will be hypertensive (30% of patients [2]). If 44% of these patients are affected by intra-operative hypotension [6], this would approximate to 66 patients. This number will allow us to attest approximately 6 to 7 variables as described in the study aims and objectives.

Inclusion criteria:
- Adult patients presenting for non-cardiac, non-obstetric, elective surgery

Exclusion criteria:
- Pediatrics
- Cardiac patients
- Obstetric patients
- Emergency surgery

Setting

Elective surgical patients at Groote Schuur Hospital, Somerset Hospital, Paarl Hospital, Victoria Hospital, Mitchell’s Plain Hospital, Worcester Hospital and George Hospital over a period of one week.

Study methods

The study will identify patients with pre-operative in hospital blood pressure measurements as follows:
- SBP<140mmHg and DBP <90mmHg
- SBP<160mmHg and DBP<100mmHg
- SBP<180mmHg and DBP<110mmHg without end organ damage
- SBP<180mmHg and DBP<110mmHg with end organ damage

The following data will be collected for all elective surgical patients:
- Intra-operative hypotension:
  - MAP<55mmHg <1min
  - MAP<55mmHg >20min
• HR > 100 beats per minute
• Volume and type of fluid administered
• Pre-operative anaemia
• ASA status
• Functional status
• Type of anaesthesia
  o General anaesthesia
  o Epidural
  o Spinal
• Type of surgery – major or not
• Duration of surgery
• Were vasopressors required as well as specific vasopressors used
• Blood pressure cuff size
**Ethical considerations**

This study is in effect a large scale clinical audit. We therefore expect that there will be no requirement for individual patient consent as all data will be anonymised and is already recorded as part of routine clinical care. All data will be recorded by anaesthetic registrars and consultants on a separate case report form designed for the purpose of this study during the patients theatre visit. Patient identifying data will not be captured on the case report form and thereby data will be kept confidential.

The study will record pre-operative blood pressure measurements, pre-operative anaemia, intra-operative hypotension (MAP<55mmHg) and duration thereof, HR > 100 beats per minute, volume and type of fluid administered intra-operatively, ASA status, functional status, type of anaesthesia, type of surgery, duration of surgery, intra-operative vasopressors requirements as well as specific vasopressors used as well as blood pressure cuff size.

The aforementioned are all documented routinely during a patient’s anaesthetic and will not influence patient management or theatre practice but would rather reflect current clinical practice.

The study is purely observational and therefore no interventions will take place and no adverse events as a result of participation in this substudy are anticipated. Standard theatre safety precautions and clinical practice apply. It will be a once off anonymous data collection and no patient follow up will be required.
Study administration

Logistics, time schedule and action plan

The logistics, time schedule and action plan, will be as per the main study; ‘Prior to commencement of the study, the researcher will communicate the intention, purpose and execution of the study with fellow registrars and colleagues, and recruit and encourage their participation in data collection verbally, by electronic mail as well as instant messaging. Posters will be placed in the anaesthetic department as well as in all the theatres in which the elective lists take place to serve as reminders.

Prior to each surgical elective day for the period of the study, the surgical lists for all the disciplines will be collected from the theatre matron and collated with the weekly anaesthesiology theatre allocation roster. Each anaesthesiology registrar/consultant will receive a data collection sheet for each patient on the elective list for the following day, as well as a brief summary of the information to be documented on the data capture sheet.

All information to be recorded on the data capture sheet is routinely captured prior to anaesthetic or surgical intervention. Demographic, medical and surgical information is generally routinely available following patient assessment. Furthermore, these blood pressure measurements are routinely performed and documented. These details will be recorded on the data collection form so patient files, records or notes will not be altered or removed for study purposes.

Finally, no additional measurements, tests or investigations will be performed which might place the patient at risk, or discomfort, or impose any additional cost or other burden on patient or institutional resources.

On arrival at the theatre complex, each patients’ folder or anaesthetic chart will be checked for the presence of the study data capture form, as well as for any errors in the completion thereof.
Data for each patient will be recorded on a separate, specifically designed data collection form, completed by the anaesthesiology registrar and/or consultant providing the anaesthetic for the patients prior to and during the surgical time period. This will serve as a further reminder regarding the information to the captured as well as ensure that no patient records are removed or altered from the patients’ hospital folder.

The forms will be collected by the researcher or research assistants in the recovery room of the main theatre, or as each patient exits the theatre complex.

The forms collected will be collated with the hospital record of all patients having entered the theatre complex each day, so as to determine the degree of uptake of data.

The study will take place over a period of one week and involve all elective non-cardiac, non-obstetric surgical cases scheduled from a Monday morning at 07h00 to a Friday evening at 07h00.[11]

**Resources and Cost**

The resources and cost, are as per the main study; ‘Elective patient preoperative, intraoperative assessment and blood pressure measurement is a routine procedure undertaken by all anaesthesiology registrars/consultants prior to and during surgical intervention. The predominant use of resources will thus involve time taken to complete the data capture form from information already available and recorded in patient’s clinical notes and anaesthesiology records.

Printing of the data capture forms, posters and other stationary required will be provided for by the researcher.

The researcher will require time out of theatre during the chosen week of the study to ensure data capture forms are distributed, completed in full, and then collected.
The collation of data capture forms, correlation with theatre records, as well data capture will be effected by the researcher, during research allocated time.

Departmental appointed statisticians will provide assistance with statistical analysis as required. Research monies will be motivated for, to ensure this cost is covered.'[11]
Data management and analysis

All data will be captured on the case report forms and entered into excel and then SPSS for data analysis.

