The utility of occlusion of the pulse oximeter trace in the estimation of systolic blood pressure during spinal anaesthesia for caesarean section: the effect of body mass index

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Part A: Study protocol

As approved by the Departmental Research Committee and Human Research Ethics Committee, University of Cape Town.

Introduction and aim of study

In South Africa, the preferred anaesthetic technique for emergency or elective caesarean section (CS) is single shot spinal anaesthesia (SA), where a combination of local anaesthetics and opiates is used. Spinal hypotension is a common complication that demands prompt recognition and treatment to prevent associated morbidity/mortality.1,2

The standard method of blood pressure (BP) monitoring is with an automated non-invasive blood pressure (NIBP) device, which utilises oscillometry. This method measures oscillation amplitudes as the cuff pressure changes. Pressure pulsations against the cuff cause oscillations. The mean arterial pressure is the point of maximal oscillation and the most accurate parameter measured by the oscillometric method. The systolic and diastolic pressures can then be derived with reference to the mean pressure by use of an algorithm.3

Rapid recording of the blood pressure is of cardinal importance so that timely intervention with fluids and vasopressors can restore maternal blood pressure and uteroplacental perfusion. For an improved response time, an alternative method can be used to obtain an indication of the patient’s systolic blood pressure (SBP), by observing the disappearance (DOT) or return (ROT) of the pulse oximeter waveform trace during inflation and deflation of the BP cuff respectively.

Both the accuracy and precision of- and the time taken for this estimate are important. Regarding accuracy, our clinical impression is that the rate of increase of pressure in the cuff is more rapid in underweight and normal body mass index (BMI) patients, where a smaller, lower volume cuff is used. This could make the accurate visual estimation of blood pressure using DOT/ROT
more difficult than in obese patients, where the escalation of pressure in the larger cuffs used is usually more gradual.

With regard to response time, NIBP readings often take longer in obese patients. Therefore it is important to establish the time taken for the estimate of blood pressure, as well as the time saved by doing the visual estimate, across the physiological range of body mass indices.

In the morbidly obese population, an arterial line can be sited to give a more accurate blood pressure measurement. In the developing world with its limited resources, usually only noninvasive blood pressure devices are available. Therefore, our study aim was to examine the accuracy of estimation of SBP by disappearance and reappearance of the pulse oximeter trace (DOT/ROT) with cuff inflation during SA for caesarean section, and to examine the effect of body mass index on accuracy and precision of the estimated SBP measurement, the time taken to achieve this estimate and the time taken for the NIBP measurement.

The primary outcome will be a Bland and Altman comparison (bias and limits of agreement) between DOT/ROT and NIBP, in three BMI ranges, namely < 30 kg/m², 30-40 kg/m², and >40 kg/m². The secondary outcome will be a comparison of the time to measurement of DOT/ROT and NIBP, in these BMI ranges.

The results of the study should hopefully improve the safety of spinal anaesthesia for caesarean section in resource-limited areas in the developing world, by rapid and accurate identification of spinal hypotension, particularly in morbidly obese parturients.

Patients and methods

Approval for the study will be obtained from the Health Sciences Faculty Human Research Ethics Committee of the University of Cape Town. This prospective observational study will be performed at the Groote Schuur
Hospital Maternity Centre and Mowbray Maternity Hospital. Written informed consent will be obtained from all participants in the ward at the time of recruitment to the study.

Three groups of 25 patients per group requiring elective or emergency caesarean section (with no prior epidural inserted), will be recruited. Group 1 will comprise parturients with normal body mass index (BMI), defined as less than 30 kg/m$^2$; Group 2 will comprise obese parturients, with BMI 30-40 kg/m$^2$, and Group 3 will include morbidly obese parturients with a BMI of $> 40$ kg/m$^2$. Height and weight values at the time of presentation for CS will be used for calculation of BMI.

Inclusion criteria:

- Age $>$ 18 years
- ASA Class 1 to 3
- Gestation $>$ 36 completed weeks

Exclusion criteria:

- Pre-existing hypertension
- Preeclampsia or eclampsia
- Failed spinal anaesthesia
- Treatment with drugs that are known to affect blood pressure
- Any respiratory disease affecting arterial oxygen saturation
- Any condition causing impaired circulation to the hands
- Gestation $<$ 36 completed weeks
- Multiple pregnancy

The same DASH® 3000 monitor (GE Health Care, United Kingdom) will be used for all measurements for the study.

Referring to the DASH® 3000 monitor (GE Health Care, United Kingdom) operator manual:
“The oscillometric method uses a sensitive transducer, which measures cuff pressure and minute pressure oscillations within the cuff to determine mean pressure and calculate the systolic and diastolic BP. The parameter window on the monitor displays the cuff inflation pressure during a measurement. After inflating the cuff, the monitor begins to deflate the cuff and the oscillations in the cuff are measured. Systolic, mean and diastolic BP is calculated and the display updated. The monitor deflates the cuff one step each time it detects two pulsations of relatively equal amplitude. The time between deflation steps depends on the frequency of these matched pulses (pulse rate of the patient). However, if the monitor is unable to find any pulse within several seconds, it will deflate to the next step. The process of finding two matched pulses at each step provides artifact rejection due to patient movement and greatly enhances the accuracy.”

An appropriately sized blood pressure (BP) cuff for noninvasive SBP measurements will be applied to patients in both groups. The American Heart Association states that the width of the compression bladder of the BP cuff should be about 40% of the circumference of the limb. The circumference of the extremity is measured at the midpoint of the limb. The midpoint of the arm is measured at half the distance between the shoulder and the elbow joints. If the patient’s limb measurement falls on the borderline of two different cuff sizes, the likelihood of an erroneous measurement is decreased if the larger of the two cuff sizes is used. Loosely wrapped cuffs may result in falsely raised measurements. Cuffs will be tightly applied, leaving only enough space for one finger to be slipped between the skin and the cuff. The BP cuff and the pulse oximeter probe will be applied to the arm and index finger on the ipsilateral side.5

BP measurements for the study will be taken before and 5 minutes after induction of spinal anaesthesia.

Standard practice for spinal anaesthesia at UCT will be employed. An intravenous cannula will be sited and baseline measurements taken. Spinal analgesia will be induced in the sitting position using 2.0 mL hyperbaric 0.5%
bupivacaine plus 10 µg fentanyl, with co-loading of crystalloid 15 ml/kg.

All patients, after induction of spinal anaesthesia, will lie supine on the operating table with a standardised 15° left lateral tilt using an obstetric wedge.

Prevention and management of hypotension will be at the discretion of the attending anaesthetist. The usual practice is bolus administration of 50-100 µg of phenylephrine or 5-10 mg ephedrine.

Two SBP measurements will be taken. During the first measurement, the investigator will observe the dynamic pressure readings of the NIBP machine as the cuff inflates, recording the systolic pressure at the point when the pulse oximeter waveform disappears. The time taken for this estimation and the actual NIBP measurement will be noted.

During the second measurement, the investigator will observe the dynamic pressure readings of the NIBP machine as the cuff deflates, recording the systolic pressure at the point when the pulse oximeter waveform reappears. Once again, the time taken for this estimation and the actual NIBP measurement will be noted.

