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Haemodynamic Consequences of Spinal Anaesthesia for Non-Emergency Caesarean Section

Robert A Dyer

Presented for the Degree of Doctor of Philosophy

Division of Obstetric Anaesthesia
Department of Anaesthesia
Faculty of Health Sciences, University of Cape Town

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Declaration

I, Robert A Dyer, hereby declare that this thesis is my own work, both in concept and execution, but for the normal guidance received from my supervisor and contributions from others as outlined in the acknowledgements. Neither the substance nor any part of this thesis has been, is being submitted or is to be submitted for another degree at this university or at any other university.

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This thesis is presented for examination for the degree of Doctor of Philosophy.

Signed

Dated
Abstract

Single shot spinal anaesthesia for caesarean section is currently accepted as the favoured method in the absence of contraindications, for reasons of safety and comfort. Firstly, there is an increased risk of failed intubation associated with general anaesthesia. Secondly, spinal anaesthesia, if practiced correctly, allows for a superior experience of the delivery and improved bonding with the infant. Maternal haemodynamic stability is desirable both for maternal and neonatal safety, and to diminish maternal side-effects such as nausea and vomiting. Therefore, after an extensive literature review, clinically relevant aspects of spinal anaesthesia were studied, with a view to contributing to knowledge which could improve safety and outcome.

The central themes explored in this thesis were fluid management during spinal anaesthesia for caesarean section in healthy parturients, the haemodynamic effects of the vasoactive agents ephedrine, phenylephrine and oxytocin during spinal anaesthesia for caesarean section in healthy patients and in patients with preeclampsia, and short term neonatal outcome after spinal anaesthesia in patients with severe preeclampsia. Research methodology included non-invasive measures as well as the use of a pulse wave form analysis monitor to measure maternal cardiac output. A validation study was performed comparing this method with thermodilution in patients with postpartum complications of preeclampsia.
The results of these studies showed that:

- The pulse wave form monitor employed showed acceptable limits of agreement with the thermodilution method.
- Crystalloid coload was associated with lower vasopressor requirements than conventional preload.
- Spinal anaesthesia was associated with afterload reduction, which was more pronounced in healthy patients than in preeclamptics.
- Ephedrine maintained or increased, and phenylephrine reduced maternal cardiac output in healthy patients.
- Oxytocin was associated with transient haemodynamic instability in healthy and preeclamptic patients, which was obtunded by phenylephrine in the healthy population.
- Spinal anaesthesia for caesarean section was associated with a greater umbilical arterial base deficit than general anaesthesia in patients with preeclampsia.

Overall, these studies should contribute to improved knowledge of haemodynamic responses during spinal anaesthesia for caesarean section, and ultimately to improved maternal morbidity and mortality.
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Foreword

My role since 1999 as lead clinician in Obstetric Anaesthesia in the Department of Anaesthesia at the University of Cape Town, has involved anaesthesia and analgesia for healthy parturients, as well as a large proportion of high risk mothers with a number of life-threatening comorbidities, of which the most frequent is preeclampsia. Currently our Department provides anaesthesia support for approximately 18,000 obstetric admissions per annum. Single shot spinal anaesthesia is the technique of choice for caesarean section in our institution in the absence of contraindications, due to the fact that this technique allows for rapid onset and very reliable surgical anaesthesia, while permitting maternal enjoyment of the delivery and immediate bonding with the infant.

I became increasingly interested in the haemodynamic consequences of this technique, both from the maternal and neonatal point of view, because haemodynamic stability impacts upon maternal safety and comfort and on neonatal outcome. This interest was further stimulated by my involvement as an assessor for the South African Confidential Enquiry into Maternal Deaths, as I realised that although the paradigm shift from general to spinal anaesthesia in obstetrics was beneficial, spinal anaesthesia is associated with a significant morbidity and mortality. My research is strongly aligned with Millennium goal 5: “Improve maternal health”.

The initial research preceded the intention to write a dissertation. Some of the studies presented in the thesis have already been published in international peer reviewed journals, but the data have been re-worked and expanded to form a single coherent text. The central research question that was followed was, “What are the haemodynamic consequences of spinal anaesthesia for non-emergency caesarean section, and what are the most appropriate interventions for improvement of maternal stability and fetal outcome?”
The intention was thus to make a contribution to the improvement of local and international obstetric anaesthesia practice by throwing light on the mechanisms of the maternal response to spinal anaesthesia. In this regard, the work includes basic research involving mothers with a normal cardiovascular system, as well as patients with preeclampsia. In the latter patients, my research has contributed to establishing the safety of the practice of spinal anaesthesia for caesarean section in this high risk group, as well as to knowledge regarding neonatal outcome. Very rapid changes in maternal haemodynamics may occur during spinal anaesthesia for caesarean section. New research tools, such as pulse wave form-derived minimally invasive methods for cardiac output measurement, have facilitated this work, since beat by beat responses can be measured, giving a unique perspective into the mechanism of the changes. In turn, some of my studies have contributed to the scientific validation of these monitors.

In addition, the studies contributing to this thesis have also stimulated the interest of my junior colleagues in research, and have been hypothesis-generating, in that several further studies are envisaged in this field, to be commenced in the near future.
Aim and outline of the dissertation

In our unit, and in most units worldwide, standard single shot spinal anaesthesia for caesarean section is contraindicated in patients with severely impaired cardiac function, and in patients with significant valvular heart disease, particularly in the presence of stenotic lesions. In these patients, epidural, sequential combined spinal-epidural, or general anaesthesia is preferred. This thesis thus examines the haemodynamic consequences of single shot spinal anaesthesia for caesarean section in patients with clinically good ventricular function, namely healthy and pre-eclamptic patients. Interventions to reduce haemodynamic instability due mainly to spinal anaesthesia but also to the administration of oxytocin, are also studied.

Chapter 1 is a review of the literature pertinent to this field of study.

Chapter 2 outlines the setting in which the studies were conducted, and presents some relevant considerations concerning research methodology.

Chapter 3 presents the results of a comparison between thermodilution and pulse wave form analysis in the measurement of maternal cardiac output in patients with postpartum complications of severe preeclampsia. These data contribute to the validation of the non-invasive cardiac output monitor.

Chapter 4 describes a randomised trial which examines the influence of the timing of intravenous crystalloid administration on vasopressor requirements during elective caesarean section.

In Chapter 5, the effects of spinal anaesthesia on the haemodynamics of healthy subjects, is described. The results are presented of a randomised study comparing the effects of the two most commonly used vasopressors on maternal haemodynamics, using pulse wave form analysis and transthoracic bioimpedance measurements.
Again, using the former technique, the haemodynamic changes associated with spinal anaesthesia and vasopressor management in patients with severe preeclampsia are described in an observational study in Chapter 6.

The administration of oxytocin at delivery during caesarean section is associated with haemodynamic instability. Non-contemporaneous observational data of haemodynamic changes in response to oxytocin in healthy and pre-eclamptic women are presented in Chapter 7. Also shown, are the results of a pilot study comparing the effects of oxytocin with those of a mixture of oxytocin and an α-agonist, on maternal haemodynamics.

Neonatal outcome has been extensively studied in healthy parturients (see Literature review, above). Chapter 8 presents the only randomised trial in patients with severe preeclampsia comparing the effects of spinal versus general anaesthesia on neonatal acid base balance.

In the final chapter (Chapter 9) the conclusions derived from the research are presented and recommendations made for the practice of spinal anaesthesia for caesarean section. Overall, these studies contribute to improved knowledge of haemodynamic responses during spinal anaesthesia for caesarean section, and improved management strategies. Ultimately, the aim is to reduce maternal morbidity and mortality.
The following abbreviations are used in the text throughout the thesis:

CO  = cardiac output
CS  = caesarean section
HR  = heart rate
IV  = intravenous
MAP = mean arterial pressure
SA  = spinal anaesthesia
SV  = stroke volume
SVR = systemic vascular resistance
1.1. Background

The benefits of regional anaesthesia in obstetrics were first recognised in July 1900, when the obstetrician Oscar Kreis administered spinal cocaine to 6 parturients in labour. Cleland’s classic experiments on anaesthetised dogs provided the anatomical basis for regional anaesthesia in obstetrics in 1933 (Cleland, 1933). However these pain relief methods in obstetrics were initially to fall into disrepute, since inadequate training and monitoring led to a high morbidity and mortality; a recent editorial points out that the mortality after spinal anaesthesia (SA) was 1 in 1000 surgical patients prior to 1944, and as high as 1 in 139 in obstetrics (Gogarten and Van Aken, 2000).

As understanding of maternal and fetal physiology developed, outcomes improved. Of particular importance was the early work on aortocaval compression in the third trimester (Marx, 1992). Initially, caudal and epidural anaesthesia were more popular than SA in labour, due to the fear of post dural puncture headache associated with SA. A major advance in SA in obstetrics was the introduction of atraumatic pencil point needles by Whitacre in 1951 (Hart and Whitacre, 1951).

Since the first Confidential Enquiry into Maternal Deaths was performed (1952 – 1954), the decreasing mortality associated with obstetric anaesthesia in the UK has been due both to the adoption of SA for caesarean section (CS) as the preferred method, and to safer general anaesthesia. The incidence of failed tracheal intubation in obstetrics is approximately 1/250 (Hawthorne et al, 1996), and this complication continues to contribute significantly to maternal deaths (Cooper and McClure, 2005; Cooper and McClure, 2008). The development of obstetric anaesthesia as a subspeciality, and the introduction
of strict supervision of junior anaesthetists have also influenced obstetric anaesthesia safety.

In the USA, general anaesthesia for CS was shown to be associated with a 16.7 times higher case fatality rate than general anaesthesia for the period 1985-1990 (Hawkins et al, 1997). More recently the case fatality rate for general anaesthesia has decreased, and the fatality rate for regional anaesthesia has increased from 1.9 (1985 – 1990) to 3.8 (1997 – 2002) per million anaesthetics, so that the risk ratio for general versus regional anaesthesia has decreased to 1.7. Thus SA does have an associated morbidity and mortality, although mortality is rare (Hawkins, 2009).

In South Africa, the first report of the National Committee for the Confidential Enquiries into Maternal Deaths (1999 – 2001) showed that although more deaths were associated with general anaesthesia, there was a significant mortality associated with SA for CS. During this period 25 patients died under SA, with little or no co-morbidity in most cases (Kruger, 2003). During the latest triennium (2005 – 2007), there were 74 direct anaesthesia deaths, of which 53 were associated with spinal and 18 with general anaesthesia. Although denominator data are not known, the use of spinal anaesthesia has increased significantly since the previous triennium, and 93% of deaths due to spinal anaesthesia were deemed avoidable. Contributing factors included inappropriate case selection for spinal anaesthesia, and inadequate management of severe hypotension or high motor block, including failed intubation in one case (Lamacraft G, Rout CC, personal communication). Most problems are avoidable or amenable to treatment by attention to details of safe practice, hence the importance of the provision of detailed recommendations for the management of haemodynamic instability during SA for CS (Dyer et al, 2004). Such recommendations, as well as ongoing research into this important subject, should contribute to improved maternal and neonatal safety and greater maternal comfort during and after the procedure.
1.2. Haemodynamic consequences of spinal anaesthesia for non-emergency caesarean section

SA for CS is associated with hypotension, due to a combination of increased venous capacitance and a decreased systemic vascular resistance (SVR). Since uterine blood flow is pressure dependent, hypotension results in a decrease in uterine blood flow and potential compromise to fetal oxygenation. Maternal cardiovascular collapse may rarely occur. Unpleasant symptoms such as nausea and vomiting are common.

Haemodynamic stability during single shot SA for non-emergency CS (defined as cases in which there is no immediate threat to the life of the woman or fetus [Levy, 2006]) depends, first and foremost, upon the effects of SA in a pregnant patient predisposed to aortocaval compression.

These effects may be modified by:
- The baricity and dose of local anaesthetic and opioid employed
- The rational use of fluids
- The goal-directed use of vasopressors
- Careful administration of oxytocin

All of these aspects impact on maternal and neonatal safety and comfort. Special considerations apply in the management of SA for patients with severe preeclampsia.

Intraoperative assessment tools have included maternal symptoms, non-invasive measures such as heart rate (HR) and manual or oscillometric blood pressure readings, as well as central venous pressure and cardiac output (CO) measurements, including non-invasive, minimally invasive and invasive methods (Dyer and James, 2008). In addition, recent studies have suggested that haemodynamic instability may be predictable preoperatively in some patients, either by virtue of an assessment of preoperative sympathovagal balance (Hanss et al, 2006), or employing a preoperative supine stress test
(Dahlgren et al, 2007). Short term neonatal outcome has most commonly been assessed by umbilical arterial and venous blood gas values and Apgar scores (Reynolds and Seed, 2005).

1.2.1. Effects of spinal anaesthesia and aortocaval compression

The association between arterial hypotension and the supine position in late pregnancy was first recognised by the Swedish obstetrician Ahltorp in 1931, as described in a recent review (Kinsella, 1994). The correct aetiology was described in 1951, and classic case reports alerted anaesthesiologists to the importance of avoiding this complication (Holmes, 1960). Early studies demonstrated both vena caval and aortic compression in late pregnancy. The methodology included the measurement of right heart filling and inferior vena caval pressures, CO, differences in brachial arterial and femoral arterial pressures in the supine and the lateral or lateral tilt position, and abdominal angiography (Marx, 1992). Aortic compression, shown by a decrease in femoral artery pressure, occurs earlier in pregnancy than inferior vena caval compression, as indicated by a decreased femoral artery pressure in the supine position (Marx et al, 1980). Compensatory increases in SVR and HR in the supine position, result in the phenomenon that less than 20% of women experience arterial hypotension and the “supine hypotensive syndrome”; however the fetus may be subjected to diminished intervillous blood flow because of a rise in uterine vascular resistance secondary to aortic compression. Fetal bradycardia has been shown to occur during supine recumbency of the mother associated with hypotension (Reed et al, 1970), and HR decelerations can be reversed by turning the mother into the lateral position.

During SA, sympathetic blockade diminishes the compensatory mechanisms and results in a higher incidence of clinically significant hypotension. An early study of intermittent CO measurement during SA for CS, using indicator dilution, showed that SA was associated with a significant depression of CO in 10/12 patients (Ueland et al, 1968). A more recent study employing
intermittent suprasternal Doppler flow measurements, showed that SA employing a median dose of 11mg bupivacaine was associated with a decrease in CO of >1L/min in 9/16 patients (the comparison in this study with a group of patients receiving epidural anaesthesia was made difficult to interpret in view of co-administration of adrenaline with the epidural local anaesthetic) (Robson et al, 1992). By contrast, a further investigation employing lower doses of local anaesthetic (7mg and 10mg bupivacaine) in conjunction with subarachnoid sufentanil, demonstrated an increase in CO following SA, using pulse wave form analysis (Langesaeter et al, 2008). These different findings may relate to the limitation of aortocaval compression by effective lateral tilting of the parturient in more recent studies, after the demonstration of the importance of adequate venous return by earlier researchers. Improved stability may also relate to the recent use of smaller doses of spinal local anaesthetic. Pulse wave form analysis may also allow for more accurate beat by beat analysis of CO changes immediately after induction of SA.