Collection of data will depend on fellow anaesthetic registrars and consultants under the supervision of the research team. The research team will include the authors of the primary study and substudy as well as supervisors, co-supervisors and statisticians. Data will be handled by the research team as described. Data will be kept anonymous as no patient identifying details will be recorded on the case report forms. Completed case report forms will be kept in the GSH Anaesthetic department (D23).
Reporting of results

Study results will be recorded and submitted in the form of a MMed dissertation to the University of Cape Town for assessment as per postgraduate requirements. These results will also be made available to the public.
Attachments

1. Case report form
2. Elective theatre list schedule
3. Anaesthetic record
4. Karen Van der Spuy’s research proposal
References


5. Sanders RD: How important is peri-operative hypertension? *Anaesthesia* 2014, **69**:948-953.


8.b) Ethics approval documents
18 October 2016

HREC REF: 708/2016

Dr F Roodt
Anaesthesia
D24
NGSH

Dear Dr Roodt

PROJECT TITLE: IS THERE A RELATIONSHIP BETWEEN PREOPERATIVE BLOOD PRESSURE MEASUREMENT AND INTRAOPERATIVE HAEMODYNAMIC CHANGES THAT ARE KNOWN TO BE ASSOCIATED WITH POSTOPERATIVE MORBIDITY? (Sub-study linked to 661/2016) [MMED CANDIDATE DR M CROWTHER]

Thank you for submitting your study to the Faculty of Health Sciences Human Research Ethics Committee for review.

It is a pleasure to inform you that the HREC has formally approved the proof of concept for phase 1 of the above-mentioned study.

Approval is granted for one year until the 30th October 2017.

Please submit a progress form, using the standardised Annual Report Form if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.

(Forms can be found on our website: www.health.uct.ac.za/fhs/research/humanethics/forms)

We acknowledge that the student Dr M Crowther will be involved in this study.

Please note that for all studies approved by the HREC, the principal investigator must obtain appropriate institutional approval before the research may occur.

Please quote the HREC REF in all your correspondence.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Yours sincerely

Signature Removed

PROFESSOR M BLOCK
CHAIRPERSON, FHS HUMAN RESEARCH ETHICS COMMITTEE
Federal Wide Assurance Number: FWA00001637.
Institutional Review Board (IRB) number: IRB00001938

This serves to confirm that the University of Cape Town Human Research Ethics Committee complies to the Ethics Standards for Clinical Research with a new drug in patients, based on the Medical Research Council (MRC-SA), Food and Drug Administration (FDA-USA), International Convention on Harmonisation Good Clinical Practice (ICH GCP), South African Good Clinical Practice Guidelines (DoH 2006), based on the Association of the British Pharmaceutical Industry Guidelines (ABPI), and Declaration of Helsinki (2013) guidelines. The Human Research Ethics Committee granting this approval is in compliance with the ICH Harmonised Tripartite Guidelines E6: Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) and FDA Code Federal Regulation Part 50, 56 and 312.
### FHso17: Annual Progress Report/ Renewal

**HREC office use only (FWA00001637; IRB00001938)**

This serves as notification of annual approval, including any documentation described below.

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<td>Annual progress report Approved until/next renewal date 30/10/18</td>
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<td>See attached comments</td>
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**Signature Chair:**

**Signature Removed**

**Date Signed:** 24/1/2018

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**Principal Investigator to complete the following:**

1. **Protocol information**

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<td>708/2016</td>
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<td>30 October 2017</td>
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<tr>
<td>Protocol title</td>
<td>The relationship between pre-operative hypertension and intra-operative haemodynamic changes known to be associated with post-operative morbidity.</td>
</tr>
<tr>
<td>Principal Investigator</td>
<td>Dr F Roodt (MMed Candidate Dr M Crowther)</td>
</tr>
<tr>
<td>Department / Office Internal Mail Address</td>
<td>023 Department of Anaesthesia and Perioperative Medicine, Groote Schuur Hospital</td>
</tr>
</tbody>
</table>

1.1 Does this protocol receive US.Federal.funding? □ Yes □ No

2. **Protocol status (tick )**

<table>
<thead>
<tr>
<th>Item</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>☐ Research-related activities are ongoing</td>
<td></td>
</tr>
<tr>
<td>▢ Data collection is complete, data analysis only</td>
<td></td>
</tr>
</tbody>
</table>

Please indicate if the block below the title an HREC refer to project number(s) as referenced in your use of the Database registry repository.

This substudy is linked to HREC ref 661/2016. An audit of the prevalence of hypertension disease in patients presenting for elective surgery. MMed Candidate Or K van der Spuy

3. **Protocol summary**

<table>
<thead>
<tr>
<th>Item</th>
<th>Description</th>
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</thead>
<tbody>
<tr>
<td>Total number of records collected, reviewed or stored since the original approval</td>
<td>397</td>
</tr>
<tr>
<td>Total number of records collected, reviewed or stored since last progress report</td>
<td>397</td>
</tr>
<tr>
<td>Have any research outputs (e.g. publications, abstracts, conference presentations) resulted from this research? If yes, please list and attach with this report. X Yes □ No</td>
<td></td>
</tr>
</tbody>
</table>

4. **Signature**

<table>
<thead>
<tr>
<th>Item</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Signature of PI</td>
<td>Signature Removed</td>
</tr>
<tr>
<td>Date</td>
<td>22 January 2018</td>
</tr>
</tbody>
</table>
Dear Professor Marc Blockman

Please find attached the FHS 017 document for an extension of the ethics approval for the following study:

The relationship between pre-operative hypertension and intra-operative haemodynamic changes known to be associated with postoperative morbidity. (HREC ref 708/2016)

The study was presented in part at the South African Society of Anaesthesiologists National Congress, in Johannesburg, March 2017 in the registrar research category.

The study is aimed for publication in the journal, Anaesthesia during 2018.

Should you have any queries please do not hesitate to contact me.

Sincerely

Signature Removed

Dr Francois Ro
Email: f.roodt@uct.ac.za
### FHS017: Annual Progress Report / Renewal

**HREC office use only (FWA 00001637; IR 800001938)**

This serves as notification of annual approval, including any documentation described below.

| D Approved | Annual progress report / Approved until/next renewal date |
| D Not approved | See attached comments |

**Signature Chairperson of the HREC**

**Date Signed**

### Principal Investigator to complete the following:

#### 1. Protocol information

<table>
<thead>
<tr>
<th>Date (when submitting this form)</th>
<th>22 January 2018</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>HREC REF Number</th>
<th>708/2016</th>
</tr>
</thead>
</table>

**Current Ethics Approval was granted until**

| 30 October 2017 |

**Protocol title**

The relationship between pre-operative hypertension and intra-operative haemodynamic changes known to be associated with postoperative morbidity.