For both readings, the investigator will be blinded to the NIBP measurements of systolic, diastolic and mean BP, and recorded by the attending anaesthetist.

The same investigator will take all the measurements to eliminate inter-observer variability.

**Calculation of sample size**

A previous study compared non-pregnant healthy volunteers with parturients with normal body mass index (< 30 kg/m²), with a sample size of 40 (20 per group). In the present study, it was decided after consultation with our statistician, to study a total of 75 parturients (25 per group), since this should
ensure good modeling employing Bland and Altman analysis, considering the results of the previous study.6

References


Part B: Narrative Literature Review:

The use of pulse oximetry to estimate systolic blood pressure

1. Objectives

This literature review aims to examine studies utilising pulse oximetry to estimate the systolic blood pressure, especially in the context of caesarean sections (CS). In this situation, spinal hypotension is a common complication that demands prompt recognition and treatment to prevent associated morbidity/mortality.

2. Literature Search Strategy

The full text of relevant publications was obtained online, from the University of Cape Town Health Science Library search facility, which accesses 17 medical digital archive databases worldwide. Pubmed/Medline was also searched for relevant articles. Literature not published in the English language was excluded.

3. Quality criteria

The keywords used for the search included each of the following, in various combinations: estimation, non-invasive systolic blood pressure, pulse oximetry, spinal anaesthesia, pregnancy, non-invasive blood pressure machines, caesarean section, body mass index. By using reference lists, further relevant papers were identified.

4. Summary of the literature

4.1. Introduction

Continuous noninvasive assessment of arterial oxygenation with a pulse oximeter has been part of clinical practice since 1983. Operating on the principle that fully oxygenated blood is only present during arterial pulsations,
the oximeter uses pulse detection algorithms to identify the absorbance of arterial light in a vascular bed. Oxyhemoglobin and reduced hemoglobin are detected at two wavelengths of light (660 nm and 940 nm respectively), and application of Beer’s law allows the hemoglobin oxygen saturation to be determined.¹

The BP cuff was first used in clinical practice in the early nineteenth century. The original method of SBP measurement was by occlusion of the palpable radial arterial pulse. This method was replaced by auscultation of Korotkoff sounds, allowing the diastolic and systolic pressure to be easily measured.²

The oscillometric technique of blood pressure measurement involves the use of a sensitive transducer, which measures minute pressure oscillations within the BP cuff and cuff pressure during gradual deflation. The mean arterial pressure is the BP cuff pressure at the point of maximal oscillation, with systolic and diastolic pressures derived with an algorithm.³ The various manufacturers of NIBP devices use different algorithms, and there is no generic oscillometric technique.³,⁴,⁵

Continuous pulse oximetry and blood pressure measurement (at least every five minutes) form part of our standard intra-operative monitoring during anaesthesia.⁶,⁷,⁸ To detect the rapid changes after induction of SA for CS, blood pressure is measured every minute, at least until delivery.

In the developing (and developed) world, the equipment and resources for intra-arterial blood pressure monitoring are not always available, and anaesthetists have to rely on an automated NIBP device. During SA for CS, rapid blood pressure measurement using an NIBP monitor may be difficult, especially if there is excessive patient movement.⁹ In such a situation, the anaesthetist may obtain an estimate of the patient’s systolic blood pressure by observing the disappearance or reappearance of the pulse oximeter trace during NIBP cuff inflation and deflation respectively.
Sensitivity of the pulse oximeter probe to blood flow

An important consideration is the sensitivity of the pulse oximeter in detecting the disappearance or return of pulsatile blood flow during BP cuff inflation or deflation. Lawson et al. used a laser Doppler flow probe to determine the magnitude of peripheral blood flow during manual inflation and deflation of a BP cuff with a pulse oximeter probe placed on the ipsilateral arm. They noted pulse oximeter signal loss once the occluding pressure during inflation reduced the relative blood flow to 8.6 % (SD ±5.9%) of the original blood flow. A relative flow of only 4% (SD ±3.1%) of the baseline blood flow was required to restart the oximeter function. Thus, for the oximeter to detect signals, the relative blood flows during inflation and deflation were different (p value < 0.02). Theoretically, this should mean that estimation of SBP with disappearance of the pulse oximeter trace during cuff inflation should be higher than estimation of SBP with reappearance of the trace during cuff deflation. Their conclusion was that the pulse oximeter is an extremely sensitive monitor for the detection of pulsatile blood flow.10

SBP estimation using the pulse oximeter trace, and correlation with NIBP methods

Wallace et al. in their study of 51 patients with an age range of newborn to 79 years (average age of 25 years), compared blood pressure measurement by Doppler flow meter and estimation of SBP by pulse oximetry techniques. A standard manual BP cuff, pulse oximeter probe and Doppler probe (over the radial artery) were all applied on the ipsilateral arm. SBP was recorded when the oximeter waveform disappeared during BP cuff inflation. The mean difference between methods was 4.9 mmHg with an SD of 7 mmHg. They observed a good correlation between estimation of SBP with pulse oximetry and the Doppler method (r = 0.93). Of note in this study, is that 729 pairs of SBP were measured in only 51 patients, which implies that repeated BP measurements were taken in each patient, serving as an explanation for their high degree of correlation.11
Talke et al. did a study on 20 healthy awake volunteers and 42 patients under general anaesthesia. They compared the more traditional cuff methods of SBP measurement by Korotkoff sounds, Doppler ultrasound and direct measurement with an intra-arterial line, to the pulse oximeter method of estimating systolic blood pressure. A manual BP cuff was used with a deflation speed of 2-3 mmHg per second, with SBP estimated during cuff deflation with pulse oximeter waveform reappearance. They found good correlation between SBP estimation obtained by the pulse oximeter and the different conventional methods with the best correlation observed with Doppler ultrasound ($r = 0.996$) and the worst with intra-arterial measurements ($r = 0.880$). A good correlation was observed with Korotkoff sounds ($r = 0.958$). Their conclusion was that this method can be used intra-operatively to measure SBP.\(^1\)

Three studies were found evaluating pulse oximetry for estimating SBP in an out-of-hospital setting:

Talke measured SBP using a pulse oximeter during the helicopter transport of ten critically ill patients. The SBP measured by pulse oximetry was compared with the SBP measured by the arterial occlusion and direct intra-arterial methods. SBP by pulse oximetry was measured with the use of a manual BP device, placed ipsilateral to the pulse oximeter probe, by observing the return of the pulse oximeter waveform as the BP cuff was slowly deflated. For the arterial occlusion pressure method, measurement was taken by observing the return of the intra-arterial waveform during slow deflation of the BP cuff, placed ipsilateral to the arterial cannula. They recorded seventy-three sets of measurements and found the best correlation ($r = 0.99$) between pulse oximetry and the arterial occlusion method. The indirect methods (pulse oximetry and arterial occlusion) correlated better with each other than with the direct intra-arterial measurements. They found that the helicopter’s noise and vibrations did not cause significant interference with the functioning of the pulse oximeter. They concluded that a pulse oximeter waveform could accurately estimate SBP during helicopter transport.\(^1\)
In another study of 116 patients during transport in a helicopter air ambulance, estimation of SBP with disappearance of the pulse oximeter waveform during BP cuff inflation was compared to a baseline BP obtained by an automated BP device by oscillometry one minute earlier. The estimated SBP obtained by disappearance of the pulse oximeter waveform showed a strong correlation with the measured baseline SBP with an $r = 0.90$ and $p < 0.001$. The investigators concluded that disappearance of the pulse oximeter waveform is an accurate method of estimating SBP, with the additional advantages of being inexpensive and freely available.\textsuperscript{14}