CO has been shown to be greatly improved by a change from the supine to the left lateral position, during SA for CS (Ueland et al, 1968). Umbilical venous and arterial saturation was demonstrated to improve during SA in patients receiving lateral tilt (Ansari et al, 1970). However, as much as 34 degrees of lateral tilt may be necessary to completely eliminate the effects of aortocaval compression (Kinsella et al, 1992), and some investigators have recommended the performance of SA for CS in the lateral or modified lateral position (Stoneham et al, 1999). The effects of maternal position on the human fetal circulation have been studied using umbilical artery scanning with real-time Doppler signals during epidural anaesthesia. The results showed a higher umbilical artery vascular resistance in the supine position (Marx et al, 1986).

Overall, maternal and fetal morbidity have been greatly reduced by the recognition of the effects and the avoidance of aortocaval compression during SA for CS. A recent editorial discusses the relative contribution of the venous and arterial circulation to spinal hypotension during CS (Sharwood-Smith and
Drummond, 2009). The point is made that despite careful attention to fluid management and positioning in order to minimise aortocaval compression, significant hypotension still occurs in a large percentage of patients, due to the effects of SA on the arterial circulation. This thought-provoking publication suggests that there is a “lesson” to be learned “from preeclampsia”, in that one would expect greater haemodynamic instability in these patients if intravascular depletion and decreased venous were the predominant contributor to spinal hypotension. Chapters 5 and 6 of this thesis address in detail the important issue of the effects of SA and vasopressors on the arterial circulation in healthy and preeclamptic patients.

1.2.2. Baricity, dose and volume of spinal local anaesthetic, and combination with opiate

Currently, most anaesthetists employ hyperbaric bupivacaine for SA for CS. In support of this practice, a recent randomised trial suggested that isobaric and hypobaric solutions were associated with more motor block, as well as more hypotension and a higher number of cervical blocks than hyperbaric bupivacaine, if SA was performed in the sitting position (Hallworth et al, 2005).

Since the early adoption of 0.5% bupivacaine for SA for CS, interest has focussed on the optimal local anaesthetic/opioid combination and dose to achieve the goals of effective surgical anaesthesia and postoperative analgesia, with minimal maternal and neonatal side effects. This is particularly important in view of the fact that maternal pain is the commonest reason for failure of technique, particularly if the uterus is exteriorised. Pain is also the most commonly cited anaesthetic cause of litigation in obstetric practice (Bogod, 2000). Despite several recent studies on dose response and efficacy, currently there seems no advantage of either levobupivacaine or ropivacaine over bupivacaine (Dyer and Joubert, 2004).

Most anaesthetists employ hyperbaric 0.5% bupivacaine in a dose of 7.5mg – 15.0mg (1.5mL - 3.0mL). The use of less than 10mg alone or 8mg in combination with an opioid is considered “low dose”. Some investigators have
examined the lower dose range, with a view to reducing side-effects such as hypotension, nausea and vomiting, and prolonged motor blockade. The incidence of visceral pain has been shown to be related to the dose of spinal bupivacaine. In a comparative study of three different doses of hyperbaric bupivacaine, the use of 7.5mg of bupivacaine was advocated in the interests of haemodynamic stability; however many patients rated analgesia as poor (Kiran and Singal, 2002). Furthermore, a recent study, employing a suprasternal Doppler flow technique, was unable to demonstrate improved haemodynamic stability when comparing the initiation of SA for CS with a standard local anaesthetic dose versus a smaller dose as part of a combined spinal-epidural technique (Bray et al, 2006). The addition of various doses of different intrathecal opiates may allow the reduction of the local anaesthetic dose, with an equivalent success rate and less severe side effects. Adequate surgical anaesthesia has been reported in parturients receiving only 5mg hyperbaric bupivacaine, to which 25µg fentanyl was added, with less hypotension, and less nausea and vomiting than the group receiving 10mg of bupivacaine only (Ben David et al, 2000). Other investigators reported that 8mg of bupivacaine was sufficient if 10µg fentanyl was added (Choi et al, 2000). All studies suggest that a combination of local anaesthetic and opiate allows for a reduction in local anaesthetic dose. Most studies investigating low local anaesthetic doses have employed hyperbaric bupivacaine, which allows the use of positioning to manipulate dermatomal spread. In this regard, low dose (6.6mg) hyperbaric bupivacaine has been shown to produce more reliable cephalad spread of anaesthesia, with less hypotension and nausea, than the isobaric solution (Vercauteren et al, 1998).

When the effects of low dose SA are studied, a combined spinal-epidural (CSE) technique is often employed, since this allows for epidural supplementation should analgesia be inadequate. It should be noted that the interpretation of the results of these studies may however be influenced by the fact that single shot SA may result in less sensorimotor anaesthesia than an identical dose administered as part of a CSE technique for elective CS (Ithnin et al, 2006). A recent study, in which cerebrospinal fluid pressure was measured, has been unable to reproduce these findings (Horstman et al,
2009). One recent investigation into the dose-response relationship for intrathecal hyperbaric bupivacaine coadministered with intrathecal fentanyl and morphine, demonstrated an ED50 of 7.6mg and an ED95 of 11.2mg for bupivacaine (Ginosar et al, 2004).

The analgesic benefits of the addition of intrathecal opiates to the local anaesthetic are to be balanced against side effects, namely nausea and vomiting, sedation, pruritis, urinary retention and hypotension, which are dose related. Respiratory depression, early and delayed, does occur, but is seldom life-threatening in obstetric patients (Carvalho, 2008). In a systematic review of randomised controlled trials investigating intra- and postoperative analgesic efficacy of intrathecal opiates, intrathecal morphine consistently reduced postoperative pain and analgesic consumption (median time to first analgesic 27 hours). However there was no clear dose response effect using 0.05mg, 0.1mg and 0.2mg, and in view of the dose dependent increase in risk of pruritis, nausea and vomiting and possibly respiratory depression, the authors recommended a maximum dose of 0.1mg (Dahl et al, 1999).

Using various effective doses of fentanyl, the median time to first analgesic request was 4 hours. There was evidence of a dose response relationship in a study where 20µg, 40µg or 60µg was administered (analgesia prolonged from 3[control] to 13 hours); the higher doses were associated with increased pruritis. Overall, only 24% of patients in the control groups receiving no intrathecal opioids, required intraoperative analgesia supplementation, hence many patients were exposed to unnecessary side effects (Dahl et al, 1999).

The addition of intrathecal sufentanil (2.5µg - 5µg) to hyperbaric bupivacaine has been shown to provide effective postoperative analgesia for approximately 4 - 5 hours (Dahlgren et al, 1997).

Meperidine (pethidine) is a unique opioid, which has local anaesthetic properties independent of its µ-agonist activity. It has a molecular weight and pKa similar to the commonly used amide local anaesthetics, and a lipid solubility intermediate between that of fentanyl and morphine.
Two studies employing intrathecal pethidine as the sole agent for CS, showed that while the drug gave effective surgical anaesthesia, the duration was short (60 and 78 minutes) (Talafre et al, 1987; Kafle, 1993), and the incidence of hypotension was high (32 and 50%) when an intrathecal dose of 1 mg/kg was used.

Recent studies have investigated the intraoperative efficacy of diamorphine, which has kinetics resulting in an onset time is similar to that of fentanyl (6 – 9 minutes), and considerably shorter than that of morphine (30 – 60 minutes). The lowest dose of intrathecal diamorphine required to reduce intraoperative supplementation, has been determined (Saravanan et al, 2003). The study showed that an ED95 of 0.4mg for intrathecal diamorphine was required to reduce the requirement for intraoperative analgesic supplementation to < 5% of patients. Other agents have been investigated for intrathecal administration. Although neostigmine has recently been shown to produce modest postoperative analgesia, shivering and sedation were increased (Kaya et al, 2004). A high incidence of nausea and vomiting were associated with its intrathecal use (Krukowski et al, 1997). Intrathecal midazolam has a significant antinociceptive effect (Sen et al, 2001), and may reduce postoperative nausea and vomiting (Prakash et al, 2006). There is currently insufficient evidence to recommend either of these drugs for clinical intrathecal use.

In summary, surgical anaesthesia during single shot SA should not be compromised due to unrealistic concerns about the management of cardiovascular instability. A dose of no less than 8mg hyperbaric bupivacaine combined with an opioid, or 10mg of hyperbaric bupivacaine alone, would seem appropriate. If doses lower than these are envisaged, SA should only be performed as part of a CSE technique. The use of a long-acting opioid as part of a single shot SA technique depends upon facilities available for postoperative monitoring. Having selected the optimal combination of local anaesthetic and opiate for SA in this manner, with a view to attaining ideal surgical anaesthesia and a minimal requirement for intraoperative supplementation of analgesia, haemodynamic instability will occur in a
significant percentage of patients. This requires careful attention to fluid and vasopressor therapy.

1.2.3. Fluid management during spinal anaesthesia for caesarean section

Considerable controversy exists as to the most appropriate IV fluid regimen for SA for elective CS. Widespread use of crystalloid preload was initiated by the demonstration of improvements in uterine blood flow in pregnant ewes in response to rapid fluid administration after SA-induced hypotension (Greiss and Crandell, 1965). The rationale for “preload” was that SA-induced venodilatation results in a decrease in stroke volume (SV) which more than offsets the increase due to afterload reduction, and thus CO may decrease precipitously. Early promising results (Wollman and Marx, 1968; Marx et al, 1969) may have been due to the inclusion of patients in labour, an inadequate understanding of the importance of prevention of aortocaval compression, and other aspects of study design such as blinding, randomisation and local anaesthetic dose.

A qualitative systematic review evaluated the efficacy of increasing blood volume in reducing the incidence of hypotension during elective SA for CS (Morgan et al, 2001). Secondary outcomes were maternal nausea, vasopressor use, and umbilical cord pH and Apgar scores. The studies fell into 4 categories: large versus small volumes of crystalloid, colloid versus crystalloid, different colloid regimes, and mechanical methods for increasing blood volume (total n = 1504). Crystalloid solutions were ineffective as a preload. Of the 9 studies examining crystalloids, only three showed a significant reduction in the incidence of hypotension in the group receiving a higher volume of preload (Marx et al, 1969; Clark et al, 1976; Rout et al, 1993b). There were considerable differences in the study protocols, which probably accounts for the heterogeneity of the results (Morgan et al, 2001). Colloids were effective in reducing, but not eliminating, hypotension in all but one of a total of 23 randomised controlled trials. Of the 7 studies comparing crystalloid and colloid (albumin, hetastarch, gelatin, pentastarch or dextran), 5 showed a decreased incidence of hypotension in the colloid relative to the
crystalloid group (Mathru et al, 1980; Riley et al, 1995; French et al, 1999; Lin et al, 1999; Ueyama et al, 1999). Only one study showed a better neonatal outcome in the colloid group (Mathru et al, 1980). A limitation of the results was the variability in the volumes of colloids chosen in the studies, as well as differing definitions of hypotension and ephedrine protocols. Due to variation in study design, it was also not possible to determine whether prophylactic fluid administration affected vasopressor requirements. Wrapping the legs consistently reduced the incidence of hypotension compared with leg elevation or controls (Rout et al, 1993a). However, this is not regarded as a readily practicable intervention.

The latest update of the Cochrane Data Base in this field is in general agreement with findings from the above systematic review, reporting that “Crystalloids were more effective than no fluids (relative risk 0.78, 95% confidence interval 0.60 to 1.00; one trial, 140 women, sequential analysis) and colloids were more effective than crystalloids (relative risk 0.68, 95% confidence interval 0.52 to 0.89; 11 trials, 698 women) in preventing hypotension following SA at CS. No differences were detected for different doses, rates or methods of administering colloids or crystalloids” (Cyna et al, 2006).

Despite the proven advantages of colloids in terms of reducing hypotension, colloids have not been uniformly adopted for fluid management for elective CS. This is partly because of their expense, as well as the risk of anaphylactic reactions, albeit very low in the case of the hydroxyethyl starches. Recent studies have therefore investigated the timing of administration of crystalloid. The relevance of the duration and timing of infusion of a crystalloid preload prior to SA for CS, has been evaluated (Rout et al, 1992a). This study demonstrated that there was no difference in the incidence of hypotension whether 20 mL/kg of crystalloid was given over 10 or 20 minutes prior to induction of SA. Central venous pressure increases were greater, but increases in HR were less, and HR returned to baseline in a shorter period in the 10 minute group than in the 20 minute group, suggesting a benefit in administering the fluid closer to the time of induction of SA.
In a more recent investigation the authors hypothesised that in order for a fluid bolus to effectively reduce post-spinal hypotension, the administration of the fluid should produce a sustained increase in CO. Patients were preloaded with 1.5L Ringer’s lactate, 0.5L or 1.0L hydroxyethyl starch. CO and blood volume were assessed before and 30 minutes after fluid loading, using a non-invasive pulse spectrophotometric technique for detecting indocyanine green. All groups had an increase in blood volume after fluid loading, but only 28% of the Ringer’s lactate solution remained in the intravascular space after 30 minutes, compared with 100% of the hydroxyethyl starch solution. CO was only increased in the hydroxyethyl starch groups, and only in the 1.0L hydroxyethyl starch group was spinal hypotension statistically and clinically significantly reduced, with an incidence of 17%, versus 75% in the Ringer’s and 58% in the 0.5L hydroxyethyl starch group (Ueyama et al, 1999).

In the non-obstetric population, a sustained rise in CO has been demonstrated in a group of patients given lactated Ringer’s solution after the initiation of SA (Kamenik and Paver-Erzen, 2001). A kinetic analysis of an IV infusion of Ringer’s solution as preload, suggested that a rapid fluid load given over 2 minutes after induction of both spinal and general anaesthesia for non-obstetric surgery, might prevent hypotension caused by central hypovolaemia (Ewaldsson and Hahn, 2005).

These findings prompted a study of crystalloid administration after initiation of SA for CS (coload), to overcome the problem of rapid re-distribution of crystalloid fluid (see Chapter 4, below). Subsequent to this study, crystalloid coloading has been employed in combination with phenylephrine infusion, in an attempt to obtain optimal haemodynamic stability during SA for CS (Ngan Kee et al, 2005). Patients receiving rapid coloading in combination with phenylephrine had significantly less hypotension than those who received only a phenylephrine infusion.

Recent studies have also examined the optimal volume and timing of colloid administration. In this regard, a pentastarch preload of 10 mL/kg has been found to be more effective than 5 mL/kg at preventing hypotension following
SA (Davies and French, 2006). As might be expected, colloid coloading with 6% hydroxyethyl starch was found to be similarly effective in reducing hypotension compared with preloading (Nishikawa et al, 2007). Similar results were shown using hetastarch (Carvalho et al, 2009). There are no studies comparing crystalloid coload with colloid preload.

In summary, colloids are more effective than crystalloids in preventing hypotension during SA for elective CS, particularly in women who have a positive preoperative supine stress test (Dahlgren et al, 2007). Routine use of colloids is probably not justified in view of the expense, the potential for anaphylactic reactions, and the efficacy of crystalloid co-loading in combination with judicious use of vasopressors.

1.2.4. Vasopressor use

Fluids alone are inadequate to treat spinal hypotension in 40 – 60% of cases (Macarthur and Riley, 2007). Worldwide, the most commonly used vasopressors are ephedrine and phenylephrine; this discussion will thus be mostly limited to the intravenous administration of these agents, since prophylactic intramuscular administration may cause hypertension (Rout et al, 1992b) or inadequate reduction of hypotensive episodes (Ayorinde et al, 2001), depending on the exact timing. The choice of vasopressor should be based upon a knowledge of the maternal haemodynamic effects of the agent, efficacy (preferably rapid onset and short duration), maternal and fetal side-effects.