**Principal Investigator**

Dr F Roodt (MMed Candidate Dr M Crowther)

**Department / Office**

D23 Department of Anaesthesia and Perioperative Medicine.

**Internal Mail Address**

Groote Schuur Hospital

1.1 Does this protocol receive US Federal funding? / D Yes / X No

### 2. Protocol status (tick )

- D Research-related activities are ongoing
- X Data collection is complete, data analysis only

Please indicate (in the block below) the titles and HREC reference numbers of any projects currently making use of the Database/registry/repository.

This substudy is linked to HREC ref 661/2016. An audit of the prevalence of hypertension disease in patients presenting for elective surgery. MMed Candidate Dr K van der Spuy

### 3. Protocol summary

| Total number of records collected, reviewed or stored since the original approval | 397 |
| Total number of records collected, reviewed or stored since last progress report | 397 |

Have any research-related outputs (e.g. publications, abstracts, conference presentations) resulted from this research? If yes, please list and attach with this report. / X Yes / D No

### 4. Signature

**Signature of PI**

**Signature Removed**

**Date**

| 22 January 2018 |
8.c) Case report form
Hypertension and Surgery Study (HASS)

Consent given ☐ Yes ☐ No

Age [__________] years Gender ☐ M ☐ F Current smoker ☐ Y ☐ N

Ethnicity: ☐ Black ☐ Coloured ☐ Asian ☐ Caucasian

Height [__________] cm Weight [__________] kg ASA ☐ I ☐ II ☐ III ☐ IV ☐ V

Blood results (no more than 30 days before surgery): Haemoglobin [__________] g/dL Creatinine [__________] µmol/L

Chronic co-morbid disease (tick all that apply):

☐ Coronary artery disease ☐ Heart failure ☐ Advanced retinopathy
☐ Stroke or Transient ischaemic attack ☐ COPD / Asthma ☐ HIV / AIDS
☐ Known hypertension ☐ Chronic renal disease ☐ Peripheral arterial disease
☐ Diabetes (without insulin) ☐ Diabetes (requiring insulin) ☐ High cholesterol or statin Rx

Functional status: ☐ Totally independent ☐ Partially dependent ☐ Totally dependent

Pre-operative ECG (within the last 6 months) (tick all that apply):

☐ LVH (left ventricular hypertrophy) ☐ Rhythm irregular ☐ ECG not done

Surgical procedure category (select single most appropriate):

☐ Anorectal ☐ Aortic ☐ Bariatric
☐ Brain ☐ Breast ☐ ENT (except thyroid/parathyroid)
☐ Foregut (hepatopancreaticobiliary) ☐ Gallbladder, appendix, adrenal, spleen ☐ Hernia (ventral, inguinal, femoral)
☐ Intestinal ☐ Neck (thyroid/parathyroid) ☐ Gynaecology
☐ Orthopaedic/ nonvascular extremity ☐ Other abdominal ☐ Peripheral vascular
☐ Skin ☐ Spine ☐ Non-oesophageal thoracic
☐ Vein ☐ Urology

Current antihypertensive medications i.e. taking for at least 30 days prior to hospital admission (tick all that apply):

☐ ACE-I or ARB ☐ Diuretic ☐ Beta-blocker
☐ Calcium channel blocker ☐ Alpha-blocker ☐ Other

Drug compliance (tick all that apply): Do you ever forget to take your medication? ☐ Y ☐ N

Are you careless at times about taking your medication? ☐ Y ☐ N

When you feel better, do you sometimes stop taking your medication? ☐ Y ☐ N

Sometimes if you feel worse when you take the medicine, do you stop taking it? ☐ Y ☐ N

Reasons for non-drug compliance (only answer if 2 or more drug compliance questions above marked ‘Yes’):

Health system ☐ Condition ☐ Patient ☐ Therapy ☐ Socioeconomic ☐

Blood pressure during pre-operative assessment:

1st BP reading: SBP [__________] DBP [__________] MAP [__________] HR [__________]

2nd BP reading (if 1st >140/90): SBP [__________] DBP [__________] MAP [__________]

3rd BP reading (if 1st >140/90): SBP [__________] DBP [__________] MAP [__________]

HASS unique patient ID [__________]

Patient name: ____________________________ DOB [d d m m y y y y]

Patient hospital number: ____________________________
Perioperative data capture

Surgery performed:  □ Yes  □ No  If no, reason: ________________________________

Pre-induction blood pressure: SBP □□□□□□□□ DBP □□□□□□□□ MAP □□□□□□□□ HR □□□□□□□

Anaesthetic technique (✓)  □ General  □ Spinal  □ Epidural  □ Sedation  □ Local  □ Other regional

Major surgery:  □ Y  □ N

Blood loss during surgery: □□□□□□□□ ml  Duration of surgery: □□□□□□□□ minutes

Vasopressors:  □ Phenylephrine  □ Ephedrine  □ Adrenaline

Intraoperative fluid administration:

<table>
<thead>
<tr>
<th></th>
<th>Total volume given (ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crystalloid</td>
<td></td>
</tr>
<tr>
<td>Colloid</td>
<td></td>
</tr>
<tr>
<td>Blood</td>
<td></td>
</tr>
</tbody>
</table>

Intraoperative haemodynamics (please record total intra-operative time in minutes):

Heart rate > 100:  □ No  □ Yes  If yes, total time HR > 100 □□□□□□□□ minutes

MAP < 55mmHg  □ No  □ Yes  If yes, total time MAP < 55mmHg □□□□□□□□ minutes
1. Baseline data on page one should be collected on the preoperative anaesthetic visit on the day before surgery.