McKluskey et al. estimated SBP by observing the return of the pulse oximeter waveform during cuff deflation in a moving ambulance and compared the accuracy to automated NIBP measurements, as well as auscultation and palpation. Sixty-nine patients’ blood pressure measurements were taken. They used regression analysis and found a significant correlation between the pulse oximetry method and the other methods used. Their correlation values were $r = 0.92$ for the automated NIPB measurements; $r = 0.95$ for auscultation, and $r = 0.97$ for palpation; all deemed significant at a $p < 0.0001$. Their conclusion was that this is a quick, easy, and accurate method to estimate SBP in an out-of-hospital setting, where more traditional methods of auscultation or palpation may be problematic.\textsuperscript{15}

A major limitation of the above studies evaluating the use of the pulse oximeter waveform to estimate SBP was the analysis of correlation rather than agreement. The latter can be achieved by using Bland-Altman analysis, which is a graphical method to evaluate the extent of agreement between two techniques measuring the same physiological variable. Bland and Altman published their landmark study in the Lancet in 1986 and observed that in clinical measurement when comparing the accuracy and precision of a new measurement technique with an established method, the acceptability of the new method depends upon bias and limits of agreement. They remarked that previous comparisons between measuring devices were often analysed inappropriately. Specifically by the use of correlation coefficients, which can be misleading, as high degrees of correlations do not per se justify
substituting one technique with another.  

The following in-hospital investigations of the use of pulse oximetry to estimate SBP did employ the Bland and Altman method:

Chawla et al. published a study in Anesthesia and Analgesia in 1992 evaluating the use of pulse oximetry to monitor systolic blood pressure in 100 healthy volunteers: 50 men and 50 women. The SBP was measured by three techniques: using the pulse oximeter waveform, by Korotkoff sounds, and with a manual oscillometric NIBP monitor. Using the oximetry method, SBP was estimated at the disappearance of the waveform during manual blood pressure cuff inflation (BP\textsubscript{DIS}), at the reappearance of the waveform during manual cuff deflation (BP\textsubscript{APP}), and by averaging the two estimations (BP\textsubscript{AV}). A manual BP cuff was used allowing control of inflation and deflation of the cuff in 2-5 mmHg increments. The SBP estimates obtained by pulse oximetry were then compared with the arterial blood pressures obtained by Korotkoff sounds (BP\textsubscript{K}) and noninvasive blood pressure equipment (BP\textsubscript{NI}) By using Bland-Altman analysis, they found good agreement between the BP\textsubscript{AV} of oximetry-based SBP estimates and the BP\textsubscript{K} and BP\textsubscript{NI}. In nearly 95% of cases, the differences between BP\textsubscript{AV} and conventional methods were likely to be within $\pm$14 mmHg. Mean (SD) bias between BP\textsubscript{AV} and BP\textsubscript{K} was -0.4 (6.69) mmHg and between BP\textsubscript{AV} and BP\textsubscript{NI} was -0.9 (7.09) mmHg respectively. Best correlation was observed when BP\textsubscript{AV} was compared with BP\textsubscript{K} and BP\textsubscript{NI} ($r = 0.8714$ and $r = 0.8472$, respectively.) They concluded that the pulse oximeter waveform could be used to measure systolic blood pressure, with the best agreement between BP\textsubscript{AV} and conventional methods. The authors did not estimate the disappearance and reappearance of the pulse oximeter trace with an automated NIBP machine.  

The same authors described two case studies in patients known with aorto-arteritis with pulseless upper limbs where conventional NIBP measurements failed. Using the disappearance of pulse oximeter trace during BP cuff inflation and reappearance of the oximeter trace during BP cuff deflation and averaging the two values, they were able to obtain an estimate of the SBP.
A study in 46 children post-cardiac surgery compared estimation of SBP using pulse oximeter waveform disappearance/reappearance during manual BP cuff inflation/deflation (in 2-5 mmHg increments), with an oscillometric BP measurement and the gold standard, intra-arterial BP measurement. Children were divided into three weight groups: 2 - < 6 kg; 6-15 kg and > 15 kg. Blood pressure measurements were obtained simultaneously using three different extremities from the arterial catheter, the oscillometric device, and the pulse oximeter. Pearson correlation coefficients and limits of agreement were calculated to evaluate the three different BP measurement techniques. BP measurements using the pulse oximeter method correlated better with intra-arterial measurements than those from the oscillometric device, with pulse oximeter waveform reappearance providing the most accurate estimation of SBP with narrower limits of agreement, in all weight groups. In the three weight groups comparing intra-arterial measurements to the oscillometric measurements, correlation (r) ranged from 0.75 to 0.79. Comparing intra-arterial measurements to the oximetry method, correlation (r) ranged from 0.77 to 0.96 during pulse oximeter disappearance and 0.83 to 0.95 during pulse oximeter reappearance. They found that the oximeter estimations remained reliable at lower blood pressures, whereas the accuracy of the oscillometric measurements deteriorated further. The oximeter SBP estimations were also shown to be more accurate in the smallest patients (2 - < 6 kg) where blood pressure also tended to be lower. Their conclusion was that observation of the reappearance of the pulse oximeter waveform is a reliable and accurate way to measure non-invasive blood pressure in children, and is superior to the oscillometric method for small patients < 15 kg when compared with direct intra-arterial measurements.\textsuperscript{19}

Khalili et al. in 2002 measured blood pressure in 50 healthy adult volunteers with conventional and pulse oximeter methods. Measurement of SBP using a pulse oximeter involved evaluation of the pulse oximeter waveform during manual BP cuff inflation and deflation with subsequent calculation of the degree of agreement between the two methods. They found a mean difference between systolic blood pressure and pulse oximeter blood pressure during inflation of the cuff of 0.06 +/- 1.75 mmHg. The highest correlation was
also between these two pressures ($r = 0.988$). This study concluded that the best agreement was between SBP and pulse oximeter blood pressure during manual cuff inflation. They found that inflation of the BP cuff at a slow speed was necessary for accurate estimation of SBP by the pulse oximeter method.\textsuperscript{20}

Only one study could be found comparing automatic NIBP measurement and pulse oximetry-derived SBP during regional anaesthesia. Yentis et al. applied Bland and Altman analysis to radial artery palpation and observation of the oximeter trace to estimate the automated non-invasive SBP in two groups of 20 women: healthy non-pregnant volunteers and parturients undergoing SA for elective CS. An NIBP cuff and a pulse oximeter probe were applied to the same arm. By observation of the real-time values of cuff pressure during cuff inflation or deflation, the SBP was noted on disappearance or reappearance of the manually palpated radial arterial pulse or pulse oximeter waveform. They also noted the actual measured SBP and compared the results utilising Bland–Altman analysis. In the volunteers using the radial artery palpation method, the bias/precision was -12.9 / 22.1 mmHg (during cuff inflation) and -9.7 / 16.7 mmHg (during cuff deflation). Bias/precision for oximetry was 29.5 / 18.8 mmHg (during cuff inflation) and -20.7 / 21.7 mmHg (during cuff deflation). In the parturients, the bias or precision was -19.0 / 47.6 mmHg (during cuff inflation) and -15.5 / 51.0 mmHg (during cuff deflation) for arterial palpation, and 22.6 / 16.1 mmHg (during cuff inflation) and -14.2 / 19.9 mmHg (during cuff deflation) for oximetry.