Ephedrine is a slow onset and relatively long-acting, non-catecholamine, direct-acting β-receptor agonist, with indirect α-effects via noradrenaline release. However the exact mechanism of action remains controversial; one study in a rat model suggested mainly indirect effects via noradrenaline release (Kobayashi et al, 2003), and another supported direct α effects (Liles et al, 2006). In either case, the fact that the uteroplacental circulation is relatively devoid of sympathetic innervation, suggests a resistance to uterine arterial vasoconstrictive effects of this agent (Kobayashi et al, 2003). In
support of this finding, ephedrine has been found to cause relatively more femoral than uterine artery vasoconstriction in pregnant ewes (Tong and Eisenach, 1992). The vasodilatory effects of increased nitric oxide synthase activity in the uterine artery endothelium of pregnant ewes (Li et al, 1996) suggests that ephedrine might preferentially shunt blood to the uterus in pregnancy (Macarthur and Riley, 2007). A dose response meta-analysis of prophylactic IV ephedrine for the prevention of spinal hypotension, suggested a dose of 12mg as a balance between benefit as a vasopressor and risk of causing hypertension. Clinical disadvantages in terms of haemodynamic effects include a low efficacy for vasopressor effect (Ngan Kee et al, 2000), the development of tachyphylaxis to the pressor effects (Persky et al, 2004), and tachycardia and arrhythmias (Ngan Kee and Khaw, 2006). Probably due to the low efficacy, and possibly due to an inherent emetic effect of ephedrine, phenylephrine may be preferable for the reduction of nausea and vomiting (Cooper et al, 2002).

One of the further chief objections to ephedrine is the fetal acidosis associated with its use. The decreased umbilical arterial pH and increased base deficit have been attributed to an ephedrine-generated increase in fetal metabolic rate, evidenced by an increase in an umbilical arteriovenous PCO\textsubscript{2} difference in patients receiving ephedrine when compared with phenylephrine (Cooper, et al, 2002). Ephedrine also increases fetal catecholamine concentrations (LaPorta et al, 1995). No study of the use of ephedrine has demonstrated acid base derangements as severe as those which are associated with an increased risk of cerebral palsy in the infant (pH < 7.00, base deficit > 16 mmol/L [MacLennan, 1999]). This suggests that its use is safe in healthy, low risk deliveries, but in compromised infants already at risk of acidosis and intrapartum hypoxia, ephedrine may have a clinically deleterious effect, particularly by virtue of increased oxygen consumption. Minor increases in fetal metabolic rate may be beneficial to the normal fetus; one investigation showed that neonatal respiratory rates were higher in patients randomised to placebo than the \(\beta\)-agonist terbutaline prior to elective CS. Neonates in the
treated group also had lower airways resistance and higher pulmonary compliance (Eisler et al, 1999).

The basis for the long-established use of ephedrine as a first-line drug for the management of spinal hypotension in obstetrics, was a paper showing reductions of uterine blood flow in pregnant ewes following administration of $\alpha$-agonists (Ralston et al, 1974). Extrapolation from sheep to humans may be invalid, since the epitheliochorial placenta of the sheep differs vastly from the human haemochorial system. In the latter case, flow is very dependent upon pressure in the uterine arteries.

Phenylephrine is a potent direct-acting $\alpha$-1 agonist which has a rapid onset and is shorter acting by virtue of metabolism by monoamine oxidase. A study comparing infusions of phenylephrine and ephedrine suggested a potency ratio of 81.2 (95% confidence intervals 73.0 – 89.7) (Saravanan et al, 2006). The time to peak pressor effect has been studied employing beat by beat finger arterial pressure. Phenylephrine has a significantly shorter time to peak effect than ephedrine (median 27 seconds vs. 78 seconds, $P$-value = 0.006) (Thomas and Gardner, 2004).

Several studies have searched for the ideal method of administration of phenylephrine (Ngan Kee et al, 2004a; Ngan Kee et al, 2004b; Ngan Kee et al, 2005). A comparison of a prophylactic infusion of 100 µg/min phenylephrine with the administration of 100µg boluses in response to a decrease in blood pressure to < 80% of baseline, showed a greater number of hypotensive episodes in the treatment group, with no benefit in terms of cord blood gases. The prophylaxis group received approximately 3 times the dose of phenylephrine (Ngan Kee et al, 2004b). A subsequent investigation, using phenylephrine infusions to control blood pressure at 80, 90 or 100% of baseline values, suggested that tight control of blood pressure was associated with a lower incidence of nausea and vomiting, and a statistically, but not clinically significantly higher umbilical arterial pH (Ngan Kee et al, 2004a). Recently, a closed -loop feedback computer controlled infusion has been used
to maintain baseline blood pressure, using an on-off algorithm for a phenylephrine infusion at 100 µg/min (Ngan Kee et al, 2007). No patients were symptomatic, and umbilical arterial pH was above 7.2 in all 53 cases. Hypertension occurred in 38% of patients. A study of pregnant ewes has shown that the uterine artery in pregnancy is less responsive to α-agonist effects than in the non-pregnant state (Magness and Rosenfeld, 1986). This finding, together with the well preserved cord gas values after high dose phenylephrine (Ngan Kee et al, 2004a), suggests that phenylephrine is effective in sustaining uterine blood flow during SA by its effects on uterine artery perfusion pressure.

Combinations of ephedrine and phenylephrine have been studied. Phenylephrine added to an infusion of ephedrine halved the incidence of hypotension and increased umbilical cord pH (Mercier et al, 2001), but there is no apparent benefit over phenylephrine alone. In a study employing varying proportions of the two vasopressors by infusion, increasing proportions of ephedrine resulted in less favourable haemodynamic control as assessed by HR and blood pressure, and decreasing umbilical arterial pH and base excess (Ngan Kee et al, 2008).

There are few available data on maternal CO responses to ephedrine and phenylephrine during SA for elective CS. Three published investigations have employed intermittent suprasternal doppler flow measurements. In the first study, comparing bolus doses of the vasopressors, overall CO changes were not different between groups; however, bradycardia in the phenylephrine group was treated with atropine, which make the results difficult to interpret (Thomas et al, 1996). The primary outcome variable in this study was umbilical artery pH, and not maternal haemodynamic changes. A second study, employing infusions of vasopressors, suggested that phenylephrine may depress maternal CO (Ashpole et al, 2005). Recently a reduction in HR and CO has been shown in parturients receiving phenylephrine at 100 µg/min (Stewart et al, 2008). Pulse wave form analysis has been employed to compare the effects of two different intrathecal doses of bupivacaine, with or
without intravenous phenylephrine infusion, on CO and systolic blood pressure. It was concluded that low dose bupivacaine plus sufentanil, in combination with fluid coload and an infusion of phenylephrine (0.25 µg/kg/min) gave “the best haemodynamic stability”, although no conclusions can be drawn about any treatment regimes other than those employed in the study (Langesaeter et al, 2008). A detailed consideration of CO responses to SA and to the two vasopressors is the subject of Chapter 5 of this thesis.

1.2.5. Administration of oxytocin

The nonapeptide oxytocin is an essential drug for the prevention of postpartum haemorrhage, and is the first line drug for this purpose. Oxytocin has complex cardiovascular effects, including peripheral vasodilatation and hypotension, probably via calcium dependent stimulation of the nitric oxide pathway, as well as release of atrial and brain natriuretic peptide (Carvalho et al, 2004). Oxytocin and/or the preservative chlorbutanol also has a negative inotropic effect on atrial myocytes (Rosaeg et al, 1998). It causes selective vasoconstriction of coronary, renal, splanchnic and skeletal muscle arteries, as well as of the umbilical vessels (Evron et al, 1986). A recent study employing vectorcardiography showed signs of myocardial ischaemia after 10IU oxytocin given IV after delivery at CS, and to non-pregnant controls (Svanstrom et al, 2008). By contrast, a further investigation using Holter monitoring during CS, found that ST segment changes were infrequent, and there was no evidence of myocardial injury (Dogan et al, 2008). Due to a structural similarity with vasopressin, oxytocin in large doses may cause water retention and hyponatraemia in large doses.

Common maternal side effects are nausea, vomiting, headache and arrhythmias. Less common, but potentially serious, are chest pain, pulmonary oedema (Chilvers et al, 2003), anaphylaxis, and amniotic fluid embolism, presumably associated with tetanic uterine contractions (James et al, 2004).

During SA for CS, the haemodynamic effects of oxytocin have been studied by measuring transthoracic bioimpedance changes (Pinder et al, 2002), and
by pulse wave form analysis (Langesaeter et al, 2006). Both investigations showed statistically and clinically significant increases in HR and CO following oxytocin boluses of 5 – 10IU. The second study, employing an intra-arterial catheter for blood pressure measurement, showed a 67% decrease in systolic blood pressure, a 39% decrease in SVR, and a 61% increase in cardiac index. These effects occurred 45 seconds after administration of oxytocin. The effects of oxytocin during SA in normal and in preeclamptic patients, as well as a study examining the efficacy of the co-administration of phenylephrine with oxytocin in obtunding the unwanted cardiovascular effects, are the subject of Chapter 7 of this thesis. HR and blood pressure changes can be restricted to within 10% of baseline in elective healthy parturients, if 5IU oxytocin is given as a slow infusion rather than as a rapid bolus, although the efficacy of this method in terms of prevention of blood loss remains to be established (Thomas et al, 2007). In addition, less changes in heart rate and blood pressure are have been demonstrated after a bolus of 2 than 5IU (Sartain et al, 2008).

There are little published data on a dose-response curve for oxytocin during SA for CS, both in terms of efficacy as an oxytocic, and with respect to cardiovascular effects. Using an up-down sequential allocation technique, the ED90 was found to be only 0.35IU in 40 patients not at high risk of uterine atony (Carvalho et al, 2004). The authors concluded that no more than 1IU oxytocin is required in cases at low risk for postpartum haemorrhage. Using similar methodology, the dose required at CS for labour arrest, was 3IU, suggesting the possibility of receptor desensitisation in this situation (Balki et al, 2006). Further work is required on oxytocin dose-response curves and on the issue of receptor desensitisation with multiple doses (Magalhaes et al, 2009).

1.2.6. Special considerations in preeclampsia

When one considers the cardiovascular pathophysiology of severe preeclampsia, including decreased intravascular volume and markedly raised SVR (Young and Johanson, 2001), there has been an understandable caution
as regards regional anaesthesia in these patients, due to the theoretical possibility of precipitous hypotension, decreased CO and associated placental hypoperfusion. Epidural anaesthesia for labour has been found to be associated with remarkable haemodynamic stability, as demonstrated by the use of pulmonary artery catheterization, in patients with severe preeclampsia who were receiving magnesium therapy (Newsome et al, 1986).

SA has only recently been recognized to have a place in operative management in preeclampsia. In 1995, 3 groups of patients with severe preeclampsia were randomised to receive epidural, combined spinal-epidural or general anaesthesia for CS, with similar haemodynamic stability (as assessed by HR and blood pressure) and fetal outcome in each group. Patients with non-reassuring fetal heart traces were excluded from this study (Wallace et al, 1995).

Thereafter an editorial highlighted a study demonstrating, albeit retrospectively, that haemodynamic stability was equivalent in patients receiving spinal or epidural anaesthesia for non-emergency CS (Hood and Curry, 1999; Santos, 1999). Fluid requirements were however higher in the spinal group. Despite the gradually emerging evidence that SA was safe in preeclampsia, at least one editorial called for caution, and stressed the value of epidural anaesthesia (Howell, 2001).

In a recent randomised multicentre study, SA was associated with a higher incidence of hypotension and a higher ephedrine requirement than epidural anaesthesia for CS for preeclampsia, but these differences were not of clinical significance (Visalyaputra et al, 2005).

Several authors have shown that SA for CS in severe preeclampsia is associated with less hypotension and/or vasopressor requirements than in healthy parturients (Sharwood-Smith et al, 1999; Aya et al, 2003; Aya et al, 2005; Clark et al, 2005). One such study used a control group consisting of healthy patients having a preterm caesarean delivery, in whom the neonatal weights were similar to those in the preeclampsia group. This ensured that
observed differences in blood pressure were not due to varying degrees of aortocaval compression in the two groups, as might have been the case in a previous study by the same authors (Aya et al, 2005). Although the findings are valid, some methodological aspects in this study should be noted, including differing blood pressure criteria for interventions with vasopressors in each study group. Also, their recommended administration of large volumes (1500 - 2000 mL) of crystalloid fluid in the preeclamptic group would be considered by many to be inadvisable, since the risk of pulmonary oedema is very real in these patients, and may be associated with life-threatening hypoxia. There are however no definitive data on fluid management during SA for CS in patients with severe preeclampsia. Mean central venous pressure has been shown to increase significantly after a preload of one litre of crystalloid, but returned to normal shortly after induction of anaesthesia (Karinen et al, 1996). Atrial natriuretic peptide release after a crystalloid preload is exaggerated in patients with preeclampsia relative to healthy parturients, and this may aid in the adaptation of maternal circulation to a volume load at elective caesarean delivery (Pouta et al, 1996a).

There are limited CO data in the setting of SA for CS in severe preeclampsia. Due to a significant incidence of complications using the pulmonary artery catheter (Young and Johanson, 2001), the research focus has moved to non-invasive technologies. Employing whole body impedance changes in the first study of maternal CO changes associated with SA for CS in preeclampsia, the authors reported on 10 preeclamptics, of whom 6 had severe disease (Tihtonen et al, 2006). After recovery from SA, stroke index and cardiac index in the preeclamptic group were significantly lower than pre-surgery levels. A further study employing pulse wave form analysis during SA for CS in patients with severe preeclampsia, forms the basis of Chapter 6 of this thesis. Such studies could provide useful information on best practices for fluid management and administration of vasopressors and oxytocic drugs.
1.2.7. Neonatal outcome

The direct effect of drugs on the neonate is insignificant when SA is administered. However indirect effects secondary to maternal physiological or biochemical changes are considerable. A multivariate analysis of factors associated with umbilical arterial pH and base deficit after CS under SA, factors predicting umbilical arterial pH included use of ephedrine, uterine incision-to-delivery time, and maximum decrease in systolic arterial pressure. Factors predicting umbilical artery base deficit were ephedrine use and the interaction between its use and the duration of hypotension (Ngan Kee and Lee, 2003).

A realistic cut-off point for defining pathological fetal acidaemia that correlates with an increasing risk of neurological deficit has been found to be a pH of less than 7.00 and a base deficit of more than 16 meq/L (MacLennan, 1999). Decreased umbilical arterial pH and increased base deficit are currently the most widely accepted markers of poor short-term neonatal outcome, although some degree of fetal catecholamine stimulation before delivery may be beneficial (Eisler et al, 1999; Cooper et al, 2002).

The effects of the generic methods of anaesthesia, spinal epidural and general, on neonatal acid-base balance, the most widely accepted marker of short term neonatal outcome, have recently been the subject of a meta-analysis (Reynolds and Seed, 2005). In view of the fact that there was little precise information on vasopressors, and that no studies stated whether vasopressor was given before delivery, a “surrogate ephedrine score” was created, based on the total dose used and on the difference in dose between groups. This was an attempt to establish the effect of ephedrine on umbilical arterial pH and base deficit, and is a limitation of the analysis.