2. BP assessment during the preoperative anaesthetic visit should ideally be measured as follows;
   Allow patient to sit for 3–5 minutes before commencing measurement. The SBP should be first estimated by palpation to avoid missing the auscultatory gap. If the 2nd and 3rd readings 1–2 minutes apart, are only required if the 1st reading >140/90. If there is a discrepancy in readings between arms, then use the side with the higher BP. The patient should be seated, back supported, arm bared and arm supported at heart level. Patients should not have smoked, ingested caffeine-containing beverages or food in previous 30 min. An appropriate size cuff should be used: a standard cuff (12 cm) for a normal arm and a larger cuff (15 cm) for an arm with a mid-upper circumference > 33 cm (the bladder within the cuff should encircle 80% of the arm). Measure BP after 1 and 3 minutes of standing at first consultation in the elderly, diabetics and in patients where orthostatic hypotension is common. When adopting the auscultatory measurement use Korotkoff 1 and V (disappearance) to identify SBP and DBP respectively. Take repeated measurements in patients with atrial fibrillation and other arhythmias to improve accuracy.¹

3. Baseline data on page two should be collected on the anaesthetist who provides the anaesthesia for the patient.

4. Definitions:
   a. Advanced retinopathy: defined as haemorrhages or exudates or papilloedema
   b. LVH ECG definitions; defined as;
      i. S in V1 plus R in V5 or V6 > 35 mm or
      ii. R in aVL > 11 mm or
      iii. (R in aVL + S in V3 + 6 in females) × QRS duration > 2 440 (mm/ms)
   c. Major surgery: defined as Aortic and other major vascular surgery, peripheral vascular surgery, or intraperitoneal or intrathoracic surgery with major fluid shifts
   d. Non-drug compliance definitions;²
i. Health system: Poor quality of provider-patient relationship; poor communication; lack of access to healthcare; lack of continuity of care

ii. Condition: Asymptomatic chronic disease (lack of physical cues); mental health disorders (eg, depression)

iii. Patient: Physical impairments (eg, vision problems or impaired dexterity); cognitive impairment; psychological/behavioural; younger age;

iv. Therapy: Complexity of regimen; side effects

v. Socioeconomic: Low literacy; higher medication costs; poor social support

5. Please try to ensure complete data submission. If an ECG or blood results are not available at the time of the preoperative anaesthetic assessment, please can the anaesthetist for the operative procedure complete these data.

Reference


8.d) Informed consent document
INFORMED CONSENT FORM

Title of Studies:

An audit of the prevalence of hypertensive disease in patients presenting for elective surgery. HREC ref: 661/2016

Is there a relationship between pre-operative blood pressure measurement and intra-operative haemodynamic changes that are known to be associated with postoperative morbidity? HREC ref: 708/2016

Investigators: Dr Karen van der Spuy, Dr Marcelle Crowther, Dr Marcin Nejthardt, Dr Francois Roodt, Prof Bruce Biccard

Department of Anaesthesia and Perioperative Medicine, University of Cape Town, South Africa

INFORMATION

You are being approached to be a part of a research study on blood pressure. The doctors that are part of this study are trying to understand more about your blood pressure before and during surgery.

If you have no objection, the doctors would appreciate your permission to collect information relating to your blood pressure measured in the ward, in theatre and during your surgery. This study will have no benefits for you, but may help doctors treat patients in the future.

If you agree to be a part of this study, the doctors will be collect the following information, which is routinely written down as part of your standard patient care in hospital:

• Your blood pressure, factors known to be associated with high blood pressure and blood pressure medication, and

• Details about your operation which include how long the operation took, the type of intravenous fluids, any changes in your blood pressure and heart rate, and whether any medication was given to manage your blood pressure.

Being a part of this study will not result in any additional measurements, tests or investigations during your time in the hospital. The only difference for patients in the study when compared to standard care patients, is that the above information will be taken down by one of the doctors. This information will be stored both on paper and on computer. To protect your privacy, the information will be labelled in a way that will not identify you. If the results of these studies are published, your identity will be kept confidential.
By signing this form, you are allowing the use of this information for the research study. These research projects have been approved by the University of Cape Town’s Human Research Ethics Committee. If you have any ethical concerns or questions about your rights or welfare as a participant in this research, the Human Research Ethics Committee can be contacted on 021 406 6338.

Please read this form carefully and ask the investigator (study doctor) to explain any words or information that are not clear to you. This will help to ensure you understand the details of your participation before you give your consent. You will be given a copy of this consent form to take home with you. The doctors will answer any questions you may have about this consent form and about the studies.

CONSENT STATEMENT

I therefore certify the following:

• I have read the above information form and understand that the study involves research.

• I understand that the doctors will make a copy of some of my routinely recorded data from my standard patient care.

• I have had the opportunity to ask questions. All my questions have been answered to my satisfaction.

• I understand that any information that leaves the doctor’s office will be de-identified (i.e., identifying information will be removed from the documents).

_______YES __________ NO

Participant/Legal Representative’s name (printed)  Signature  Date:

Name of person obtaining consent (printed)  Signature  Date:
8.e) *Anaesthesia* author guidelines
Anaesthesia author guidelines

PREPARATION OF MATERIAL

Layout
A typical manuscript will have the following sections in the following order:
Title page
The name and full postal address of the corresponding author should appear in the top left-hand corner. The rest of the page should follow this example:

Title of paper that does not state the conclusion or pose a question*
A. B. Author,¹ C. D. Author² and E. F. Author³
1 Position/designation of 1st author, primary institution, city, country.
2 Position/designation of 2nd author, primary institution, city, country.
3 Position/designation of 3rd author, primary institution, city, country.

Correspondence to: Dr Corresponding Author (incl. e-mail address)

*footnote if presented in part at any national or international meetings, with details including location and date.

Short title of up to 60 characters suitable for a running header
N.B. Place the superscript number after the commas in the list of authors. Please do not include authors’ qualifications.
Please note that statements such as 'Author XX and Author YY both contributed equally to this work' are not used.

Keywords
Each manuscript should have 3 to 5 keywords identified on the title page. Please only use keywords from this list here.
The title should describe the purpose and contents of the paper as well as possible; in general, this should not exceed 20 words. Include relevant key-words e.g. randomised controlled trial, prospective, observational, etc.