They found that both methods tended to underestimate the SBP recorded by the NIBP machine (by an average of 10-20 mmHg), the exception being pulse oximetry during cuff inflation, which tended to overestimate SBP by an average of 20-30 mmHg. They concluded that although relatively inaccurate and imprecise, both the arterial palpation and pulse oximetry methods may be used to estimate SBP during CS under SA. In this study, mean (SD) BMI was 23.6 (4.0) kg/m\textsuperscript{2} in the volunteers and 23.0 (4.0) kg/m\textsuperscript{2} in the parturients, so the effect of BMI was not considered.\textsuperscript{21}
Conclusions and rationale for the research proposal

It is clear from this literature review that occlusion of the pulse oximeter trace can be used to estimate SBP, although accuracy and precision do vary depending on the exact methodology. Many studies made use of a manual blood pressure cuff with control of the inflation and deflation rate, usually in 2-5 mmHg increments, which could clearly have allowed for more accuracy and precision.\textsuperscript{11–13,17,19,20} Automated NIBP devices have a faster speed of inflation and deflation and so it might be more technically difficult to estimate SBP during faster cycling speeds. BP measurement devices often inflate to a higher cuff pressure on the first measurement and subsequently inflate to a different cuff pressure based on the initial BP value.\textsuperscript{22}

Only a limited number of studies could be found that utilised Bland and Altman analysis.\textsuperscript{17,19–21} Only one study was found in the obstetric population during regional anaesthesia.\textsuperscript{21} No studies could be found in the obese population. The obstetric anaesthetist is increasingly being confronted with the problem of rising number of obese parturients presenting for caesarean section.\textsuperscript{23} Obesity is known to increase the risk of maternal morbidity and mortality.\textsuperscript{24} Morbid obesity, in particular, has been identified in The Confidential Enquiry into Maternal and Child Health (CEMACH) report as an independent risk factor for maternal mortality. The CEMACH report, ‘Saving Mothers’ Lives’, was published in 2011, reviewing the 261 maternal deaths in the UK between 2006 and 2008. This report highlighted obesity (BMI > 30 kg/m\textsuperscript{2}) as one of the top ten most common conditions requiring pre-pregnancy counselling.\textsuperscript{25} The latest MBRRACE-UK report (Mothers and Babies: Reducing Risk through Audits and Confidential Enquiries across the UK) published in 2014, showed that of the maternal deaths reported, over 22\% of women were overweight and 27\% obese. The report also highlighted the increasing prevalence of obesity amongst the pregnant population.\textsuperscript{26,27}

There is considerable evidence highlighting obesity in pregnancy and its association with an increased occurrence of Caesarean sections. It would be of clinical value to know whether estimation of SBP during occlusion of the
pulse oximeter trace in obese patients, in whom the larger cuff is associated
with more gradual inflation, could be more accurate and precise than in
patients with normal BMI. Particularly in obese patients, rapid and accurate
identification of spinal hypotension is of the utmost clinical importance.
Therefore, it was decided to investigate the utility of occlusion of the pulse
oximeter trace in the estimation of systolic blood pressure during spinal
anaesthesia for caesarean section, and the effect of body mass index on this
estimation. This is particularly important in resource-limited environments,
where invasive blood pressure monitoring is not always available.

References


2. Crenner C. Introduction of the blood pressure cuff into U.S. medical

3. Ogedegbe G, Pickering T. Principles and Techniques of Blood Pressure
Measurement. Cardiol Clin 2010;28(4):571-86. doi:

4. van Montfrans GA. Oscillometric blood pressure measurement:

Recommendations for Blood Pressure Measurement in Humans and
Experimental Animals: Part 1: Blood pressure measurement in Humans:
A Statement for professionals from the Subcommittee of Professional
and Public Education of the American Heart Association Council on

6. The American Society of Anesthesiologists. ASA Standards for Basic
Anesthetic Monitoring. Available from http://www.asahq.org/quality-and-
and amended 1 July 2011.


The utility of occlusion of the pulse oximeter trace in the estimation of systolic blood pressure during spinal anaesthesia for caesarean section: the effect of body mass index

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Acknowledgements

The theatre staff at Mowbray Maternity Hospital
The theatre staff at Maternity Centre, Groote Schuur Hospital
Abstract

Background: The aim of this study was to improve the safety of spinal anaesthesia (SA) for caesarean section (CS) for morbidly obese parturients, by rapid and accurate identification of hypotension. We compared the accuracy and precision of estimation of the systolic blood pressure (SBP) by disappearance of the pulse oximeter trace (DOT), with noninvasive blood pressure (NIBP) measurement during cuff inflation and deflation, across the range of body mass index (BMI), during SA for CS.

Methods: Three groups of 25 parturients were recruited, with BMI of < 30- (Group 1), 30-40- (Group 2), and > 40 kg/m² (Group 3) respectively. SBP was measured using the DASH® 3000 monitor (GE Health Care, UK) NIBP monitor, placed on the same arm as the pulse oximeter probe. Estimations of SBP were done before- and 5 minutes after induction of SA, during cuff inflation and deflation. The times taken for the estimations and the actual NIBP measurements were noted. Bland and Altman analysis was performed and the concordance correlation coefficient (r) estimated.

Results: Concerning the most clinically relevant estimation, namely SBP during inflation post-SA:

For Groups 1, 2 and 3, r = 0.56, 0.74 and 0.91; bias = -0.4, -2.9 and 0.8 mmHg, and limits of agreement = -27.7 to 26.9, -27.7 to 21.9 and -15.9 to 17.5 mmHg respectively.

The mean (SD) time required for estimation of the SBP during inflation post-SA was 7.5 (1.1) s, 11.8 (3.8) s and 16.8 (4.2) s in the Groups 1, 2 and 3 respectively. The mean (SD) time required for measurement of post-SA SBP during inflations in Groups 1, 2 and 3, was 30.3 (13.1) s, 41.3 (10.2) s and 49.8 (14.6) respectively. In the post-SA period, mean time saved by estimating SBP during inflation was approximately 28.5 seconds, compared with 9 seconds during deflation. The time saved in Groups 1, 2 and 3 was 22.8 (13.2) s, 30.0 (11.6) s and 33.0 (15.6) s respectively.
In the BMI > 40 kg/m² group, the percentage error is ±13% of the mean systolic blood pressure observed, and the absolute error is ±16 mmHg, compared to ±27 mmHg in the normal BMI group.

**Conclusion:** Post-SA estimation of SBP during cuff inflation in morbidly obese patients is more accurate and precise than in the other BMI Groups. Time to estimation is shorter than measurement by a clinically relevant period (33 s). This should improve patient safety in morbidly obese parturients.