In 27 of 33 studies identified it was possible to extract the minimum data required. In 6 out of 12 randomised studies included in the analysis, general anaesthesia was associated with lower Apgar scores at one minute, but not at 5 minutes, than regional anaesthesia. When only randomised studies were
included in the analysis, pH was significantly lower with spinal than general anaesthesia ($P$-value = 0.034), but there was no difference between the spinal and epidural groups ($P$-value = 0.074). Too few of the randomised trials reported base deficit to allow useful analysis. When all 16 studies including the base deficit were analysed, this parameter was significantly greater for spinal than for general (difference 1.109; 95% confidence interval 0.434 - 1.784 meq/L; seven studies, n = 695) and epidural anaesthesia (difference 0.910; 95% confidence interval 0.222 - 1.598 meq/L; seven studies, n = 497). Random effects maximum likelihood regression suggested that larger doses of ephedrine contributed to the differences between pH values in the epidural and spinal groups, as well as in the spinal and general anaesthesia groups. These between-group differences could be reduced with the resurgence of the use of phenylephrine since this meta-analysis was performed (Ngan Kee et al, 2004a). The authors of the meta-analysis point out, however, that the mean values for base deficit, indicating metabolic acidosis, were higher in every study for spinal than epidural or general anaesthesia, independent of ephedrine use.

In the context of preeclampsia, Chapter 8 of this thesis addresses the issue of neonatal acid base balance in a randomised comparison of general versus SA for CS.

### 1.3. Summary and Research Questions

In summary, the above literature review emphasises that there are many influences on maternal haemodynamic stability during CS. When aortocaval compression has been minimised, effective fluid management can further improve stability, but by no means eliminate hypotension.
A formula fundamental to safe practice in anaesthesiology, is:

\[ CO = \frac{MAP}{SVR} = SV \times HR \]

CO is thus only proportional to mean arterial pressure (MAP) if SVR is constant, which is seldom the case during SA for CS. This makes the interpretation of blood pressure problematic. An understanding of the detailed haemodynamic effects of SA would thus be advantageous, as would a detailed knowledge of the effects of the commonly used vasopressors, and vasoactive substances such as oxytocin. Thus this review posed certain as yet unanswered research questions in the management of patients undergoing SA for non-emergency CS, which were addressed in Chapters 3 – 8 of the thesis:

- Is pulse wave form analysis a useful research tool, and can this minimally invasive technique be usefully applied in the management of critically ill obstetric patients?
- What is the most effective method of administration of crystalloid?
- What are the haemodynamic effects of phenylephrine and ephedrine?
- What are haemodynamic effects of SA in healthy and preeclamptic patients?
- What are the haemodynamic effects of oxytocin?
- How does SA affect neonatal outcome in patients with severe preeclampsia?

The answers to these questions would constitute an advance in the safe anaesthesia management of healthy and critically ill mothers and their infants.
Chapter 2  
Research setting and methods

2.1. Introduction

The details of research methodology in each study in this thesis are outlined in the relevant chapters. This chapter outlines the research setting, the basis for the methodology employed, and the ethical issues involved.

2.2. Research setting

All the research upon which this dissertation is based, was conducted in one of two settings. In South Africa, the public health system is structured into primary, secondary and tertiary health care. The first location for the research was the Mowbray Maternity Hospital, situated 3km away from Groote Schuur Hospital in Cape Town. This is a secondary level hospital, where approximately 7000 deliveries are performed per annum, many in patients with no co-morbidity, but also in patients with uncomplicated preeclampsia or fetal indications requiring referral from the primary health care level. This site was appropriate for the study of the influence of SA, fluids, vasopressors and oxytocin on maternal haemodynamics. The second site for the research was the Maternity Centre of the New Groote Schuur Hospital, Cape Town, which is a tertiary referral centre for high risk obstetrics (approximately 6000 deliveries per annum). A high proportion of deliveries involve patients with severe preeclampsia. This provided the opportunity for the study of clinically relevant aspects of SA in these patients. Close cooperation with the Department of Obstetrics and Gynaecology of the University of Cape Town was required at all times for the success of the work. In two of the studies, a senior obstetrician was a co-author and provided valuable assistance with the recruitment process. The research was conducted under the auspices of the University of Cape Town and the Provincial Government of the Western Cape.
2.3. Research methodology

For some of the studies undertaken, it was appropriate and clinically relevant to measure simple markers of maternal and fetal wellbeing such as HR, non-invasive blood pressure, vasopressor requirement, Apgar scores and umbilical cord acid base balance. In the studies analysing the detailed haemodynamic effects of SA, vasopressors and oxytocin on the maternal circulation, more advanced technology was necessary. Minimally invasive measurement of maternal CO was performed, using beat by beat pulse wave form analysis in two clinical and one validation study (LiDCOplus™, LiDCO, Cambridge, UK). In one of these studies, this was combined with the non-invasive measurement of CO, using transthoracic bioimpedance measurements (BioZ, Cardio Dynamics International, San Diego, CA, USA).

2.2.1. Pulse wave form analysis

As early as 1904, Erlanger and Hooker stated that “Upon the amount of blood that is thrown out by the heart during systole then, does the magnitude of the pulse-pressure in the aorta depend” (Erlanger J, 1904). Estimation of the SV from the aortic/arterial pulse pressure is complicated by a number of factors. Firstly, calibration is required. Secondly, early studies showed that aortic compliance is lower at higher blood pressures, so that pulse pressure must be corrected for the non-linearity of the compliance of the arterial wall (Remington and Noback, 1948). SV can thus not simply be estimated from the pulse pressure. Early “pulse contour” methods were based upon the integration of the area of the systolic part of the corrected linear pressure/volume waveform (Kouchoukos et al, 1970; Jansen et al, 1990). Wave reflection and damping are further limitations on the accuracy of pulse contour methods. Theoretically, the pulse power algorithm employed in the LiDCOplus monitor has certain advantages over traditional Fourier analysis-based pulse contour algorithms. These include the ability to derive CO accurately independent of the artery from which the measurement is made, the ability to correct for the non-linearity of aortic compliance, as well as being
minimally affected by changes in systemic vascular resistance, and a lack of
dependence upon identifying details of wave morphology (Rhodes and
Sunderland, 2005). In addition, its performance is less affected by damping of
the arterial trace (Pittman et al, 2005).

The LiDCOplus device uses Lithium indicator dilution to calibrate an arterial
waveform analysis algorithm. Lithium dilution for CO determination was first
described in 1993 (Linton et al, 1993), and has been well validated (Kurita et
al, 1997; Linton et al, 1997). Lithium 0.3mmol is injected via a central or
peripheral venous line (Mason et al, 2002), (a single lithium chloride
determination at 0.3mmol is the equivalent to a steady state plasma lithium
concentration of 1/240th of the therapeutic level). A concentration-time curve
is then generated by an ion-selective electrode. The sampling is from an
arterial catheter at 4 mL/minute, using a peristaltic pump. CO is calculated
from the lithium dose and the area under the concentration-time curve,
according to the equation:

\[ CO = \text{Lithium dose (mmol)} \times 60 / \text{Area} \times (1 - \text{PCV}) \text{ (mmol/second)}, \text{ where the area is the integral of the primary curve, and PCV is packed cell volume} \]

At the levels used, lithium is pharmacologically inert (Jonas et al, 2001), and a
high signal to noise ratio is generated since lithium does not normally occur in
the plasma.

The LiDCOplus machine calculates SV on a beat by beat basis, using a 3 step
transformation of the arterial blood pressure trace (Jonas et al, 2002; Rhodes
and Sunderland, 2005). The first step transforms the arterial pressure trace
into a volume-time waveform, using the following equation:

\[ \Delta V / \Delta bp = \text{calibration} \times 250 \times e^{-k \cdot bp}, \]

where V = volume, bp = blood pressure, and k is the curve coefficient
The number 250 is the maximal additional volume in mL above the starting volume, to which the aorta and arterial tree can fill.

Using a look-up table, the pressure waveform can thus be used as the basis for generating a trace, which describes the general form of the arterial volume changes with every cardiac cycle. The second step involves the derivation of a nominal SV (a value proportional to the actual SV) and the heart beat duration. This is done by applying the mathematical technique of autocorrelation to the standardised volume waveform obtained in step one. Finally, the nominal SV is scaled to actual SV by a lithium dilution measurement. The calibration factor changes the value of the maximum volume of the arterial tree which is used in the compliance correcting equation described above.

When comparing two methods for CO determination employing bias and precision statistics, a meta-analysis suggests that acceptance of a new technique should rely on limits of agreement of up to 30% (Critchley and Critchley, 1999). However, a knowledge of the precision of the reference technique is important if the conclusions relating to the new technique are to be accepted as valid (Cecconi et al, 2009b). Two recent studies have confirmed good agreement between beat by beat CO measurement using this monitor calibrated with lithium dilution, and thermodilution or lithium dilution (Hamilton et al, 2002; Pittman et al, 2005; Kim et al, 2006;). In 2 of these studies, measurements remained reliable without re-calibration for at least 8 hours, but a recent investigation in critically ill patients suggests a limit of 4 hours (Cecconi et al, 2008). A validation study in patients with preeclampsia complicated by pulmonary oedema, which compared thermodilution CO measurements with the LiDCOplus system calibrated with lithium dilution, is the subject of Chapter 3 of this thesis.

Three studies have demonstrated acceptable agreement between the LiDCOplus-derived CO and Lithium dilution (Hallowell and Corley, 2005; Pittman et al, 2005), or thermodilution (Yamashita et al, 2007) in the setting of SVR changes of up to 200%. This system was regarded as the best device
for the demonstration of rapid haemodynamic changes which occur during SA for CS, and following the administration of vasopressors and oxytocin during this procedure. The limitations of other available devices for CO determination in the setting of obstetric anaesthesia are the subject of a recent editorial (Dyer and James, 2008).

2.3.2. **Transthoracic electrical bioimpedance (TEB) techniques**

In studies examining short term haemodynamic changes in response to SA, vasopressors and oxytocin, described in Chapters 5 and 7 in this thesis, transthoracic bioimpedance changes were measured simultaneously with pulse wave form analysis using the LiDCO plus monitor. This was done in order to corroborate the findings recorded by LiDCO plus in the setting of rapidly changing SVR.

TEB CO measurements are non-invasive and provide continuous real-time data. In 1966, a method of CO measurement was developed based on measuring impedance changes in the thorax during left ventricular ejection (Kubicek et al, 1966). Clinically, an alternating current of constant magnitude, low amplitude (1 – 4 mA), and high frequency (50 – 100 kHz) is “injected” through the thoracic volume, and any changes in voltage measured by the sensing electrodes, are a result of changes in thoracic impedance during the cardiac cycle (Critchley, 1998). The current is introduced by electrodes placed on either side of the neck, and via another pair on both sides of the lower thorax. The potential difference is sensed by two further pairs of electrodes in the neck and thorax. The impedance changes during the cardiac cycle are small, resulting in a low signal to noise ratio. The algorithms developed depend upon three variables to calculate SV. The first is the baseline impedance of the thorax ($Z_0$). The second factor is the maximum upslope of the impedance waveform at the beginning of systole ($dZ/dt (\text{max})$), which is proportional to peak blood flow in the thorax, and the third is the ventricular ejection time (Critchley, 1998).
The basic principle is embodied in the formula:

\[ \frac{\Delta V}{V} = \frac{\Delta Z}{Z_0}, \]

Where \( \Delta V \) is the SV, \( V \) is the aortic volume immediately before the onset of systole; \( \Delta Z \) is the impedance variation during systole, and \( Z_0 \) baseline impedance (Moshkovitz et al, 2004).

A calibration factor is employed, which represents the volume of conducting thoracic tissue, and which depends upon thoracic shape and the resistance of the blood. In the generation of devices developed by Bernstein and Sramek in the 1980’s, the BoMed NCCOM3 series, the thorax is treated as a truncated cone. The BioZ device, employed in the studies described in Chapters 5 and 7, is a stand-alone version of the BoMed NCCOM3, with an analogue visual display and digital signal processing. The mathematical basis of the algorithm employed depends upon a modification of the original formula employed by Kubicek (Bernstein, 1986).

Many validation studies have been performed comparing TEB with invasive CO determination. Most deal with accuracy and repeatability, and few examine the ability to produce trend data, which was the goal in the studies described in Chapters 5 and 7. Several reports using the BioZ device have shown good correlation with the thermodilution and Fick methods, but results are not consistent, with correlation coefficients varying from 0.71 - 0.82 (Raaijmakers et al, 1999). Disadvantages of TEB devices include movement artefact, and inaccuracies in the setting of thoracic fluid overload, making the use of TEB devices unreliable in critically ill patients. Further inaccuracy arises in patients with valvular heart disease, intra-and extracardiac shunts and tachyarrhythmias (Moshkovitz et al, 2004).
Several studies have examined the validity of TEB techniques in the pregnant patient. Using the BoMed NCCOM3 device in a study of 9 patients requiring pulmonary artery catheterisation for peripartum management, good agreement was reported in 8 cases (+/- 20%) (Masaki et al., 1989). Fair agreement was found in a study of 15 patients with preeclampsia, comparing the BioZ device with echocardiographic M-mode estimates of CO (Scarido et al., 2000). In a comparison of the BoMed NCCOM3 device with oxygen extraction estimates of CO, good agreement was demonstrated. However bioimpedance estimates were only reliable in the lateral recumbent positions (Clark et al., 1994). In the field of obstetric anaesthesia, two studies have used whole body impedance cardiography during SA for CS (Tihtonen et al., 2005; Tihtonen, 2006). A further investigation employed a TEB device to demonstrate the haemodynamic effects of oxytocin during this procedure (Pinder et al., 2002). In healthy parturients for elective CS, the BioZ instrument was considered an appropriate device for comparison of short term trends in CO, in order to corroborate the results obtained from the LiDCOplus device in the setting of rapid changes in SVR (Chapters 5 and 7).

2.4. Research Ethics

All studies contributing to this thesis were conducted in keeping with ethical guidelines for research in obstetric anaesthesia (Yentis, 2001). Informed consent was obtained from all study participants. All studies were approved by the Ethics Committee of the University of Cape Town, Faculty of Health Sciences. In each case, the purpose of the study was explained to the patient in a sensitive manner, and relevant written information was supplied in English, Afrikaans or Xhosa. In the case of Xhosa speaking patients, trained translators fluent in Xhosa were present at the recruitment interviews, in order to ensure a full understanding of the study.

In one of the studies, there were time constraints on the recruitment, in that CS was urgent, but not an emergency. These patients were recruited immediately after the decision to proceed to operative delivery, in order to
allow the maximum time for an adequate explanation to the patient. In the case of recruitment of a patient in labour, consent was witnessed by a practitioner independent of the research. All patients recruited were assured that their participation was voluntary, and that declining to participate would in no way affect the quality of their management. Patients were also informed that all data would be handled anonymously and confidentially.
Chapter 3
A comparison between pulse wave form analysis and thermodilution cardiac output determination in patients with severe preeclampsia

3.1. Introduction

Validation of the LiDCO plus system is discussed in Chapter 2. There are no validation studies in the peripartum period. Indications for invasive monitoring in severe preeclampsia include pulmonary oedema, persistent oliguria, and hypovolaemic shock (American College of Obstetricians and Gynecologists, 1993; Martin and Foley, 2006). The pulmonary artery catheter (PAC) provides valuable haemodynamic data in this setting, in particular pulmonary capillary wedge pressure, CO, SVR and mixed venous oxygen saturation. A knowledge of these variables guides management decisions on fluid, diuretic and vasodilator therapy, which affect morbidity and mortality. The insertion of the PAC is however an invasive procedure, with well described complications, particularly in patients with thrombocytopaenia (Young and Johanson, 2001). It would thus be desirable to use a minimally invasive monitor of CO in this setting.