Summary
The Summary should follow the sequence of the main body of the text, i.e. introduction, methods, results, discussion, but should not be structured. It should briefly state the purpose of the study or investigation; basic procedures; important results (giving numbers studied, values for results with p values) including relevant findings from Results, Tables and Figures; and principal conclusions.
Use the same sequence when presenting the methods and results as in the main body of the text, always mention the groups in the same order, and ensure that the numbers in the Summary exactly match those in the main body; it may be preferable to write the summary after having finished writing the main paper, in order to ensure that these features match.
The Summary should only exceed 250 words in exceptional circumstances. Abbreviations should not be used except for units of measurement.

Introduction
The Introduction should give a concise account of the subject’s background. Previously published work should only be quoted if it has a direct bearing on the present study. The Introduction should clearly and explicitly state the aims of the project.
Methods
A statement confirming Local Research Ethics Committee approval and written informed consent should be at the beginning of this section (see Ethical Considerations, below).
The Methods section must describe in sufficient detail the techniques and processes used so that the investigation can be interpreted and repeated by readers. Any modification of previously published methods should be described and the appropriate reference given. If the methods are commonly used, only a reference to the original source is required. If special equipment is used, then the manufacturer’s details (including town and country) should be given in parentheses. Drugs should be identified by their recommended international non-proprietary names (NB adrenaline and noradrenaline are used in preference to epinephrine and norepinephrine). Label groups in a way that is easy to follow; thus ‘propofol group’ and ‘thiopental group’ instead of ‘Group P’ and ‘Group T’. (Occasionally, abbreviated group titles may be better, e.g. ‘Group BLAB’ instead of ‘bupivacaine-lidocaine-adrenaline-bicarbonate group’). Remember to include inclusion/exclusion criteria and a justification of sample size. For randomised controlled trials, sufficient detail should be given on the following to allow readers to properly judge the risk of bias in the study: random sequence generation, allocation concealment, blinding (of patients, investigators, clinical staff, observers/assessors as appropriate) and handling of dropouts/withdrawals (intention to treat principle). Selective reporting bias will be assessed by comparison of the report with its protocol/trial registry entry (see above). The statistical methods used to investigate data should be given at the end of the Methods section (see below).

Results
Express results as mean (SD), median (IQR [range]) or number (proportion) as appropriate. Results (including actual p values) must be presented for all measurements detailed in the Methods section, and in the same order. Results should not be repeated unnecessarily. For example, if a graph is used, do not also present the same information in the text or in a Table. Results should not be given to an unwarranted number of decimal places and 95% confidence intervals should be used where possible (see Statistics, below).

In randomised trials, baseline data (age, ASA physical status, duration of operation, etc.) should not be subjected to statistical comparison, since it is already known that the subjects were randomly allocated and that any difference is therefore due to chance. Describe characteristics and, if possible, allow for differences in the analysis and discussion.

When reporting the effect of an intervention, absolute risk (AR), relative risk (RR) and ‘number needed to treat’ (NNT) are more easily understood by readers and may be preferable to odds ratio (OR).

Graphs and tables should be appropriate for the data to be displayed. Tables usually convey more precise numerical information; graphs should be reserved for highlighting changes over time or between treatments.

Avoid judgemental terms such as ‘very’ or ‘highly’ significant.

Report actual p values, rather than ranges or limits (e.g. p=0.032, rather than p<0.05).

Suggestions:

- Use ‘survival’ curves for outcomes that are time e.g. ‘time to extubation’ or ‘time to hospital discharge’, particularly if it is the primary outcome
- Means should be expressed to a sufficient precision that they are different, with a minimum of three significant digits e.g. 372, 37.2, 3.72, 0.372 etc.
- Means should be followed by the standard deviation, not the standard error.
- Standard deviations do not need to be different and should be a minimum of two significant digits.
- Rates should be followed by proportion if the denominator exceeds 100, e.g. 90/200 (45%) but 9/20.

Discussion
The Discussion should not merely recapitulate the results but should present their interpretation against a background of
existing knowledge. Any conclusions must be warranted by the results. In general, avoid a paragraph headed ‘Conclusions’ that merely repeats a summary of the results. Also avoid ending with ‘further work is needed’ (it almost always is) unless you have specific areas of research to suggest.

Acknowledgments

The authors should acknowledge those who have made substantial contributions to the study or preparation of the manuscript but whose contributions do not fulfil the requirements for authorship (see above). For Case Reports, a statement ‘Published with the written consent of the patient(s)’ should be included. The trial registration site and number should be included in this section.

Competing interests

A statement should be made at the end of all manuscripts, stating any funding obtained and any potential competing interests. For example: ‘No external funding and no competing interests declared’ or ‘Funded by the XXXX Association, grant no. yyyy. Author AB has received payments from ZZZZ Ltd for consultancy work’, etc. as appropriate.

Appendices

Information or data not directly a result of the study but necessary for the reader to understand the manuscript should be included as an Appendix. Examples might include copies of questionnaires used, recognised mathematical processes used to generate results or previously published and validated classification systems. All should be appropriately referenced and the authors must obtain permission from the copyright holders if the contents have been previously published.

References

References must be numbered sequentially as they appear in the text. References cited in figures or tables (or in their legends and footnotes) should be numbered according to the place in the text where that table or figure is first cited. Reference numbers in the text should be inserted after one space and before punctuation, e.g. [6].

Where more than one reference is cited, these should be separated by a comma, e.g. [1, 4, 39]. For sequences of consecutive numbers, give the first and last number of the sequence separated by a hyphen, e.g. [22-25]. Please note that if references are not cited in order, the manuscript may be returned for amendment before it is passed on to the Editor for review.