**Keywords:**
Pulse oximeter trace, systolic blood pressure, spinal anaesthesia, caesarean section, body mass index (BMI)
3. Main text

Introduction

The latest CEMACH report published in 2014, MBRRACE-UK: Saving Lives, Improving Mothers’ Care, showed that of the maternal deaths reported, over 22% of women were overweight and 27% obese. The report also highlighted the increasing prevalence of obesity amongst the pregnant population.\textsuperscript{1,2} Hence, the obstetric anaesthetist is increasingly being confronted with the problem of a rising number of obese parturients presenting for caesarean section.\textsuperscript{3} In South Africa, the preferred anaesthetic technique for emergency or elective caesarean section is single shot spinal anaesthesia (SA), where a combination of local anaesthetics and opioids is used. Spinal hypotension demands prompt recognition and timely intervention with fluids and vasopressors, particularly in morbidly obese patients.

The usual method of blood pressure (BP) monitoring is with an automated non-invasive blood pressure (NIBP) device, which utilises the oscillometric measuring method. To improve response time, an alternative method to obtain an indication of the patient’s systolic blood pressure (SBP) is to observe the disappearance (DOT) or reappearance (ROT) of the pulse oximetry trace during BP cuff inflation and deflation respectively.

One previous study in women with a normal body mass index undergoing SA for caesarean section included an assessment of blood pressure by disappearance of the oximeter trace. The investigators showed moderate accuracy and precision.\textsuperscript{4}

Both the accuracy and precision as well as the time taken for this estimate are important. Regarding accuracy, our clinical impression has been that the rate of increase of pressure in the cuff is more gradual in the high body mass patients, where a larger, higher volume cuff is used. This could make the accurate visual estimation of blood pressure using DOT/ROT easier in obese patients than in low body mass patients, where the escalation of pressure is
more rapid. As regards response time, NIBP readings often take longer in obese patients, and it is important to establish the time taken for the estimate of blood pressure, as well as the time saved by doing the visual estimate, across the physiological range of body mass indices.

In the morbidly obese population, an arterial line can be sited to give a more accurate blood pressure measurement. In the developing world with its limited resources, usually only noninvasive blood pressure devices are available. It was therefore decided to study the accuracy of estimation of SBP by disappearance and reappearance of the pulse oximeter trace (DOT/ROT) with cuff inflation during SA for caesarean section, and to examine the effect of body mass index on accuracy and precision of the estimated SBP measurement, the time taken to achieve this estimate and the time taken for the NIBP measurement.

The primary analysis was an agreement comparison (bias and limits of agreement) between DOT/ROT and NIBP, across the full BMI range (normal to morbidly obese). Concordance between measured and estimated values was also evaluated. The most clinically relevant estimation of SBP was during inflation of the cuff after induction of SA. The secondary analysis was a comparison of the time to measurement of DOT/ROT and NIBP, in the BMI range.

The aim of the study was to improve the safety of SA for caesarean section in resource-limited areas in the developing world, by rapid and accurate identification of spinal hypotension, particularly in morbidly obese parturients.

**Patients and methods**

Approval for the study was obtained from the Health Sciences Faculty Human Research Ethics Committee of the University of Cape Town (UCT). This prospective observational study was performed at the Groote Schuur Hospital Maternity Centre and Mowbray Maternity Hospital, Cape Town, South Africa. Written informed consent was obtained from all participants in the ward at the
time of recruitment to the study.

Three groups of 25 patients each, requiring elective or emergency caesarean section, were recruited. Group 1 comprised parturients with normal body mass index (BMI), defined as 30 kg/m$^2$ or less, Group 2 were obese parturients with BMI 30 - <40 kg/m$^2$, and Group 3 included morbidly obese parturients with a BMI of $\geq$40 kg/m$^2$.

Inclusion criteria were age >18 years, ASA Class 1 to 3 and gestation >36 completed weeks. Exclusion criteria were pre-existing hypertension, preeclampsia or eclampsia, failed SA, chronic treatment with drugs that are known to affect blood pressure, any respiratory disease affecting arterial oxygen saturation, any condition causing impaired circulation to the hands, and multiple pregnancy.

The same automated DASH® 3000 monitor (GE Health Care, United Kingdom) was used for all measurements for the study. An appropriately sized blood pressure (BP) cuff for noninvasive SBP measurements was applied to patients in all groups, following American Heart Association guidelines$^5$ (Adult cuff 27.5 – 36.5 cm and Large Adult cuff 35.5 – 46 cm [UNIMED Medical Supplies Inc. Shenzhen, China]). Cuffs were applied snugly, allowing only enough room for one finger to be slipped between the cuff and the skin surface. The BP cuff and the pulse oximeter probe were applied to the arm and index finger on the ipsilateral side.

An intravenous catheter was placed. For all NIBP measurements, patients were placed supine on the operating table with 15° left lateral tilt, using an obstetric wedge. The first two NIBP readings were taken for the study, 1 minute apart, immediately before the induction of SA, using the dedicated DASH monitor. During the first measurement, the investigator observed the dynamic pressure readings of the NIBP machine as the cuff inflated, recording the SBP at the point when the pulse oximeter waveform disappeared (DOT). The time taken for this estimation and the actual NIBP measurement were noted. With the second measurement, the investigator observed the dynamic pressure readings of the NIBP machine as the cuff deflated, recording the
SBP at the point when the pulse oximeter waveform reappeared (ROT). Once again, the time taken for this estimation and the actual NIBP measurement were noted.

SA was induced with the patient in the sitting position, using 2.0 mL hyperbaric 0.5% bupivacaine plus 10 µg fentanyl, with co-loading of crystalloid (Modified Ringer’s lactate) 15 mL/kg after induction of spinal anaesthesia. All patients, after induction of SA, were positioned supine on the operating table, with 15° left lateral tilt using an obstetric wedge. Five minutes post induction of SA, a further two NIBP readings were taken for the study, 1 minute apart, using the dedicated DASH monitor, employing the same methodology as the pre-SA readings. For all readings, the investigator was blinded to the NIBP measurements of systolic, diastolic and mean BP, which were recorded by the attending anaesthetist. This was done by placing an opaque rectangular cover over the blood pressure display panel of the DASH monitor. The same investigator took all the measurements, to eliminate inter-observer variability.

Prevention and management of hypotension were at the discretion of the attending anaesthetist. The usual practice is administration of a bolus of 50-100 µg of phenylephrine or 5-10 mg ephedrine.

**Statistical analysis**

Recruitment was stratified by BMI categories as indicated, to ensure that the agreement analysis would be possible across the whole BMI spectrum, as well as BMI group-specific.

Descriptive statistics of the demographic and anthropometric variables were compiled, as well as for the blood pressure measurements (means and standard deviations) by phase, type, pre- and post-SA and by BMI group. The main agreement analysis was a Bland and Altman comparison of DOT/ROT and NIBP measurements. The concordance correlation coefficient of Lin was also estimated. Graphical plots of the limits of agreement were
constructed. For the period and measurement of clinical interest, namely SBP post-SA inflation, the association of BMI with the bias and the variability of the difference were investigated. For the association of the bias, the significance of a Spearman correlation coefficient between the difference and BMI was determined, whereas for the variability the Spearman correlation between the absolute value of the difference and BMI was calculated and tested.