A prospective validation study was thus undertaken in patients who had had a PAC placed for the management of complications of severe preeclampsia in the immediate postpartum period. In view of the fact that only approximately 0.5% of patients with severe preeclampsia who are admitted to the Groote Schuur Hospital Maternity Unit require a PAC, the study period was 3 years, during which time 18 patients were recruited.
3.2. Patients and methods

After approval from the University of Cape Town Ethics Committee, informed written consent was obtained for the use of the LiDCOplus monitor in 18 patients in whom a PAC (Edwards Life Sciences, Irvine, CA, USA) had been introduced via the right internal jugular vein, to assist in the medical management of complicated severe preeclampsia. Arterial cannulation had been performed in all cases to assist blood pressure control and for arterial blood gas determinations, before recruitment into the study. The aim of the study was to establish the bias and limits of agreement between CO measurements using the two monitors, after central and peripheral venous calibration with lithium chloride. In addition, the comparison was continued in 8 patients for up to 4 hours after peripheral calibration, in order to establish whether there was a time-based effect necessitating re-calibration.

The protocol for the comparison between the CO measurements was as follows: During stable haemodynamic conditions (< 15% change in heart rate and MAP for 3 minutes), two calibrations, 5 minutes apart, were performed with 0.3 mmol lithium chloride administered via the central venous pressure port of the PAC. If the calibration factors differed by more than 15%, a third determination was performed, and the average calibration factor of the two closest readings used for subsequent beat by beat estimation of the CO from the LiDCOplus monitor. Four consecutive thermodilution (TD) determinations, one minute apart, were then performed via the central venous port of the PAC, using cold saline. The three closest values were averaged and recorded. This step was repeated twice at 15 minute intervals. At each epoch, the CO obtained from the TD measurements was compared with the mean of the LiDCOplus values averaged during the 30 seconds subsequent to the injection of the cold saline for the TD measurements. The LiDCOplus monitor was then re-calibrated by an identical method using lithium chloride injection via a forearm vein, and the comparison with the TD method repeated as described above. In addition, further comparisons were performed in 8 patients at 120 and 240 minutes after peripheral venous calibration.
**Statistical Analysis:**

A linear mixed effects regression model was used to examine the CO method (LiDCOplus and TD), calibration method (central and peripheral venous) and measurement time epochs, and the possible interactions of these factors. This model takes into account the repeated measurements done in each patient. The patient was specified as the random effect. The difference between methods at each time point or for pooled data was estimated by least square means based on the model specified. Since there was an interaction between CO method and calibration method, separate analyses were done for each route of calibration. The comparison between CO methods at 120 and 240 minutes after peripheral calibration also employed a linear mixed effects regression model and this analysis included all the measurement time epochs in all patients to improve precision and power.

The mean values for LiDCOplus and TD were compared during each measurement time epoch (0, 15 and 30 minutes). Using the method described by Bland and Altman for assessing agreement between measurement techniques (Bland and Altman, 1986), differences between LiDCOplus and TD CO determinations were plotted against the mean values for these pairs at each measuring point. The bias (mean difference) and limits of agreement (bias ± 2 SD of the difference) were determined and used to summarise the level of agreement between the methods.

### 3.3. Results

Eighteen patients were recruited during the period April 2006 – March 2009. These patients were admitted to the Special Care Unit at the Maternity Centre at Groote Schuur hospital, Cape Town with complications of severe preeclampsia. The indication for pulmonary artery catheterisation was a clinical diagnosis of pulmonary oedema in 13 cases. Two of these patients had abruptio placentae. The remaining 5 patients had oliguric renal failure. One of these was associated with severe Haemolysis, Elevated Liver Enzymes and Low Platelets (HELLP) syndrome, 3 with abruptio placentae and 1 with a ruptured uterus.
No patients were mechanically ventilated during the study. The median (range) time post-delivery at recruitment was 48 (24-96) hours.

Five patients required 3 central venous calibrations, and 6 required 3 peripheral venous calibrations. For central and peripheral lithium calibration, the data from 17 of 18, and 16 of 18 recruited subjects respectively, were analysed. In one exclusion, peripheral oedema precluded adequate flow for a peripheral calibration curve, and in the other, the arterial cannula was dislodged by a restless patient.

A description of mean values for the two CO methods at the specified measurement time epochs, appears in Table 3.1.
Table 3.1. Mean cardiac output values for each cardiac output method and calibration method at the specified measurement time epoch

<table>
<thead>
<tr>
<th>CO Method</th>
<th>Calibration method</th>
<th>Time (min)</th>
<th>N</th>
<th>Mean CO (L/min)</th>
<th>SD</th>
<th>Minimum</th>
<th>Maximum</th>
</tr>
</thead>
<tbody>
<tr>
<td>LiDCO</td>
<td>Peripheral</td>
<td>0</td>
<td>16</td>
<td>7.27</td>
<td>1.63</td>
<td>3.9</td>
<td>10.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>15</td>
<td>16</td>
<td>7.36</td>
<td>1.65</td>
<td>4.0</td>
<td>10.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>30</td>
<td>16</td>
<td>7.41</td>
<td>1.72</td>
<td>4.1</td>
<td>10.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>120</td>
<td>7</td>
<td>7.38</td>
<td>1.74</td>
<td>5.2</td>
<td>9.7</td>
</tr>
<tr>
<td></td>
<td></td>
<td>240</td>
<td>7</td>
<td>7.66</td>
<td>1.65</td>
<td>4.9</td>
<td>9.4</td>
</tr>
<tr>
<td>Central</td>
<td></td>
<td>0</td>
<td>17</td>
<td>7.16</td>
<td>1.48</td>
<td>3.6</td>
<td>9.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>15</td>
<td>16</td>
<td>6.87</td>
<td>1.38</td>
<td>3.6</td>
<td>8.9</td>
</tr>
<tr>
<td></td>
<td></td>
<td>30</td>
<td>17</td>
<td>7.00</td>
<td>1.49</td>
<td>3.7</td>
<td>9.1</td>
</tr>
<tr>
<td>TD</td>
<td>Peripheral</td>
<td>0</td>
<td>16</td>
<td>7.49</td>
<td>1.43</td>
<td>4.3</td>
<td>9.6</td>
</tr>
<tr>
<td></td>
<td></td>
<td>15</td>
<td>16</td>
<td>7.44</td>
<td>1.44</td>
<td>4.3</td>
<td>10.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>30</td>
<td>16</td>
<td>7.57</td>
<td>1.58</td>
<td>4.4</td>
<td>11.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>120</td>
<td>7</td>
<td>7.57</td>
<td>1.52</td>
<td>5.4</td>
<td>9.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>240</td>
<td>7</td>
<td>8.14</td>
<td>1.93</td>
<td>5.2</td>
<td>11.1</td>
</tr>
<tr>
<td>Central</td>
<td></td>
<td>0</td>
<td>17</td>
<td>7.75</td>
<td>1.52</td>
<td>4.2</td>
<td>9.2</td>
</tr>
<tr>
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<td>15</td>
<td>16</td>
<td>7.55</td>
<td>1.58</td>
<td>4.1</td>
<td>10.8</td>
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<td></td>
<td></td>
<td>30</td>
<td>17</td>
<td>7.47</td>
<td>1.44</td>
<td>4.3</td>
<td>9.8</td>
</tr>
</tbody>
</table>

There was no time based effect associated with the comparison between LiDCOplus and TD for the time epochs 0, 15 and 30 minutes after calibration. There was a significant difference between the comparisons between monitors, related to whether calibration was central or peripheral. For the comparison between TD and LiDCOplus employing central venous calibration, TD exhibited a significant positive bias. After peripheral venous calibration, there was no significant bias between the methods.

Since the bias or lack thereof was consistent with time, data were pooled for the epochs 0, 15 and 30 minutes. Scatter plots of individual CO measurements by LiDCOplus versus TD are shown in Figures 3.1. and 3.2., and Bland – Altman plots are depicted in Figures 3.3. and 3.4. The estimated
limits of agreement for central venous and peripheral venous calibration were -2.12 to 0.96 and -1.50 to 1.20 L/min respectively.
Figure 3.1. Scatter plot of individual cardiac output measurements at 0, 15 and 30 minutes post central venous calibration

Figure 3.2. Scatter plot of individual cardiac output measurements at 0, 15 and 30 minutes post peripheral venous calibration
Figure 3.3. Bland and Altman comparison between thermodilution and LiDCOplus after central venous calibration

Bias -0.58 L/min, 95% confidence interval: -2.12 to 0.96 L/min

Figure 3.4. Bland and Altman comparison between thermodilution and LiDCOplus peripheral venous calibration

Bias - 0.16 L/min, 95% confidence interval: -1.5 to 1.2 L/min
Of the 8 patients in whom the measurements were continued to 120 and 240 minutes after peripheral calibration, the data from 7 were analysed. (In one patient peripheral calibration was performed before central venous calibration, in error). Employing a linear mixed effects regression model, differences in mean CO at the specified measurement times, were derived (Table 3.2.). When comparing LiDCOplus and TD, there was no time based effect at 120 or 240 minutes post calibration. There was a significant time effect overall with the 0,15, and 30 minutes mean values being significantly lower than the CO mean at 240 minutes.

Table 3.2. Differences in cardiac output at the specified measurement time epochs (least squares means)

<table>
<thead>
<tr>
<th>Time</th>
<th>Difference in CO (LiDCO−TD)</th>
<th>P-value</th>
<th>95% CI lower</th>
<th>95% CI upper</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>−0.23</td>
<td>0.30</td>
<td>−0.65</td>
<td>0.20</td>
</tr>
<tr>
<td>15</td>
<td>−0.08</td>
<td>0.71</td>
<td>−0.51</td>
<td>0.35</td>
</tr>
<tr>
<td>30</td>
<td>−0.16</td>
<td>0.45</td>
<td>−0.59</td>
<td>0.27</td>
</tr>
<tr>
<td>120</td>
<td>−0.19</td>
<td>0.57</td>
<td>−0.84</td>
<td>0.46</td>
</tr>
<tr>
<td>240</td>
<td>−0.49</td>
<td>0.14</td>
<td>−1.14</td>
<td>0.16</td>
</tr>
<tr>
<td></td>
<td>−0.23*</td>
<td>0.06</td>
<td>−0.46</td>
<td>0.01</td>
</tr>
</tbody>
</table>

*Mean value over 5 measurement times
CI = confidence intervals

3.4. Discussion

This study is the first in the peripartum period to compare CO measurements obtained from TD, with central and peripheral lithium chloride calibration of the LiDCOplus device. In addition, the effect of time on the agreement between TD and LiDCOplus measurements after peripheral calibration, was examined.

Three studies in the non-obstetric population have examined the validity of the peripheral versus central venous route for calibration (Jonas et al, 1999; Garcia-Rodriguez et al, 2002; Mason et al, 2002). All showed good
correlation between CO measurements obtained after central and peripheral venous calibration. One investigation showed that there was better agreement between CO readings if the peripheral injection was made proximal to the wrist (Garcia-Rodriguez et al, 2002). In the present study, the first in the peripartum period, the peripheral calibration injection was done via a forearm vein. In only one patient was flow inadequate for calibration, due to severe peripheral oedema. At least two calibrations were performed via each route. This has recently been shown to improve the coefficient of variation to 6% and allows for the detection of a change of 17% between 2 measurements (Cecconi et al, 2009a).

The present investigation suggests that in the immediate postpartum period in preeclamptic patients, peripheral venous calibration is associated with an insignificant bias when compared with TD, and that bias is less than when calibration is via the central route. Results from a previous study differed in that CO measurements after both central and peripheral lithium calibration were lower than simultaneously obtained TD measurements, by 0.53 and 0.54 L/min respectively (Garcia-Rodriguez et al, 2002).

The absence of a time based effect when comparing the monitors for the first 4 hours after calibration, is in agreement with 2 publications from the non-obstetric literature (Hamilton et al, 2002; Pittman et al, 2005). A recent investigation in a small number of critically ill patients suggested that recalibration is required after 4 hours (Cecconi et al, 2008). In all the studies presented in this thesis, the CO monitoring period was less than 4 hours after calibration.

Current opinion is that a new CO technique should be accepted if the limits of agreement are up to 30% when compared with current reference methods (Critchley and Critchley, 1999). This study showed confidence intervals of \(-1.5 \sim 1.2\) L/min, which are very similar to those quoted in a recent study on post cardiac surgical patients, comparing LiDCOplus to continuous cardiac index monitoring via a pulmonary artery catheter (\(\pm 1.3\) L/min) (McCoy et al,
2009). For the average cardiac output in the region of 7 L/min in the present study population group, this is well within the 30% range. Although the confidence intervals are relatively wide, the very low bias when compared with the pulmonary artery catheter suggests that this form of pulse wave form analysis could be used in place of the more invasive monitor in the perioperative management of complicated severe preeclampsia. This is particularly relevant in view of recent literature suggesting that the measurement of central venous and/or pulmonary capillary wedge pressure is a poor guide to fluid volume responsiveness in critical care (Kumar et al, 2004).

The comparison between bioimpedance measurements and LiDCOplus in the setting of short term significant changes in vascular tone (Chapters 5 and 7), together with the data presented in this chapter, suggest that this form of pulse wave form analysis may be of great value both in obstetric anaesthesia research, and the management of critically ill obstetric patients. In situations when vascular tone is rapidly changing, trend measurements are of greater value than absolute values. During stable monitoring conditions, the results presented in this Chapter suggest adequate accuracy for the measurement of absolute values.
Chapter 4
Fluid management during spinal anaesthesia for caesarean section

4.1. Introduction

Although colloid is superior to crystalloid in the prevention of hypotension during SA for CS, its use has not been routinely adopted during CS, as discussed in Chapter 1. As described in the literature review, recent literature has questioned the value of traditional preloading techniques prior to the administration of SA for CS, and has suggested that such preloading is relatively ineffective in the prevention of hypotension or maintenance of cardiac output (Ueyama et al, 1999). Preload is rapidly redistributed and will have a relatively brief effect on CO, and a more rational approach might be to apply fluid loading at the time that the local anaesthetic block is starting to take effect. This might maximise the expansion of intravascular volume during vasodilatation from the local anaesthesia-induced sympathetic blockade and limit fluid redistribution and excretion. Therefore a study was designed to investigate the hypothesis that rapid administration of crystalloid at the time of induction of SA (coload) is associated with less hypotension than the administration of an equivalent volume of preload over 20 minutes. Of particular importance was the analysis of ephedrine requirements pre-delivery, the time period during which the risk of maternal hypotension and consequent fetal acidosis is greatest.

4.2. Patients and methods

The study was approved by the University of Cape Town Ethics Committee, and all patients gave written informed consent. Patients considered eligible for the study were those weighing less than 90kg without significant intercurrent disease (ASA 1 and 2 status), with a singleton pregnancy and presenting for elective CS under SA. Preeclamptic patients were excluded. Patients were kept nil by mouth from 22h00, and received cimetidine 400mg
orally on the night before surgery, and again 2 hours prior to surgery. On arrival in the operating theatre, 30mL of 0.3M sodium citrate was given. A 16 gauge intravenous line was placed, and modified ringers lactate solution warmed to a temperature of 38°C was used.

Patients were randomly allocated to receive either preload (Group P) or coload (Group C), according to an allocation card contained within a sealed envelope. After urinary catheterisation, patients were placed in the left lateral position, and initial non-invasive MAP (Dinamap™, Critikon) and HR measurements performed (Table 4.1.). The patient then received either a preload of 20 mL/kg of modified Ringer’s lactate (Group P) over a period of 20 minutes, or no fluid (Group C). One complete litre bag was infused; the exact fluid volume from the second bag was determined by prior removal of excess fluid into a measuring cylinder.