Abstracts may be quoted as references so long as they have been published in peer-reviewed journals. Internet sites may be quoted as references by listing them in the normal way in the text (using Arabic numerals). Unpublished observations, personal communications and abstracts published only in proceedings of meetings should be quoted within the text of the manuscript, in parentheses. Please submit copies of any articles accepted for publication but not yet published. Information from manuscripts submitted but not yet accepted should be cited in the text as unpublished observations. References cited for the first time in Tables or Figures should be numbered in the sequence established by the first mention of the particular Table/Figure in the text. All references (including those in press) should be listed at the end of the text in the order they are quoted. For internet sites, please include the date accessed in parentheses. List all authors unless there are seven or more, in which case give the first three followed by ‘et al.’ The journal title should be written out in full and in italics, followed by a semi-colon then a space followed by the edition number in bold (no sub-edition numbers please) then a colon then a space and finally the page numbers.

Examples:

1. Author AB, Author CD. Title of paper. *Journal Title Written Out in Full in Italics* 2010; **12**: 123-4.
2. Author AB, Author CD. Title of paper published as 'ePub ahead of print'. *Journal Title Written Out in Full in Italics* 2010 Dec 15; doi xx.xxxx/xxx.xxxxxx.
3. Author AB, Author CD, Author EF, et al. Seven or more authors – what’s the point? (chapter title). In: Editor GH, Editor IJ, eds. *Title of Book*. Place: Publisher, 2010: 345-67.
5. Author(s) of website. Title of document/page, 2010. www.URL.co.uk/link.pdf (accessed 01/01/2010).

The International Committee of Medical Journal Editors has stated that: "Authors are responsible for checking that none of the references cite retracted articles except in the context of referring to the retraction. For articles published in journals
indexed in MEDLINE, the ICMJE considers PubMed the authoritative source for information about retractions. "Retracted articles can be identified by using the following search strategy in PubMed, e.g. for an author J. Smith enter "Smith*J AND retracted publication[pt]".

**Tables**

Include the Tables in the same file as the text, but after the References not in the middle of the text. Each Table should be on a separate page. Number the Tables consecutively with Arabic numerals. Each Table should have a brief Caption immediately above it; the Caption should provide enough information for readers to follow it without having to look through the text (e.g. ‘Characteristics of patients receiving vecuronium or rocuronium for caesarean section’ rather than just ‘Patients’ characteristics’). The Caption should explain whether the values refer to mean (SD), number (proportion), etc. Abbreviations should not be mentioned in the Caption without explanation. Abbreviations used in the body of the Table should be explained as footnotes in the order in which they are first mentioned.

For adults: age, weight, height and BMI should be expressed as mean (SD).

For children: age, weight, height and BMI should be expressed as median (IQR [range]).

The study groups should form the columns rather than the rows. If statistical comparisons are being made, a separate column with exact p values should appear.

Example:

**Table 2** Characteristics of intrathecal blocks with levobupivacaine or bupivacaine in patients undergoing knee replacement. Values are mean (SD), median (IQR [range]) or number (proportion).

<table>
<thead>
<tr>
<th></th>
<th>Levobupivacaine (n=40)</th>
<th>Bupivacaine (n=40)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time to T10; min</td>
<td>7.8 (1.9)</td>
<td>6.4 (2.0)</td>
<td>0.002</td>
</tr>
<tr>
<td>Time to peak sensory block; min</td>
<td>26.4 (7.2)</td>
<td>21.8 (5.7)</td>
<td>0.002</td>
</tr>
<tr>
<td>Time to two-segment regression; min</td>
<td>80.3 (9.9)</td>
<td>78.3 (10.9)</td>
<td>0.41</td>
</tr>
<tr>
<td>Time to maximum motor block; min</td>
<td>19.1 (5.4)</td>
<td>9.5 (4.2)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Time to motor block regression; min</td>
<td>145.6 (18.5)</td>
<td>139.9 (22.4)</td>
<td>0.22</td>
</tr>
<tr>
<td>Time to L5; min</td>
<td>245.5 (39.1)</td>
<td>239.7 (32.9)</td>
<td>0.41</td>
</tr>
<tr>
<td>VAS for discomfort/pain during surgery*</td>
<td>7 (6-8 [5-9])</td>
<td>6 (5-7 [4-8])</td>
<td>0.011</td>
</tr>
<tr>
<td>Supplementation with fentanyl</td>
<td>0 (29%)</td>
<td>0 (15%)</td>
<td>0.77</td>
</tr>
</tbody>
</table>

*VAS; visual analogue score

**Figures**

Please supply each Figure as a separate file, rather than embed them within the body of the Word document or in the covering email, and preferably in TIFF or high-resolution JPEG format. We ask that they are both supplied at a resolution of 300 pixels per inch for photographs and 600 pixels per inch for line art or a combination of photograph and labelling. Please do not send image files larger than 10MB.

Please ensure related graphs have the same format (fonts, use of symbols, etc.), and that the groups are presented in the same order in each graph (and in the same order as in the rest of the manuscript). The same requirements for abbreviations and units apply as for those in the text. The title, plot frame, gridlines and legend box within the graph itself should be removed, with symbols and error bars explained in the Caption. Avoid the use of 3-D unless absolutely necessary. Please note that colour Figures (e.g. photographs, complex flow diagrams, etc.) may be used without charge.

**Captions for Figures**

Each Figure Caption should include an explanation of the symbols used to provide enough information for readers to follow it without having to look through the text.
Thus this:

![Bar chart showing itching after surgery in patients receiving saline ( ) or chlorphenamine ( ). No significant difference between groups.]

Figure 1 Itching after surgery in patients receiving saline ( ) or chlorphenamine ( ). No significant difference between groups.

Is preferable to this:

![Bar chart showing itching after surgery.]

Figure 1 Itching after surgery.

See notes below for ethical considerations relating to photographs.

Supporting Information (online only)
Additional material such as video clips, lengthy Appendices (e.g. extensive reference lists or mathematical formulae/calculation), etc. that are relevant to a particular article but not suitable or essential for the print edition of the Journal, may also be considered for publication. Please refer to all supporting information in the manuscript using Table S1, Figure S1, etc. and supply such information as separate files (i.e. not embedded within the main manuscript). Further information on suitable file formats, etc. may be found here.