**Results**

Three groups of 25 women were studied (Group 1 comprised parturients with normal body mass index [BMI], defined as 30 kg/m² or less, Group 2 were obese parturients with BMI 30-40 kg/m², and Group 3 included morbidly obese parturients with a BMI of > 40 kg/m²).

The pooled demographic and anthropometric results of the 75 participants are provided in Table 1. The median age of the participants was 30 years, ranging from 18 to 40 years. The median BMI was 35.6 kg/m², with a range from 22 kg/m² to 59.2 kg/m².

Table 2 summarises the concordance, the bias and the limits of agreement of the differences between measured and estimated SBP overall, and by BMI group.

Concerning the most clinically relevant estimation, namely SBP during inflation post-SA:

For Group 1, $r = 0.56$, bias = -0.4, limits of agreement = -27.7 to 26.9 mmHg
For Group 2, $r = 0.74$, bias = -2.9, limits of agreement = -27.7 to 21.9 mmHg
For Group 3, $r = 0.91$, bias = 0.8, limits of agreement = -15.9 to 17.5 mmHg

Figure 1 is a combined Bland and Altman plot showing the bias as well as the limits of agreement of the differences between measured and estimated SBP values for post-SA inflation (DOT), in the 3 BMI groups. Also depicted are the overall limits of agreement not taking BMI into account. Overall the bias was not associated with BMI, but the variability was negatively associated with BMI (Spearman $r = -0.29$, $p = 0.01$).
The mean (SD) time (seconds [s]) required for the estimation of the pre-SA SBP during inflation, was 7.9 (1.3) s, 12.2 (3.8) s and 19.2 (3.9) s in Groups 1, 2, and 3 respectively. The mean (SD) time required for measurement of the SBP, was 31.1 (5.7) s, 35.8 (6.7) s and 43.0 (7.1) s in the 3 groups respectively. In the pre-SA period, the mean (SD) time saved by estimation during the inflation period (i.e. time for measured SBP minus time for estimated SBP during inflation) was 24 s, and 7 s during the deflation period overall. The mean (SD) time saved in Groups 1, 2 and 3, was 23.3 (5.7) s, 23.5 (5.4) s and 23.7 (5.4) s respectively. (See Tables 3 and 4)

The mean (SD) time required for estimation of the SBP during inflation after induction of SA, was 7.5 (1.1) s, 11.8 (3.8) s and 16.8 (4.2) s in Groups 1, 2 and 3 respectively. The mean (SD) time required for measurement of post-SA SBP during inflations in Groups 1, 2 and 3, was 30.3 (13.1) s, 41.3 (10.2) s and 49.8 (14.6) s respectively. In the post-SA period, mean time saved by estimating SBP during inflation was approximately 28.5 s, compared with 9 s during deflation. The time saved in Groups 1, 2 and 3 was 22.8 (13.2) s, 30.0 (11.6) s and 33.0 (15.6) s respectively. (See Tables 5 and 6)

There were no missing values in the study. There were two cases where initial blood pressure measurements post-SA could not be obtained due to acute hypotension. These measurements were repeated after treatment of the hypotension.

Discussion

This prospective observational study showed that estimation of the SBP using the DOT method during inflation post-SA is more accurate and precise in morbidly obese parturients (Group 3) undergoing CS under SA, compared with the lower BMI groups. The estimation of SBP by the DOT method also reduces the delay associated with formal NIBP measurement in this group, by a clinically relevant period.
Using the DOT method in Group 3, the limits of agreement indicate that the percentage error will be ±13% of the average SBP observed in this group (122 mmHg). In this high BMI Group, the error is ±16 mmHg compared to ±27 mmHg in Group 1. Mean (SD) time saved by estimating the SBP by this method was 33 (15.6) s, which has greater clinical relevance in the high BMI group concerning the longer measurement time required, of 49 s.

Concerning the most clinically relevant estimation, namely SBP during inflation post-SA, we found a small bias between measured and estimated SBP in Group 3, excellent concordance and acceptable limits of agreement. By contrast, Group 1 showed poor concordance and broader limits of agreement.

In two patients (one in Group 1 and the other in Group 3), it was not possible to obtain an SBP measurement on the first attempt post-SA. The investigator was able to obtain an estimated SBP using the DOT method during inflation, in both cases showing severe acute hypotension, and could alert the anaesthetist to the urgent need to administer vasopressors. For the purposes of the study, the measurements were repeated after vasopressor therapy.

The oximeter method to estimate BP has a few limitations. Only SBP can be obtained. Also, estimation of SBP using the oximeter can be subject to observer variation and differing results between the various oscillometric NIBP devices. Each NIBP device use different algorithms to calculate SBP and DBP, as well as varying speeds of inflation and deflation, so our results might not be entirely reproducible with other devices.\(^5\)\(^-\)\(^7\) We used the DASH® 3000 monitor (GE Health Care, United Kingdom) as it is one of the standard monitors worldwide. We observed that cuff inflation was more rapid than deflation, especially in the normal- compared with the large adult cuff. This device takes its measurement during deflation, which explains the slower rate of deflation compared with inflation, as well as the more accurate and precise estimation of SBP across the BMI range during deflation (Table 2). This is also in keeping with the finding that the disappearance of the trace during inflation occurs at a higher percentage of the baseline blood flow than during
reappearance of the trace during deflation. However, the delay associated with NIBP measurement is only marginally longer than estimation during cuff deflation. Therefore, it was important that acceptable accuracy and precision were associated with SBP estimation during cuff inflation in Group 3 where the delay in obtaining SBP is considerably less than using NIBP measurement.

Several studies have been performed using the pulse oximeter trace to estimate SBP. However, most of these studies assessed the degree of correlation between the different methods, and as Bland and Altman have pointed out, the more relevant comparison should involve the establishment of the limits of agreement. Most of these studies also used a manual BP cuff, which allowed control of the rate of inflation and deflation of the cuff, resulting in moderately accurate results with good correlation. However, in obstetric anaesthesia practice, an NIBP device is used for automated regular and frequent determinations.

A limited number of studies have utilised Bland-Altman analysis. A study done by Chawla et al. evaluated the use of pulse oximetry to accurately monitor systolic blood pressure in 100 healthy volunteers. Using the oximetry method, they estimated arterial blood pressure at the disappearance of the waveform during manual blood pressure cuff inflation (BPDIS), at the reappearance of the waveform during manual cuff deflation (BPAPP), and by averaging the two estimations (BPAV). By using Bland-Altman analysis, they found good agreement between the BPAV of oximetry-based SBP estimates and the BK (Korotkoff) and BPNI (Noninvasive). In nearly 95% of cases, the differences between BPAV and conventional methods were likely to be within ±14 mmHg. Using an average of two SBP estimations as in this study is time-consuming, and eliminates the advantage of an earlier response time attained in our study.