Immediately before starting SA, three MAP readings were taken in the left lateral position, with the cuff positioned at the level of the heart, at intervals of one minute. The average of the MAP (Table 4.1.) formed the baseline for later interventions. SA was induced in both groups using 0.5% hyperbaric bupivacaine 9mg and fentanyl 10µg (total volume 2.0mL) injected slowly over 20 seconds at the L3/4 level with a 25G Sprotte pencil-point needle (B Braun). At the time of identification of cerebrospinal fluid, Group C patients received an identical fluid load to that given to Group P of 20 mL/kg. A pressurised giving set was opened to the patient, to administer the fluid at the maximal possible rate. Patients in both groups were then positioned supine, with 15 degrees of left lateral tilt and no additional fluid was given other than a very slow infusion to ensure continued patency of the IV line.

Non-invasive blood pressure measurements were recorded in both groups at one minute intervals from the start of the regional block for the first 20 minutes, and then at 3 minute intervals until the completion of surgery. At least two further readings were taken 3 minutes apart after completion of surgery, and if ephedrine was still required, readings were continued until at
least ten minutes had passed without vasopressor. If surgery was concluded in less than 30 minutes, readings were continued each 3 minutes until at least 30 minutes or until no further vasopressor was required. Pulse oximetry and electrocardiograph monitors were also used.

The height of the sensory block was assessed using cold sensitivity to ethyl chloride spray. Surgery was allowed to proceed after a block to T6 had been established, and the block level at the end of surgery was also documented (Table 4.2.).

Interventions were as follows: If the mean arterial blood pressure decreased to less than 80% of the calculated baseline value, 5mg ephedrine doses were administered every minute until MAP recovered to within 80% of the starting value. If the blood pressure decreased to less than 70% of the calculated baseline value, 10mg boluses of ephedrine were administered until a return to within 80% of the baseline pressure occurred. Since there was a clearly pre-defined target MAP for vasopressor administration for each individual, the study was not blinded. In the event of excessive blood loss (>800 mL as assessed by suction bottle and weighing of swabs), the patient was to be removed from the trial and treated appropriately.

Time periods recorded were:
- Time from completion of baseline arterial pressure determination to induction of anaesthesia (CSF time)
- Induction to skin incision
- Induction to uterine incision time
- Uterine incision to delivery
- Duration of administration of calculated coload volume

At delivery all patients received 5IU of oxytocin IV, after which no ephedrine was administered within 3 minutes and no further oxytocin was given intra-operatively. Maternal urine output was noted, Apgar scores were recorded at 1 and 5 minutes, and umbilical arterial pH and base deficit were measured using an automated blood gas analyser.
Statistical Analysis:

Estimation of sample size was based on a pilot study in which fluid volume was used to assess the efficacy of the strategies in reducing the number of ephedrine doses administered. Power analysis, based on a 25% reduction in ephedrine requirement as a clinically valid endpoint, indicated that 20 patients per group were likely to be sufficient, so we included 25 subjects per group. The Null hypothesis was that there was no difference in ephedrine requirement. The primary outcome variable was the ephedrine dose requirement in the pre-delivery period.

A comparison of the number of patients in each group who did not require vasopressor employed the Fisher’s Exact Test. A between-group comparison of median ephedrine dose and median number of doses administered before and after delivery in each group used Kruskal-Wallis non-parametric ANOVA. For the purposes of this evaluation, each 5mg increment of ephedrine was regarded as a unit dose. The ephedrine dose administered at each time period, in each group, was analysed using ANOVA for repeated measures. Maternal haemodynamic recordings at the various time-points were compared using repeated measures ANOVA. Once significant differences between groups had been defined, individually significant data points were identified using Fisher's LSD test. Maternal age, height and weight were compared using a t-test, the level of block using a Mann Whitney U Test and neonatal acid-base data using unpaired Student’s t-tests.

Statistical significance was assumed at a P-value of <0.05.

4.3. Results

Demographic data and baseline blood pressures are presented in Table 4.1. No patients were withdrawn, leaving 25 patients in each group. There were no significant differences between groups with respect to demographic variables. Fluid loading resulted in no significant change in MAP in group P (1.6 (6.2) mmHg), and during the equivalent rest period in Group C there a
non-significant decrease (2.9 (5.2) mmHg). The target arterial pressures (baseline) to guide ephedrine administration were not significantly different.

Table 4.1. Demographic data, initial and baseline arterial pressures

<table>
<thead>
<tr>
<th></th>
<th>Preload (n = 25)</th>
<th>Coload (n = 25)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>26.8 (4.9)</td>
<td>27.4 (6.0)</td>
<td>0.32</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>73.3 (10.2)</td>
<td>66.8 (13.7)</td>
<td>0.89</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>156.6 (6.6)</td>
<td>158.4 (6.8)</td>
<td>0.16</td>
</tr>
<tr>
<td>Gravidity (median, range)</td>
<td>2(1-3)</td>
<td>2(1-5)</td>
<td>0.49</td>
</tr>
<tr>
<td>Parity (median, range)</td>
<td>1(0-3)</td>
<td>1(0-4)</td>
<td>0.60</td>
</tr>
<tr>
<td>Initial MAP (mmHg)</td>
<td>81.8 (7.6)</td>
<td>80.4 (9.4)</td>
<td>0.65</td>
</tr>
<tr>
<td>Baseline MAP (mmHg)</td>
<td>83.5 (8.9)</td>
<td>77.5 (9.4)</td>
<td>0.07</td>
</tr>
</tbody>
</table>

Values are mean (SD), unless stated

Data pertaining to fluid and anaesthesia management appear in Table 4.2. There were no between-group differences in crystalloid volume infused, in keeping with the study design. The coload was administered over a significantly shorter period of time, according to protocol (20 vs. 9.8 minutes, P-value = 0.01). There were no between-group differences in any of the other clinically relevant time intervals recorded. Two patients in each group experienced nausea. Neonatal data were similar (Table 4.3.).
Table 4.2. Fluid and anaesthesia data

<table>
<thead>
<tr>
<th></th>
<th>Preload</th>
<th>Coload</th>
<th>( P )-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Volume infused (mL)</td>
<td>1474(206)</td>
<td>1386(177)</td>
<td>0.13</td>
</tr>
<tr>
<td>Duration of infusion (min)</td>
<td>20(0)</td>
<td>9.8(4)</td>
<td>0.01</td>
</tr>
<tr>
<td>CSF Time (min)</td>
<td>4.8(2.0)</td>
<td>5.2(3.5)</td>
<td>0.58</td>
</tr>
<tr>
<td>Induction to skin incision (min)</td>
<td>7.0(1.9)</td>
<td>7.6(2.3)</td>
<td>0.39</td>
</tr>
<tr>
<td>Induction to uterine incision (min)</td>
<td>11.6(3.8)</td>
<td>13.1(3.8)</td>
<td>0.16</td>
</tr>
<tr>
<td>Uterine incision to delivery (min)</td>
<td>1.3(0.8)</td>
<td>1.4(0.6)</td>
<td>0.76</td>
</tr>
<tr>
<td>Duration of anaesthesia (min)</td>
<td>31(11)</td>
<td>34(7)</td>
<td>0.23</td>
</tr>
<tr>
<td>Duration of surgery (min)</td>
<td>24(10)</td>
<td>27(7)</td>
<td>0.34</td>
</tr>
<tr>
<td>Block height (median (range))</td>
<td>T3(T1-T6)</td>
<td>T4(T2-T5)</td>
<td>0.09</td>
</tr>
<tr>
<td>Blood loss (mL)</td>
<td>351(87)</td>
<td>382(101)</td>
<td>0.25</td>
</tr>
<tr>
<td>Urine output (mL)</td>
<td>223(100)</td>
<td>173(89)</td>
<td>0.07</td>
</tr>
</tbody>
</table>

Values are mean (SD), unless stated

Table 4.3. Neonatal data

<table>
<thead>
<tr>
<th></th>
<th>Preload</th>
<th>Coload</th>
<th>( P )-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neonatal weight (g)(mean (SD))</td>
<td>2969(426)</td>
<td>3140(534)</td>
<td>0.28</td>
</tr>
<tr>
<td>Apgar score 1 minute (median(range))</td>
<td>9 (5-9)</td>
<td>9 (6-9)</td>
<td>0.96</td>
</tr>
<tr>
<td>Apgar score 5 minutes (median(range))</td>
<td>10 (9-10)</td>
<td>10 (9-10)</td>
<td>0.82</td>
</tr>
<tr>
<td>Umbilical arterial pH (range)</td>
<td>7.34 (7.21-7.4)</td>
<td>7.35 (7.28-7.42)</td>
<td>0.76</td>
</tr>
<tr>
<td>Umbilical arterial base deficit (mmol/L)(median (range))</td>
<td>0.32 (-4.9-4.5)</td>
<td>1.11 (-6-1.9)</td>
<td>0.99</td>
</tr>
</tbody>
</table>

There were significant differences between groups in MAP at 7, 8 and 9 minutes after the induction of SA (Figure 4.1.). Results for vasopressor management appear in Table 4.4. The median cumulative dose of ephedrine required by Group C was significantly lower in the pre-delivery period (0 [0-10] vs. 10 [0-20] mg, \( P \)-value = 0.03). There were no significant differences between groups post-delivery or for total dose.
There was no significant difference between groups in the median number of unit doses of ephedrine required ($P$-value = 0.054), but Group C required a significantly lower number of unit doses pre-delivery (0 vs. 2, $P$-value = 0.04) (Figure 4.2). There were significant between group differences in the dose used at 2, 3, 4 and 6 minutes post induction of anaesthesia (Figure 4.3). Significantly more patients in Group C did not require ephedrine in the pre-delivery period ($P$-value = 0.047). There was a trend to more patients in Group C not requiring vasopressor during the entire procedure ($P$-value = 0.057) (Table 4.4.).

Both groups showed an increase in HR with fluid loading. In Group P, the mean maximum increase in HR (22.3 +/-19.8 beats per minute) occurred 4 minutes after the end of fluid administration. In Group C, the mean maximum increase (16.2 +/- 16.1 beats per minute) occurred at 7 minutes after commencement of the fluid load. From 8 minutes after induction of anaesthesia, the increase in HR did not differ from baseline value in either group.
Figure 4.1. Mean (SD) arterial pressure during study period

Pre = Mean arterial pressures prior to fluid loading
Post = Mean arterial pressures prior to the performance of SA
*P-value < 0.05

Table 4.4. Vasopressor management

<table>
<thead>
<tr>
<th></th>
<th>Preload</th>
<th>Coload</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ephedrine cumulative dose (mg)</td>
<td>20(10-30)</td>
<td>5(0-20)</td>
<td>0.052</td>
</tr>
<tr>
<td>Pre-delivery (mg)</td>
<td>10(0-20)</td>
<td>0(0-10)</td>
<td>0.03</td>
</tr>
<tr>
<td>Post-delivery (mg)</td>
<td>5(5-15)</td>
<td>0(0-15)</td>
<td>0.49</td>
</tr>
<tr>
<td>Ephedrine total number of unit doses</td>
<td>4(0-15)</td>
<td>1(0-12)</td>
<td>0.054</td>
</tr>
<tr>
<td>Ephedrine unit doses pre-delivery</td>
<td>2(0-13)</td>
<td>0(0-5)</td>
<td>0.04</td>
</tr>
<tr>
<td>Number of patients not requiring ephedrine pre-delivery</td>
<td>9/25</td>
<td>16/25</td>
<td>0.047</td>
</tr>
<tr>
<td>Number of patients not requiring ephedrine for entire procedure</td>
<td>4/25</td>
<td>10/25</td>
<td>0.057</td>
</tr>
</tbody>
</table>

Values are median (interquartile range)
Figure 4.2. Ephedrine doses pre-delivery

Figure 4.3. Ephedrine dose (mg) at each time point

*P-value < 0.05 (adjusted for multiple comparisons)
4.4. Discussion

This study found that, in the pre-delivery period when the parturient is most at risk for hypotension after SA, patients receiving a rapid crystalloid infusion immediately after the induction of anaesthesia (coload), required significantly less ephedrine than those receiving a conventional preload. This was represented by a reduction in both the cumulative mean and number of unit doses of ephedrine administered. In addition, more of these patients required no ephedrine pre-delivery.

The physiological objective during SA for CS is the maintenance of CO, and more specifically uteroplacental blood flow, although blood pressure is usually used as a surrogate index of CO. A judicious combination of fluid loading and vasopressor therapy appears the most logical method of obtaining this objective.

Current methods of crystalloid loading have in general been ineffective in the prevention of hypotension, and the concept of preloading has been called into question (Pouta et al, 1996b; Rout et al, 1999; Morgan et al, 2001). One study concluded that preloading only reduced the incidence of hypotension from 71% to 55% when compared with patients receiving no preload (Rout et al, 1993b). The authors recommended delay for the purpose of administration of a preload is not justified before elective CS.

As discussed in Chapter 1, colloid solutions are more effective in the prevention of hypotension. This is due to the fact that colloid solutions are not as rapidly redistributed to the extracellular compartment, thus better maintaining intravascular volume and hence CO. Significant increases in central venous pressure have been noted after both crystalloid and colloid preloading (Karinen et al, 1995), but there have been no reports of pulmonary oedema in any study (Morgan et al, 2001).
In an evaluation of the duration of infusion of a crystalloid preload prior to SA for CS, increases in HR were less, and HR returned to baseline in a shorter period in patients receiving their preload over 10 minutes than over 20 minutes (Rout, 1992a). This suggested a benefit in administering the fluid closer to the time of induction of SA. In the current study, HR changes were similar to those described above, in that there was a rapid onset of a lesser increase in HR with a shorter duration in patients who received their fluid load over a shorter time period, after induction of anaesthesia (Group C).

In the non-obstetric population, a sustained rise in CO was demonstrated in a group of patients given lactated ringer’s solution after the initiation of SA (Kamenik and Paver-Erven, 2001). A kinetic analysis of an IV infusion of Ringer’s lactate solution as preload, suggested that a rapid fluid administration over 2 minutes after induction of both spinal and general anaesthesia for non-obstetric surgery, might prevent hypotension caused by central hypovolaemia (Ewaldsson and Hahn, 2005). A study of the timing of fluid loading in general and specialty surgery patients, excluding pregnant women, reported no difference in the incidence of hypotension between groups given no fluid, a fluid preload over 20 minutes, or an identical fluid load at the time of spinal blockade. However, there was a reduction in the incidence of side effects attributable to cardiovascular instability following fluid loading coincident with induction of SA, while administration of crystalloid prior to the performance of the block failed to prevent these side effects (Mojica et al, 2002).

In keeping with clinical practice and the aforementioned study (Mojica et al, 2002), baseline blood pressure in the current study was measured immediately before the initiation of SA. Immediately following preload, there was a small increase in MAP in Group P, while Group C showed a slight decline in pressure during the rest period. However, the target blood pressures were not significantly different. There were no significant differences between groups in MAP for the first 6 minutes after induction of SA (during which period significantly more ephedrine was administered to the preload group [Figure 4.4.]). The arterial pressure was statistically significantly, lower in the coload group over a three-minute period from 7 to 9
minutes, but this was not clinically relevant. This confirms that less ephedrine was required pre-delivery in the coload group in order to maintain similar blood pressure to the preload group.