Language
Please note that Anaesthesia uses UK English spelling e.g. “ise” not “ize”, “anaes” not “anes”, etc. In general, we prefer a clear, precise style to jargon. Please avoid long, complicated sentences and the passive voice when the active is more appropriate (e.g. ‘We chose epidural anaesthesia because...’ instead of ‘Epidural anaesthesia was chosen by the authors because...’). Remove unnecessary clutter and focus on the actual message of each sentence; thus ‘Hypotension is important because...’ instead of ‘It would be remiss of us not to mention hypotension because...’). Remember that lungs are ventilated, not patients (nor are they intubated – their tracheas are).
Similarly, patients are not induced – anaesthesia is – or put on ventilators. Correct terms are tracheal (not endotracheal) tube and neuromuscular blocking drugs (not muscle relaxants). Please refer to recent issues of the Journal for preferred wording/spelling, e.g. “manikin” is preferred to “mannequin”, and “supraglottic airway device” is preferred to “extraglottic airway device”.


The abbreviation LMA is only to be used if referring to a specific device made by The Laryngeal Mask Company Ltd, and with the first mention in the Summary and in the main text highlighted by (R) and ‘LMA is a registered trade mark of The Laryngeal Mask Company Ltd, an affiliate of Teleflex Incorporated’ as a footnote. If used, the correct format is ‘LMAâ laryngeal mask’ for the first mention (n.b. not just ‘LMAâ’) and ‘LMA laryngeal mask’ thereafter. The same to apply to LMAâ Classic, LMAâ Flexible, LMAâ Fastrach (n.b. previously labelled ILMAâ), LMAâ ProSeal, LMAâ Supreme, LMAâ Unique (n.b. ‘cLMA’ not to be used). The generic term of ‘laryngeal mask’ should be used for describing inflatable-cuff supraglottic airways in general.

Abbreviations

In general, the Journal does not encourage the use of abbreviations, especially in the Summary, since their frequent use makes papers cluttered and difficult to read. However, we will accept abbreviations in the following circumstances:

- **Universal abbreviations** that do not need to be written out in full when first mentioned in the text. These include abbreviations that appear in a large proportion of the articles published in the Journal, e.g. ASA, BMI, ECG, ICU, HDU, SD, SEM, 95% CI, IQR, ANOVA, S.O.₂, F.I.O.₂, pH.

- **Acceptable common abbreviations** that can be used but should be written out in full at their first mention, e.g. CNS, CSF, HME, PEEP, PCA, SCBU, CTG, EEG, BIS, CVP, PAP, PCWP, ECT – unless they’re only mentioned a few times, in which case please spell them out throughout. Please do not use abbreviations that are clumsy or will be unfamiliar to the majority of readers, e.g. DI (difficult intubation), TTFB (time to first breath), etc.

- **Acceptable abbreviations** that do not need to be written out in full when first mentioned but whose use should be restricted to situations where space is limited, such as in formulae or in Tables and Figures, e.g. O₂, CO₂, N₂O, HCO₃⁻, Na⁺, K⁺, Mg²⁺.

Numbers and units

Numbers should be spelled out in full when they start a sentence, and when they are less than 10 (unless they are followed by units of measurement). Thus: ‘Thirteen days later, five patients each received 7 ml solution...’ Commas are used to indicate thousands above 10,000: thus, 2000 and 20,000. Please give costs in sterling (£) with equivalent Euros and US dollars (€/$) in brackets.

Use the format mg.kg⁻¹ not mg/kg for all units. Use SI units throughout the text except for vascular pressure measurements (mmHg or cmH₂O) and haemoglobin concentration (g.l⁻¹). Litres are indicated by lower case ‘l’ not upper ‘L’. Use the 24-hour clock for times.

Ethical considerations

Whatever their other merits, manuscripts will only be considered for publication in Anaesthesia if they adhere to the highest ethical standards. These are detailed in two editorials published in the journal, that are available here and here and which potential authors are strongly advised to consult.

The Editorial Board takes all cases of possible publication misconduct seriously and will investigate these according to the recommendations of the Committee on Publication Ethics (COPE). Further guidance can be found in our Editorial Policies.

All clinical trials that prospectively assign human subjects to intervention or comparison groups to study the cause-and-effect relationship between a medical intervention and a health outcome should be registered before the time of first recruitment. There are several public registries now available which meet the requirements of the ICMJE and these are listed on the WHO International Clinical Trials Registry Platform (ICTRP). The registry, registration number and date of registration must be stated in the Acknowledgements section of the manuscript. This should have been done before patient recruitment commenced. Reports of original research that were not registered before the study was carried out should include separate submission of the original protocol for the study. If the submitted report differs from the protocol, an explanation of the reason for this should be provided. Authors should be willing and able to submit their raw study data to the journal, if requested, after submission.

Anaesthesia supports and encourages the use of the EQUATOR (Enhancing the QUAlity and Transparency Of health Research) Network guidelines to ensure the transparent and accurate reporting of research studies. The authors of clinical
intervention studies are advised to review the CONSORT statement regarding the reporting of randomised trials prior to manuscript submission.

We strongly encourage authors to register systematic review protocols on a similar database (for instance, PROSPERO http://www.crd.york.ac.uk/PROSPERO/).

All clinical trials should be conducted in accordance with the ethical principles as set out in the Declaration of Helsinki. In brief, the minimum ethical standards for Anaesthesia include:

- Approval by a Research Ethics Committee (REC) or equivalent Institutional Review Board (IRB) must be obtained prospectively for all studies on human subjects, including studies in which participants’ skills are tested using manikins. Some studies involving audit and epidemiological surveys, assessments of medical equipment or analysis of previously collected, non-identifiable information from a database may be exempt from this stricture if participants are appropriately protected against coercion and there is due regard to confidentiality. Publication of the results, however, would usually still require informed consent and assurances regarding confidentiality (including approval by the Caldicott Guardian or equivalent for patient data and the relevant Research and Development department), even if the REC/IRB has indicated that formal submission is unnecessary.