Another study utilising Bland-Altman analysis to investigate occlusion of the oximeter trace to estimate SBP was the only previous investigation that could be found in an obstetric population during SA. Yentis et al. applied Bland and
Altman analysis to radial artery palpation and observation of the oximeter trace during inflation and deflation, to estimate the SBP in 20 healthy volunteers and 20 parturients undergoing SA for CS. The study found that both methods had poor accuracy and low precision for estimating the SBP recorded by the NIBP device. Both methods underestimated SBP by an average of 10-20 mmHg, except for pulse oximetry during cuff inflation, which overestimated SBP by a mean of 20-30 mmHg. Mean (SD) BMI was 23.6 (4.0) kg/m² in the volunteers and 23.0 (4.0) kg/m² in the parturients, so the effect of BMI was not considered.⁴ No studies could be found examining the influence of BMI on accuracy and precision.

As in the Yentis study, we did not study the influence that intravenous fluids or vasopressors might have on blood pressure determination but followed routine clinical practice. We also did not record heart rate, which may have an effect on our estimations since BP may change more between slow – rather than fast pulsations. In our study, heart rates ranged from 70 to 100 beats per minute.

Similar to the Yentis study, our aim was not to compare the accuracy of the DOT method to the intra-arterial pressure but to evaluate its accuracy in estimating the SBP measurement, as this is the standard monitoring used intra-operatively. This method has the added benefit of being easy to use, without demanding any new or expensive equipment. It can be especially useful in patients with very low blood pressure, for whom oscillometric measurements might be unobtainable, as was found in two instances in our study.

In conclusion, the DOT method may be used for post-SA estimation of SBP during CS in morbidly obese patients. In these patients the reading is more accurate and precise than in lower BMI patients. In addition, the delay associated with measurement using the NIBP device is reduced by a clinically relevant period. This ensures an earlier response time to hypotension. This method can be particularly helpful in low-resource settings where intra-arterial lines are not always available. The result could be safer anaesthesia for our
morbidly obese parturients.

References:


4. Figures and Tables

Table 1: Patient demographic and anthropometric details. (n=75)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Min</th>
<th>P25</th>
<th>P50</th>
<th>P75</th>
<th>Max</th>
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<td>BMI (kg/m²)</td>
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<td>28.5</td>
<td>35.6</td>
<td>42.3</td>
<td>59.2</td>
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<td>Arm circumference (cm)</td>
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<td>28</td>
<td>32.5</td>
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<td>Height (m)</td>
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<td>1.56</td>
<td>1.6</td>
<td>1.64</td>
<td>1.74</td>
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<tr>
<td>Weight (kg)</td>
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<td>70</td>
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<td>112</td>
<td>150</td>
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<tr>
<td>Age (years)</td>
<td>18</td>
<td>26</td>
<td>30</td>
<td>33</td>
<td>40</td>
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</table>

Table 2: Concordance summary between measured and estimated SBP

<table>
<thead>
<tr>
<th>Period</th>
<th>Timing of estimate</th>
<th>Concordance (95% CI)</th>
<th>Bias (SD mmHg)</th>
<th>95% Limits of agreement (mmHg)</th>
<th>Variance test p-value</th>
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</thead>
<tbody>
<tr>
<td>Pre-SA</td>
<td>Inflation</td>
<td>0.73 (0.63 – 0.84)</td>
<td>-0.9 (11.4)</td>
<td>-23.2 to 21.4</td>
<td>0.51</td>
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<td>Pre-SA</td>
<td>Deflation</td>
<td>0.9 (0.85 – 0.94)</td>
<td>-2.7 (7.3)</td>
<td>-17.0 to 11.6</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Post-SA</td>
<td>Inflation</td>
<td>0.79 (0.71 – 0.88)</td>
<td>-0.8 (11.9)</td>
<td>-24.1 to 22.4</td>
<td>0.59</td>
</tr>
<tr>
<td>Post-SA</td>
<td>Deflation</td>
<td>0.87 (0.81 – 0.92)</td>
<td>1.7 (8.9)</td>
<td>-15.8 to 19.2</td>
<td>&lt; 0.01</td>
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</table>

<table>
<thead>
<tr>
<th>BMI &lt; 30 kg/m²²</th>
<th></th>
<th></th>
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<tr>
<td>Period</td>
<td>Timing of estimate</td>
<td>Concordance (95% CI)</td>
<td>Bias (SD mmHg)</td>
<td>95% Limits of agreement (mmHg)</td>
<td>Variance test p-value</td>
</tr>
<tr>
<td>Pre-SA</td>
<td>Inflation</td>
<td>0.53 (0.26 – 0.8)</td>
<td>-5.2 (12.6)</td>
<td>-29.9 to 19.6</td>
<td>0.09</td>
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<tr>
<td>Pre-SA</td>
<td>Deflation</td>
<td>0.78 (0.64 – 0.93)</td>
<td>-3.3 (7.1)</td>
<td>-17.3 to 10.6</td>
<td>0.03</td>
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<tr>
<td>Post-SA</td>
<td>Inflation</td>
<td>0.57 (0.29 – 0.84)</td>
<td>-0.4 (13.9)</td>
<td>-27.7 to 26.9</td>
<td>0.95</td>
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<td>Post-SA</td>
<td>Deflation</td>
<td>0.68 (0.48 – 0.88)</td>
<td>3.3 (9.7)</td>
<td>-15.7 to 22.2</td>
<td>0.06</td>
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### BMI: 30 - 40 kg/m²

<table>
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<th>Period</th>
<th>Timing of estimate</th>
<th>Concordance (95% CI)</th>
<th>Bias (SD) mmHg</th>
<th>95% Limits of agreement (mmHg)</th>
<th>Variance test p-value</th>
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</thead>
<tbody>
<tr>
<td>Pre-SA</td>
<td>Inflation</td>
<td>0,73 (0.54 – 0.92)</td>
<td>-3 (9.5)</td>
<td>-21,6 to 15,5</td>
<td>0,31</td>
</tr>
<tr>
<td>Pre-SA</td>
<td>Deflation</td>
<td>0,79 (0.66 – 0.92)</td>
<td>-1 (9.2)</td>
<td>-19,1 to 17,0</td>
<td>0,01</td>
</tr>
<tr>
<td>Post-SA</td>
<td>Inflation</td>
<td>0,74 (0.55 – 0.92)</td>
<td>-2,9 (12.7)</td>
<td>-27,7 to 21,9</td>
<td>0,41</td>
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<td>Post-SA</td>
<td>Deflation</td>
<td>0,90 (0.82 – 0.97)</td>
<td>0 (8)</td>
<td>-15,7 to 15,7</td>
<td>0,09</td>
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</table>

### BMI > 40 kg/m²

<table>
<thead>
<tr>
<th>Period</th>
<th>Timing of estimate</th>
<th>Concordance (95% CI)</th>
<th>Bias (SD) mmHg</th>
<th>95% Limits of agreement (mmHg)</th>
<th>Variance test p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-SA</td>
<td>Inflation</td>
<td>0,69 (0.49 – 0.88)</td>
<td>5,5 (9.2)</td>
<td>-12,6 to 23,5</td>
<td>0,02</td>
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<tr>
<td>Pre-SA</td>
<td>Deflation</td>
<td>0,91 (0.85 – 0.98)</td>
<td>-3,8 (4.9)</td>
<td>-13,4 to 5,8</td>
<td>&lt; 0.01</td>
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<tr>
<td>Post-SA</td>
<td>Inflation</td>
<td>0,91 (0.84 – 0.98)</td>
<td>0,8 (8.5)</td>
<td>-15,9 to 17,5</td>
<td>0,89</td>
</tr>
<tr>
<td>Post-SA</td>
<td>Deflation</td>
<td>0,90 (0.82 – 0.97)</td>
<td>1,7 (9.1)</td>
<td>-16,0 to 19,5</td>
<td>0,22</td>
</tr>
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</table>
Figure 1: Bias and limits of agreement between estimated and measured SBP for post-SA inflation (DOT) in the 3 BMI groups, and overall