This study suggests that, in comparison with the prior administration of an identical fluid load, there is a maternal advantage in administering crystalloid rapidly at the time of induction of SA. In the absence of a control group receiving no intravenous fluid loading, it is possible that the results may be no better than if no preload were given. The rapid redistribution of a crystalloid preload implies that the most logical time to give such fluid is at the time of maximal risk of hypotension, which is immediately after the performance of the spinal anaesthetic. The diminution of benefit after delivery in the coload group may reflect this redistribution of crystalloid during this period. The delayed increased requirement for ephedrine in the coload group is not of clinical concern, since it occurs after delivery.

Neonatal umbilical arterial pH values were similar and base deficit values within normal limits in both groups. The good pH status of the neonates at delivery (pH values higher than in a recent meta-analysis of neonatal blood gas values [Lee et al, 2002]), may reflect the fact that only healthy parturients with no co-morbidity were studied, and that the induction to delivery and uterine incision to delivery times were short. It is noteworthy that there were no between-group differences in this study, despite a higher ephedrine requirement in the coload group.

In conclusion, an equivalent volume of crystalloid administered rapidly, immediately after the performance of SA for elective CS, is associated with a lower pre-delivery requirement for the vasopressor ephedrine than conventional preload. The technique of coloading did not appear to disadvantage the neonate. In view of the fact that colloid has not been universally adopted for the reasons discussed, crystalloid coloading appears the best option for fluid administration during elective CS.
Chapter 5
Haemodynamic effects of spinal anaesthesia and vasopressors during elective caesarean section

5.1. Introduction

Anaesthesiologists conventionally use HR and noninvasive blood pressure recordings, as well as patient symptoms, to assess patient wellbeing during SA for elective CS. Vasopressors are used to restore blood pressure to baseline values. However, both from the maternal and fetal point of view, the preservation of CO may be as important. A complete understanding of the haemodynamic responses to SA and to the administration of vasopressors would thus be of importance in the appropriate choice of vasopressor and dose in this clinical situation.

The greater degree of neonatal acidosis and higher incidence of maternal side-effects, particularly nausea and vomiting, associated with the use of ephedrine, has led to a change in practice and a resurgence of the use of phenylephrine for spinal hypotension (Macarthur and Riley, 2007). There have been very few investigations comparing the effects of the two vasopressors on maternal cardiovascular indices other than HR and blood pressure, during SA for CS. Only three previously published studies, employing intermittent suprasternal Doppler flow measurements, have compared CO changes using the two vasopressors. In the first, which compared bolus doses of the vasopressors, bradycardia in the phenylephrine group was treated with atropine, which makes the results difficult to interpret (Thomas et al, 1996). The primary outcome variable in this study was umbilical artery pH, and not maternal haemodynamic changes. The second study, employing infusions of vasopressors, suggested that phenylephrine
may depress maternal CO (Ashpole et al 2005). Most recently, phenylephrine infusions at 100 μg/minute were shown to reduce maternal CO by 20% (Stewart et al, 2008). There have been no investigations employing beat by beat CO measurements. Such measurements would give an exact description of the temporal framework of haemodynamic changes following the administration of the two vasopressors. There is currently a situation of equipoise with regards to the use of the two vasopressors, as far as the restoration of maternal blood pressure is concerned. The hypothesis was that phenylephrine, but not ephedrine, decreases CO when administered in response to hypotension during SA for CS. Phenylephrine might be the better agent to restore SVR to normal where hypotension is associated with vasodilatation and a partial compensatory increase in CO in response to SA (Langesaeter et al, 2008). Ephedrine may be preferable when marked hypotension and bradycardia occur, indicating a decrease in CO. The goal of management should be to maintain baseline maternal cardiac output and thus maintain blood pressure.

The primary outcome of this prospective randomised, double blind study was thus a comparison of the time based effects on maternal CO of bolus administration of the vasopressors phenylephrine and ephedrine during SA for CS. The LiDCO plus monitor was employed for the study. In addition, a monitor of transthoracic bioimpedance changes was also used in each patient, in order to corroborate the results (see Chapter 2).

Secondary outcomes were the effects of SA on maternal haemodynamics, a comparison of the effects of oxytocin on maternal CO as measured by the two monitors, and the effects of the co-administration of phenylephrine with oxytocin, in obtunding the unwanted haemodynamic effects of oxytocin. The oxytocin effects are described in Chapter 7. Also recorded were neonatal Apgar scores, umbilical arterial and venous pH, and base deficit.
5.2. Patients and Methods

The study was prospective, randomised and double blind. Forty three healthy patients scheduled for elective CS under SA were randomised to receive either phenylephrine (Group P) or ephedrine (Group E) as the initial vasopressor for the management of hypotension during SA. Randomisation was performed at the time at which a vasopressor was first required. Blocked randomisation was used (randomized block sizes of 4, 6 or 8, using nQuery Advisor Version 6, Statistical Solutions, Cork, Ireland), and sealed envelopes were prepared by the statistician. The trigger for vasopressor administration was defined as a 20% decrease from baseline MAP, at any time during the 45 minutes post induction of SA other than during the delivery and for the 3 minutes thereafter. In addition, a subgroup of 20 consecutive patients who had not received prior ephedrine were randomised to receive either oxytocin alone or oxytocin mixed with phenylephrine IV, after delivery. The flow diagram of the protocol is shown in Figure 5.1.

Exclusions were anaemia (Hb < 9g%), expected blood loss more than 700mL, body mass index greater than 35 kg/m², multiple gestation, preeclampsia, cardiac, respiratory or renal disease, known allergy to any protocol medication, or age below 18 years or above 40 years. Written informed consent was obtained after approval from the University of Cape Town Ethics Committee (Cape Town, Western Cape, South Africa). Technical failure or inadequate anaesthesia requiring conversion to general anaesthesia would result in inclusion in the analysis of only the data collected before the time of the decision to proceed with general anaesthesia.

A detailed consent form was supplied to the patient the day before CS, and the procedure was explained to the patient either by the recruiting investigator, or by a skilled translator. Consent was signed a minimum of 12 hours after the information sheet had been discussed with the patient. Height (cm) and weight (kg) were measured and body mass index calculated.
Sodium citrate 30mL was given orally immediately preoperatively. Prior to SA, intravenous access was established employing a 16G cannula, under local anaesthesia, and cefazolin 1g was slowly administered IV. Standard non-invasive monitoring consisted of electrocardiography and pulse oximetry. CO measurements were derived from two independent monitors in each patient. Transthoracic bioimpedance changes were monitored using the BioZ instrument (Cardio Dynamics International, San Diego, CA, USA). For this purpose, 4 pairs of bioimpedance electrodes were placed, 2 pairs opposite each other in the lower anterior cervical region, and 2 pairs in the 8th to 11th thoracic interspace in the midaxillary line. A 20 G radial arterial catheter was then placed under local anaesthesia. The LiDCOplus monitor was then calibrated using lithium dilution, employing at least 2 but not more than 3 separate determinations, 5 minutes apart. The average calibration factor was calculated and entered. Data from each consecutive pulse wave form were recorded on an Excel chart, from 5 minutes before SA until the end of surgery, or until 45 minutes after induction of anaesthesia, if the duration of surgery was less than 45 minutes. Recorded data consisted of HR, systolic, diastolic and MAP, and CO. Central venous pressure was given an arbitrary value of 5mm Hg, for the purposes of calculation of SVR. CO measurements derived from bioimpedance changes during left ventricular ejection, were averaged every 10 beats and recorded every 5 seconds on an Excel chart. Beat by beat SV estimates and CO were derived from the LiDCOplus monitor using the proprietary algorithm. The time-base for the two monitors was synchronized.

Baseline pulse wave form- and bioimpedance-derived data were recorded and averaged during a continuous 2 minute period prior to sitting up for SA, with the patient in the left lateral position. During this period, baseline MAP was also recorded. Baseline MAP was taken as the mean of three consecutive readings at least 45 seconds apart, not differing from one another by more than 10 percent. The target MAP (80% of baseline) for vasopressor administration was calculated from this baseline value.
The management of SA was as follows. Modified Ringer’s lactate solution 20 mL/kg was administered as a rapid crystalloid coload, initiated after cerebrospinal fluid appeared in the hub of the spinal needle. Less than 100mL of crystalloid solution was administered thereafter unless blood loss, estimated from suction bottle measurement and inspection of swabs, was excessive, in which case the patient would be excluded from treatment via the trial protocol, and would be treated as per the usual protocol for blood loss. All patients received 2.0mL of hyperbaric 0.5% bupivacaine (10mg), plus 10µg of fentanyl, administered over 20 seconds at the L3/4 interspace. After 20 seconds in the sitting position, patients were positioned supine, with at least 15 degrees of left lateral tilt, to minimize aortocaval compression. Block height was assessed using cold sensitivity to ethyl chloride spray. No supplemental oxygen was administered unless oxygen saturation decreased to less than 92%.

The anaesthesiologist, blinded to the LiDCO plus and BioZ measurements, responded to HR and MAP changes as is normal clinical practice during SA for CS. One 5mL syringe containing the randomly assigned vasopressor, and another containing the alternative vasopressor (i.e. either phenylephrine 80 µg/mL, or ephedrine 10 mg/mL in water) were prepared by an anaesthesiologist not involved with the intraoperative management. If MAP decreased by 20% from the baseline value, 1mL of the randomly assigned vasopressor was administered every 60 seconds until MAP recovered to within 20% of baseline. Randomisation would thus only be done at the point when a vasopressor intervention was indicated.

Should MAP continue to decrease to 40% below baseline after 45 seconds, a rescue dose of the same vasopressor would be given. Should MAP not be restored to within 20% of baseline after 2 successive doses of vasopressor within 2 minutes, the alternative vasopressor would be used, according to the same protocol. The anaesthesiologist performing SA was blinded to the vasopressor used. Should HR decrease to less than 55 beats per minute in association with severe hypotension (30% below baseline), atropine 0.5mg and ephedrine 10mg would be administered. In the event of severe
hypotension unresponsive to atropine and ephedrine, adrenaline would be administered in titrated boluses. After a total of 5 doses of the same vasopressor, if MAP again decreased by more than 20% of baseline, the alternative vasopressor was used. No patient was to be given more than 5 doses of ephedrine (50mg), since this would be interpreted as tachyphylaxis.

Thirty seconds after delivery, 2.5IU of oxytocin in 10mL water, was administered IV over a period of 30 seconds, to all patients receiving ephedrine prior to delivery, and to all other patients except for a subgroup of 20 consecutive patients not having received ephedrine prior to delivery. These 20 patients were randomised to receive IV either 2.5IU of oxytocin, or 2.5IU of oxytocin mixed with 80µg phenylephrine in 10mL water. All data pertaining to oxytocin administration are presented in Chapter 7.

Intraoperative blood loss was estimated from suction bottle measurements and inspection of swabs. Neonatal Apgar scores, umbilical arterial and venous pH and base deficit, and neonatal weight were recorded.

**Statistical Analysis**

The primary outcome variable was the change in CO in response to the initial dose of vasopressor. A pilot study in our institution employing the LiDCOplus monitor, involving the use of ephedrine and phenylephrine during SA for CS in patients with severe preeclampsia, suggested that a between-group difference in mean CO change would approximate 0.4 L/minute. A sample size of 17 in each group would have 80% power to detect a difference in means of 0.4 L/minute, assuming that the common standard deviation was 0.4L using a two group t-test with a 0.05 two-sided significance level. Since it was expected that only 70% of the women undergoing elective CS would require a vasopressor, the study would aim to recruit a minimum of 50 women.

Pre-vasopressor values were taken as the mean value for the period 30 seconds before vasopressor administration. Peak effect was taken as the mean value for the 5 seconds before and after the time of maximum change in CO value recorded in the 150 seconds after vasopressor administration. The
mean absolute CO was calculated as the average CO over 150 seconds following vasopressor administration. The peak and mean percentage change from pre-vasopressor values for each vasopressor were calculated. CO changes were related to both the pre-vasopressor value and the baseline value. The area under the curve for this period was also calculated and compared between vasopressors. The correlation between percentage change in peak CO and HR was compared using a linear regression model. The slopes of the group-specific regression lines of CO on HR were compared.

A secondary outcome was the response to SA. The haemodynamic response to SA was estimated comparing the haemodynamic measurements at baseline with those at the pre-vasopressor time interval in patients receiving vasopressor pre-delivery, or with average values for the 30 second period immediately prior to uterine incision, if no pre-delivery vasopressor was required.

The 2-sample t-test was used for comparison of all the haemodynamic parameters. The estimated mean difference and the 95% confidence intervals were reported. To account for the multiple testing performed, the false discovery rate was controlled by applying the method of Benjamini and Hochberg (Benjamini and Hochberg, 1995). The required $P$-value limit was calculated for the main and the sub-study and these bounds are indicated in the legends of the tables reporting the inference results.

To depict the summary profile of the response to vasopressor or oxytocin administration in the two groups a median smooth was used. This approach gave an estimate that was robust to extreme values and sensitive to acute changes in haemodynamic variables. These were presented as graphic ensembles.

The influence of the administration of vasopressor before or after delivery was formally evaluated by a regression analysis which included the vasopressor, timing and interaction effects for the mean and percentage peak values of the
haemodynamic parameters CO and HR during the 150 seconds after vasopressor administration.

Using the method described by Bland and Altman (Bland and Altman, 1986) for assessing agreement between measurement techniques, the bias (mean difference) and limits of agreement (bias +/- 2 SD) between CO measured by LiDCOplus and transthoracic bioimpedance technology were determined and used to summarize the level of agreement between the methods. CO was compared under baseline conditions, immediately prior to uterine incision and after delivery. The first time interval was taken as averaged CO data for the two minute period during baseline measurements, until 30 seconds before the patient sat up for SA. The second period was taken as averaged data for the 30 seconds prior to uterine incision, and the third employed averaged data for one minute, starting at 40 minutes after performance of SA. The analysis was based on all the women recruited into the study. All statistical analysis was performed using SAS Version 12 (SA Institute Inc., Cary, NC).

5.3. Results

Forty three patients were recruited to this prospective randomized study, between 20th November 2007 and 11th March 2008. The initial power analysis assumed that 70% of patients would require a vasopressor. Thus 50 patients would have been required in order to randomize 34 patients to vasopressor treatment. In fact only 3 patients of the first 43 did not require vasopressor, so that the study could be concluded at this point, with 20 patients in each treatment group at this time. The primary outcome data of two patients in Group E could not be used. One computer file was corrupted, and in the other, persistent vomiting prior to vasopressor administration necessitated the omission of the data. Thus the final analysis of the primary outcome data compared 20 patients in Group P with 18 patients in Group E. No patients received both vasopressors pre-delivery. In Group E, 9/18 and in Group P, 12/20 patients in the final analysis received the first dose of vasopressor pre-delivery (Figure 5.1.).
In Group P, 13 patients required ephedrine post-delivery, and in Group E, 6 patients required phenylephrine post-delivery as per protocol. Vasopressor use is summarized in Table 5.1.
### Table 5.1. Details of vasopressor use

<table>
<thead>
<tr>
<th></th>
<th>Group E (N = 20)</th>
<th></th>
<th>Group P (N = 20)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>Dose (mg)</td>
<td>Range</td>
<td>n</td>
</tr>
<tr>
<td>Ephedrine Pre (mg)</td>
<td>9</td>
<td>22.2</td>
<td>10-40</td>
<td>0</td>
</tr>
<tr>
<td>Ephedrine Post (mg)</td>
<td>18</td>
<td>21.7</td>
<td>10-50</td>
<td>13</td>
</tr>
<tr>
<td>Phenylephrine Pre (µg)</td>
<td>0</td>
<td>0</td>
<td>-</td>
<td>12</td>
</tr>
<tr>
<td>Phenylephrine Post (µg)</td>
<td>6</td>
<td>293.3</td>
<td>80-640</td>
<td>20</td>
</tr>
</tbody>
</table>

Demographic and relevant data pertaining to anaesthesia, surgery and neonatal outcome appear in Table 5.2. Considering patients receiving vasopressor pre-delivery, there were significant between-group differences in standard bicarbonate, umbilical arterial base excess and umbilical arterial PO$_2$. There were no other between-group differences and no patients required analgesic supplementation. The occurrence of nausea and vomiting was recorded after the first vasopressor administered. This occurred in 4 patients who received ephedrine as the initial vasopressor and 2 patients who receive phenylephrine (ns).