- While an essential preliminary step, REC/IRB approval does not guarantee that the ethical standards of a study will meet the requirements of the Editorial Board of Anaesthesia. If authors have any concerns that ethical issues might compromise publication, they are invited to contact the Editor-in-Chief before embarking on the study.

- The Editorial Board supports the view of the ICH Harmonised Tripartite Guideline for Good Clinical Practice that full prospective written informed consent should be obtained from all subjects of clinical trials, including participants in manikin studies (see above). This would normally comprise provision of written information to potential research participants, allowance of adequate time for them to consider their involvement and ask questions, and the use of specific consent forms (for the study, not just for routine surgery/anaesthesia) that should be signed by the participants to indicate their consent and then stored in case they require examination later.

- Submission of a case report requires the written consent of the subject to publication, using a specific form. Please do not submit this document together with your manuscript but note that authors may be asked to provide the signed form as evidence, should a complaint result in a subsequent investigation. While the Editorial Board recognises that it might not always be possible to seek such consent (or the assent of the next-of-kin if the patient has died), the onus will be on the authors to demonstrate that this exception applies in their case. Please state in an Acknowledgement at the end of the text: ‘Published with the written consent of the patient(s)’ or similar, as appropriate.

- Studies of novel treatments, in particular drug studies where the agent used is given via unlicensed routes (especially neuraxial or perineural), may have received approval from the REC/IRB, but the Editorial Board is likely to reject such studies if it considers that the risks posed outweigh the potential benefits. Such a conclusion is more likely to be reached if the drug in question is not widely used in routine practice (as evidenced by inclusion in standard textbooks), if the study participants are especially vulnerable (e.g. children, women in labour), if there are questions over consent, or if only modest improvements in outcome are expected where other, well established methods already exist.

- Animal studies will only be considered for publication if they have ethical and governmental approval, and have been conducted under appropriate standards of care. Researchers will be expected to follow the ARRIVE guidelines for experimentation in animal research.

**Statistics**

It is difficult to provide generic guidance on statistics, since statistics are designed to test a hypothesis in a quantitative way and hypotheses differ across studies. Nevertheless, the following guidelines may help authors present their work in a better and more rigorous way that avoids common statistical errors that frequently lead to rejection. This should not be regarded as an exhaustive list and, of course, the Editorial Board and reviewers of manuscripts may ask authors for revisions that are not detailed here. However, adherence to these guidelines in a paper that is otherwise acceptable will provide authors with a good footing.

**Methods**

Randomisation methods should be made explicit (e.g. coin toss, random numbers, etc.). Please describe if stratification of the allocation system in a randomised controlled trial is performed (e.g. by age or recruiting centre) or block (permuted sequence or otherwise). For instance, most anaesthetic RCTs have exactly the same number of patients in each group but don't mention any blocking method (which would include putting equal numbers of folded pieces of paper for each group in an urn). Blinding must be as good as possible within constraints of clinical practice.

Where there are several outcomes to be reported, the most important (primary) outcome should be clearly stated, along with any secondary outcomes. Beware of reporting as ‘significant’ or ‘important’ a positive result of a secondary outcome, when the study was in fact powered (sample sized) to a different primary outcome.
Some justification of sample size is always necessary for all observational studies, randomised or non-randomised controlled trials, or other types of study. Justification may be quantitative or qualitative (e.g. a ‘convenience sample’), although the latter may be regarded as weaker than the former. Details provided (for continuous variables) should include the power level; the significance level at which a result is sought; and the expected control and study group proportions or mean and pooled SD, in order to allow reviewers and readers to follow the calculation. The method used to justify power should be referenced and enough detail provided, so that the calculation can be repeated by readers. Conventionally, the power of study should be at least 80% but where different should be stated and justified. The ‘clinically important difference’ that the study is designed to detect should indeed be clinically relevant. Beware of setting an unreasonably large ‘clinically important difference’ to justify small sample size, as reviewers will recognise this is done simply to facilitate a small study.

**General rules:**

- Use mean (SD) unless data are discrete (e.g. Apgar scores, sedation scores) or grossly non-normally distributed: use median (IQR [range]) or you are interested in the ‘true’ value for the population (use SEM).
- Visual analogue scores (VAS) for pain may be treated as continuous data and be subjected to parametric tests as long as the sample size is large (> 50) and the data appear normally distributed. VAS for other modalities (nausea, drowsiness) have not been so extensively validated and are best treated as ordinal data.
- Scales of measurement can be problematic (e.g. Cormack-Lehane scale, VAS, etc.) because a value of say 2 on the scale does not imply something twice the value of 1, etc. So they cannot logically be regarded as linear, continuous scales. It is safer to regard them as ordinal scales. However, for some scales such as VAS for pain it appears established norm that this may be regarded as continuous, especially for large sample sizes (e.g. >50).

**Inferential statistics**

- Use simple statistical tests where possible.
- Avoid multiple comparisons, or correct for them if used.
- Reference unusual tests; and assume that the more unusual the test used, the more likely will a specialist statistical referee review the paper.
- Include details of any computer package/version used.
- When looking for relationship between variables, use correlation to describe a simple descriptive association between two variables.
- Use regression to describe a quantitative relationship between two or more variables, especially where one is predictive and other(s) dependent. Non-linear regression may be appropriate. Regression methods yield a formula to relate the variables being described.
- Use the Bland-Altman method to describe the performance of two different methods used in measurement, analysis or diagnosis.

**Conclusions**

All conclusions should be warranted by the results and not extend beyond the confines of the study conditions. A negative result does not mean that there is definitely no difference (confidence in the conclusion is dependent upon the power of the study), and a positive result does not mean that there definitely is a difference (confidence in the conclusion is dependent upon the alpha error).

The journal has a very useful statistic section containing articles which authors will find useful in preparing their manuscripts for statistical content:

8.f) Dissertation title change application documents
Please complete and return to Vuyi Mgoqi (Vuyi.Mgoqi@uct.ac.za) in the Postgraduate Office.

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The Title has been refined during the writing of our manuscript and will be submitted for publication under the new title being applied for.

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