**Solid blue line:** Limits of agreement in the three BMI groups.
**Green striped line:** Overall limits of agreement not taking BMI into account.
**Solid orange line:** Bias in the three BMI groups.
**Solid purple line:** Bias overall, not taking BMI into account.
### Table 3: Time to estimation and measurement:

#### Pre-SA inflation

<table>
<thead>
<tr>
<th>BMI</th>
<th>Time to estimation Mean (SD)</th>
<th>Time to measurement Mean (SD)</th>
<th>Time saved Mean (SD)</th>
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</thead>
<tbody>
<tr>
<td>&lt; 30 kg/m²</td>
<td>7.9 s (1.3 s)</td>
<td>31.1 s (5.7 s)</td>
<td>23.3 s (5.7 s)</td>
</tr>
<tr>
<td>30-40 kg/m²</td>
<td>12.2 s (3.8 s)</td>
<td>35.8 s (6.7 s)</td>
<td>23.5 s (5.4 s)</td>
</tr>
<tr>
<td>&gt; 40 kg/m²</td>
<td>19.2 s (3.9 s)</td>
<td>43.0 s (7.1 s)</td>
<td>23.7 s (5.4 s)</td>
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</tbody>
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### Table 4: Time to estimation and measurement:

#### Pre-SA deflation

<table>
<thead>
<tr>
<th>BMI</th>
<th>Time to estimation Mean (SD)</th>
<th>Time to measurement Mean (SD)</th>
<th>Time saved Mean (SD)</th>
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</thead>
<tbody>
<tr>
<td>&lt; 30 kg/m²</td>
<td>11.8 s (2.0 s)</td>
<td>18.5 s (3.7 s)</td>
<td>6.6 s (2.7 s)</td>
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<tr>
<td>30-40 kg/m²</td>
<td>17.1 s (5.0 s)</td>
<td>22.8 s (5.5 s)</td>
<td>5.7 s (2.5 s)</td>
</tr>
<tr>
<td>&gt; 40 kg/m²</td>
<td>25.2 s (4.2 s)</td>
<td>34.2 s (5.9 s)</td>
<td>9.0 s (4.6 s)</td>
</tr>
</tbody>
</table>
Table 5: Time to estimation and measurement: Post-SA inflation

<table>
<thead>
<tr>
<th>BMI</th>
<th>Time to estimation Mean (SD)</th>
<th>Time to measurement Mean (SD)</th>
<th>Time saved Mean (SD)</th>
</tr>
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<tbody>
<tr>
<td>&lt; 30 kg/m²</td>
<td>7.5 s (1.1 s)</td>
<td>30.3 s (13.1 s)</td>
<td>22.8 s (13.2 s)</td>
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<td>30-40 kg/m²</td>
<td>11.8 s (3.8 s)</td>
<td>41.3 s (10.2 s)</td>
<td>29.6 s (11.6 s)</td>
</tr>
<tr>
<td>&gt; 40 kg/m²</td>
<td>16.8 s (4.2 s)</td>
<td>49.8 s (14.6 s)</td>
<td>33.0 s (15.6 s)</td>
</tr>
</tbody>
</table>

Table 6: Time to estimation and measurement: Post-SA deflation

<table>
<thead>
<tr>
<th>BMI</th>
<th>Time to estimation Mean (SD)</th>
<th>Time to measurement Mean (SD)</th>
<th>Time saved Mean (SD)</th>
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</thead>
<tbody>
<tr>
<td>&lt; 30 kg/m²</td>
<td>11.5 s (2.3 s)</td>
<td>19.0 s (5.2 s)</td>
<td>7.6 s (5.4 s)</td>
</tr>
<tr>
<td>30-40 kg/m²</td>
<td>16.4 s (4.6 s)</td>
<td>27.0 s (6.9 s)</td>
<td>10.6 s (7.4 s)</td>
</tr>
<tr>
<td>&gt; 40 kg/m²</td>
<td>24.6 s (5.2 s)</td>
<td>33.2 s (5.5 s)</td>
<td>8.6 s (3.1 s)</td>
</tr>
</tbody>
</table>
Part D: Supporting Documents
Consent form for study: The utility of occlusion of the pulse oximeter trace in the estimation of systolic blood pressure during spinal anaesthesia for caesarean section: the effect of body mass index

Investigator: Theresa Samuel  
Supervisor: Professor Robert Dyer  
Email: theresas.2403@gmail.com

We are doing a study to compare our estimation of the systolic blood pressure, which is usually done as part of routine clinical practice, with the measurement that our blood pressure machine takes. We would like to take your blood pressure measurements for our study, before and approximately 5 minutes after your spinal anaesthesia. Your blood pressure monitoring will continue as per the usual protocol and our study will not influence the normal standard of care that you receive during the operation.

Information that will be used is your weight, height, arm circumference and the blood pressure measurements.

This information will be kept confidential. The study will not influence the outcome of your anaesthesia or your hospital treatment in any way and is completely voluntary.

You can withdraw from the study at any time.

I hereby consent for my blood pressure measurements to be taken and to be used in the study.
Signature: __________________________
Name: _____________________________
Date: _____________________________

UCT, Faculty of Health Sciences, Human Research and Ethics Committee  
Rm E52-24 Old Main Building  
Tel 021 404 7682  Fax 021 4066411
Data collection form for study:
The utility of occlusion of the pulse oximeter trace in the estimation of systolic blood pressure during spinal anaesthesia for caesarean section: the effect of body mass index

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</table>
30 October 2014

HREC REF: 743/2014

Prof R Dyer
Anaesthesia
D23
NGSH

Dear Prof Dyer

PROJECT TITLE: THE UTILITY OF OCCLUSION OF THE PULSE OXIMETRY TRACE IN THE ESTIMATION OF THE SYSTOLIC BLOOD PRESSURE DURING SPINAL ANAESTHESIA FOR CAESAREAN SECTION: THE EFFECT OF BODY MASS INDEX (BMI) - (MMED Candidate - Dr T Samuel)

Thank you for your response to the Faculty of Health Sciences Human Research Ethics Committee dated 21 October 2014.

It is a pleasure to inform you that the HREC has formally approved the above-mentioned study subject to adding the UCT FHS HREC contact details to the informed consent form.

Approval is granted for one year until the 30th October 2015.

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)

Please quote the HREC REF in all your correspondence.

We acknowledge that the MMED student, Dr Theresa Samuel will also be involved in this study.

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

Yours sincerely

Signed

PROFESSOR M BLOCKMAN
CHAIRPERSON, THE HUMAN RESEARCH ETHICS COMMITTEE

Federal Wide Assurance Number: FWA00001637.
Institutional Review Board (IRB) number: IRB00001938

HREC 743/2014
Guide to Authors – International Journal of Obstetric Anaesthesia

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