The primary outcome of this study was a comparison of the change in CO following the first administration of ephedrine or phenylephrine in response to hypotension. Tables 5.3. and 5.4. show haemodynamic data at baseline, at the time of randomisation to the vasopressor (i.e. at target mean arterial blood pressure, or 80% of baseline), and following vasopressor administration. There were no significant between group differences in any measure either at baseline or prior to vasopressor administration except for a small baseline difference in the CO as measured by the BioZ system.
Table 5.2. Demographic and relevant data pertaining to anaesthesia, surgery and neonatal outcome

<table>
<thead>
<tr>
<th></th>
<th>Group E</th>
<th></th>
<th>Group P</th>
<th></th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean/Median</td>
<td>SD/Range</td>
<td>Mean/Median</td>
<td>SD/Range</td>
<td></td>
</tr>
<tr>
<td>Height (cm)</td>
<td>158.4</td>
<td>6.5</td>
<td>156.6</td>
<td>5.7</td>
<td>ns</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>76.9</td>
<td>11.8</td>
<td>73.7</td>
<td>11.8</td>
<td>ns</td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>26.4</td>
<td>4.1</td>
<td>27.1</td>
<td>3.7</td>
<td>ns</td>
</tr>
<tr>
<td>Gravidity (n)</td>
<td>2</td>
<td>1-4</td>
<td>2</td>
<td>1-4</td>
<td>ns</td>
</tr>
<tr>
<td>Parity (n)</td>
<td>1</td>
<td>0-2</td>
<td>1</td>
<td>0-2</td>
<td>ns</td>
</tr>
<tr>
<td>Uterine incision (sec)</td>
<td>917</td>
<td>185</td>
<td>940</td>
<td>226</td>
<td>ns</td>
</tr>
<tr>
<td>Delivery (sec)</td>
<td>73</td>
<td>28</td>
<td>86</td>
<td>33</td>
<td>ns</td>
</tr>
<tr>
<td>Coload Volume (mL)</td>
<td>1537</td>
<td>234</td>
<td>1480</td>
<td>264</td>
<td>ns</td>
</tr>
<tr>
<td>Coload Time (sec)</td>
<td>1274</td>
<td>435</td>
<td>1259</td>
<td>416</td>
<td>ns</td>
</tr>
<tr>
<td>Block Height</td>
<td>T3</td>
<td>T2-T5</td>
<td>T3</td>
<td>T2-T5</td>
<td>ns</td>
</tr>
<tr>
<td>Blood loss (mL)</td>
<td>398</td>
<td>44</td>
<td>378</td>
<td>30</td>
<td>ns</td>
</tr>
<tr>
<td>Apgar 1 min</td>
<td>9</td>
<td>7-10</td>
<td>9</td>
<td>9</td>
<td>ns</td>
</tr>
<tr>
<td>Apgar 5 min</td>
<td>9</td>
<td>9-10</td>
<td>9.5</td>
<td>10</td>
<td>ns</td>
</tr>
<tr>
<td>UA pH *</td>
<td>7.28</td>
<td>0.06</td>
<td>7.34</td>
<td>0.04</td>
<td>ns</td>
</tr>
<tr>
<td>UA PCO₂ * (kPa)</td>
<td>6.5</td>
<td>1.8</td>
<td>7.0</td>
<td>1.1</td>
<td>ns</td>
</tr>
<tr>
<td>UA PO₂ * (kPa)</td>
<td>2.0</td>
<td>0.5</td>
<td>1.6</td>
<td>0.4</td>
<td>0.049</td>
</tr>
<tr>
<td>UA SBC * (mmol/L)</td>
<td>18.8</td>
<td>2.2</td>
<td>21.3</td>
<td>2.4</td>
<td>0.036</td>
</tr>
<tr>
<td>UA Base excess * (mmol/L)</td>
<td>-4.7</td>
<td>3.0</td>
<td>-1.3</td>
<td>3.1</td>
<td>0.025</td>
</tr>
</tbody>
</table>

Delivery = Time from uterine incision to delivery
PCO₂ = partial pressure of carbon dioxide
PO₂ = partial pressure of oxygen
SBC = Standard bicarbonate
UA = umbilical arterial
Uterine incision = time from induction of spinal anaesthesia to uterine incision
* Data pertain to patients who received vasopressor pre-delivery
(n = 9 in Group E, n = 12 in Group P)
Table 5.3. Baseline and pre-vasopressor haemodynamics

<table>
<thead>
<tr>
<th></th>
<th>Group E (n = 18)</th>
<th>Group P (n = 20)</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR Beats/min</td>
<td>83.6</td>
<td>80.4</td>
<td>3.2</td>
<td>-3.5</td>
</tr>
<tr>
<td>MAP mmHg</td>
<td>90.5</td>
<td>91.5</td>
<td>-1.0</td>
<td>-7.9</td>
</tr>
<tr>
<td>SV mL/beat</td>
<td>73.7</td>
<td>73.5</td>
<td>0.2</td>
<td>-10.7</td>
</tr>
<tr>
<td>SVR Dyne.sec.cm⁻⁵</td>
<td>1177.5</td>
<td>1241.2</td>
<td>-63.7</td>
<td>-253.0</td>
</tr>
<tr>
<td>CO(LiDCO) L/min</td>
<td>6.2</td>
<td>5.8</td>
<td>0.4</td>
<td>-0.6</td>
</tr>
<tr>
<td>CO(BioZ) L/min</td>
<td>5.3</td>
<td>4.6</td>
<td>0.7</td>
<td>0.1</td>
</tr>
<tr>
<td><strong>Pre-vasopressor</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR Beats/min</td>
<td>91.7</td>
<td>91.5</td>
<td>0.1</td>
<td>-10.1</td>
</tr>
<tr>
<td>MAP mmHg</td>
<td>71.8</td>
<td>72.8</td>
<td>-1.0</td>
<td>-5.7</td>
</tr>
<tr>
<td>SV mL/beat</td>
<td>85.7</td>
<td>80.2</td>
<td>5.5</td>
<td>-6.8</td>
</tr>
<tr>
<td>SVR Dyne.sec.cm⁻⁵</td>
<td>746.1</td>
<td>782.6</td>
<td>-36.5</td>
<td>-184.1</td>
</tr>
<tr>
<td>CO(LiDCO) L/min</td>
<td>7.9</td>
<td>7.2</td>
<td>0.7</td>
<td>-0.6</td>
</tr>
<tr>
<td>CO(BioZ) L/min</td>
<td>6.1</td>
<td>5.7</td>
<td>0.5</td>
<td>-0.4</td>
</tr>
</tbody>
</table>
CI = confidence interval
CO (LiDCO) and CO (BioZ) = cardiac output derived using the LiDCOplus and BioZ monitors respectively
HR = heart rate
MAP = mean arterial pressure
Pre-vasopressor = haemodynamic values prior to the first administration of either vasopressor (at time of randomisation)
SV = stroke volume, derived from the LiDCOplus monitor
SVR = systemic vascular resistance
Table 5.4. Haemodynamic response to vasopressor administration

<table>
<thead>
<tr>
<th></th>
<th>Group E (n=18)</th>
<th>Group P (n=20)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
</tr>
<tr>
<td>Post-vasopressor</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>absolute</td>
<td>Beats/min</td>
<td>92.4</td>
<td>12.4</td>
</tr>
<tr>
<td>auc</td>
<td>Beats/min</td>
<td>59.9</td>
<td>812.7</td>
</tr>
<tr>
<td>peak</td>
<td>Beats/min</td>
<td>97.2</td>
<td>13.3</td>
</tr>
<tr>
<td>percent-peak</td>
<td>%</td>
<td>7.0</td>
<td>14.8</td>
</tr>
<tr>
<td>time to peak</td>
<td>Sec</td>
<td>66.3</td>
<td>37.2</td>
</tr>
<tr>
<td>MAP</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>absolute</td>
<td>mmHg</td>
<td>78.2</td>
<td>8.6</td>
</tr>
<tr>
<td>auc</td>
<td>mmHg</td>
<td>1020.3</td>
<td>853.6</td>
</tr>
<tr>
<td>peak</td>
<td>mmHg</td>
<td>83.3</td>
<td>11.6</td>
</tr>
<tr>
<td>percent-peak</td>
<td>%</td>
<td>16.5</td>
<td>14.8</td>
</tr>
<tr>
<td>time to peak</td>
<td>Sec</td>
<td>89.8</td>
<td>38.5</td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>--------</td>
<td>--------------</td>
<td>-------</td>
<td>-------</td>
</tr>
<tr>
<td></td>
<td><strong>SV</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>absolute mL/beat</td>
<td>87.9</td>
<td>20.0</td>
</tr>
<tr>
<td></td>
<td>peak mL/beat</td>
<td>89.4</td>
<td>20.0</td>
</tr>
<tr>
<td></td>
<td>percent-peak %</td>
<td>5.7</td>
<td>12.6</td>
</tr>
<tr>
<td></td>
<td>time to peak Sec</td>
<td>83.2</td>
<td>40.2</td>
</tr>
<tr>
<td></td>
<td><strong>SVR</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>absolute Dyne.sec.cm^2</td>
<td>782.8</td>
<td>265.4</td>
</tr>
<tr>
<td></td>
<td>peak Dyne.sec.cm^2</td>
<td>822.6</td>
<td>315.7</td>
</tr>
<tr>
<td></td>
<td>percent-peak %</td>
<td>14.7</td>
<td>37.1</td>
</tr>
<tr>
<td></td>
<td>time to peak Sec</td>
<td>83.6</td>
<td>46.5</td>
</tr>
<tr>
<td></td>
<td>Group E (n =18)</td>
<td>Group P (n =20)</td>
<td>95% CI</td>
</tr>
<tr>
<td>----------------------</td>
<td>----------------</td>
<td>----------------</td>
<td>--------</td>
</tr>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
</tr>
<tr>
<td>CO(LiDCO)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>absolute</td>
<td>8.1</td>
<td>2.0</td>
<td>6.2</td>
</tr>
<tr>
<td>auc</td>
<td>26.9</td>
<td>150.4</td>
<td>-160.6</td>
</tr>
<tr>
<td>peak</td>
<td>9.0</td>
<td>2.7</td>
<td>5.2</td>
</tr>
<tr>
<td>percent-peak</td>
<td>16.0</td>
<td>19.5</td>
<td>-27.8</td>
</tr>
<tr>
<td>time to peak</td>
<td>58.8</td>
<td>36.2</td>
<td>32.2</td>
</tr>
<tr>
<td>CO(BioZ)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>absolute</td>
<td>6.3</td>
<td>1.1</td>
<td>5.2</td>
</tr>
<tr>
<td>auc</td>
<td>15.9</td>
<td>51.1</td>
<td>-77.1</td>
</tr>
<tr>
<td>peak</td>
<td>6.7</td>
<td>1.6</td>
<td>4.5</td>
</tr>
<tr>
<td>Percent-peak</td>
<td>8.5</td>
<td>19.3</td>
<td>-21.8</td>
</tr>
<tr>
<td>time to peak</td>
<td>92.7</td>
<td>42.2</td>
<td>68.7</td>
</tr>
</tbody>
</table>
Absolute = refers to the averaged change in the absolute value from pre-vasopressor value over 150 sec following vasopressor administration
AUC = area under curve for change in variable from pre-vasopressor value for 150 sec following vasopressor administration
CO (LiDCO) and CO (BioZ) = cardiac output derived using the LiDCO and BioZ monitors respectively
HR = heart rate
MAP = mean arterial pressure
CI = confidence interval
Peak = maximum absolute response of each variable to vasopressor
Percent-peak = percentage change in variable from pre-vasopressor value at peak value
Post-vasopressor = haemodynamic values after the first administration of either vasopressor
SV = stroke volume, derived from the LiDCOplus monitor
SVR = systemic vascular resistance
* = false discovery rate bound is 0.0247
Detailed data shown pertaining to the response to vasopressor administration are the mean absolute values, as well as peak, and percentage change in HR, SV, CO, MAP and SVR, the times after vasopressor administration to the peak values, and the area under the curve for MAP and CO changes, during the 150 seconds following the first administration of vasopressor in the two groups. The CO changes are shown as measured by both the LiDCOplus and BioZ monitors. Following vasopressor administration, between-group differences in HR were significant both in absolute terms and in the percentage change at peak effect. Phenylephrine was associated with a reduction in HR. MAP increased in both groups with a greater increase in absolute and peak pressure as well as in the sustained response as measured by the area under the curve, in Group P. The time to peak MAP was significantly shorter with phenylephrine than with ephedrine. In both groups, the objective was achieved of restoring mean arterial pressures to within 20% of baseline. The mean peak post-vasopressor MAP was 8% below the baseline value in Group E, and 8% above baseline in Group P. SV was not significantly different between the two groups. Mean CO and maximum absolute response in CO were significantly lower in the 150 seconds following phenylephrine administration than after ephedrine: 6.2 vs. 8.1 L/min, \( P\)-value = 0.001, and 5.2 vs. 9.0 L/min, \( P\)-value < 0.0001, respectively for pulse wave form analysis. The corresponding values for bioimpedance changes were 5.2 vs. 6.3 L/min, \( P\)-value = 0.01 and 4.5 vs. 6.7 L/min, \( P\)-value = 0.0001, respectively.

Figure 5.2. and 5.3. show median HR, CO and MAP, and SVR and SV changes respectively, estimated by the LiDCOplus monitor, in the 150 seconds after vasopressor. Note that the maximum rate of change in HR was early after phenylephrine administration, although the time to peak change was longer and similar to that for ephedrine (Table 5.5). The time to peak change in CO was significantly different between groups. There was a similar positive correlation between CO and HR changes in each group (\( P\)-value = 0.87 for the comparison between the regression lines) (Figure 5.4.).
Figure 5.5. shows a comparison of time-based changes in CO recorded by the LiDCOplus and BioZ monitor, in the 150 seconds after vasopressor. Individual responses are shown as thin grey lines, and the ensemble median value is depicted as a superimposed thick black line. Both CO monitors showed a significant between-group difference in the percentage CO change, and in the same direction, following the first vasopressor administration. The difference between the instruments with respect to the percentage change in CO was significantly different between the two vasopressor groups. Group P had larger differences between the instruments than Group E (Figure 5.6.) and a weaker correlation between the measurements ($r = 0.08$, $P = 0.7$ and 0.56 respectively, $P = 0.015$).

![Graph showing percentage changes from pre-vasopressor values, in cardiac output (CO, as measured by LiDCOplus), heart rate (HR) and mean arterial pressure (MAP) following the administration of vasopressor](image)

**Figure 5.2.** Percentage changes from pre-vasopressor values, in cardiac output (CO, as measured by LiDCOplus), heart rate (HR) and mean arterial pressure (MAP) following the administration of vasopressor
Figure 5.3. Percentage changes from pre-vasopressor values, in stroke volume (SV, as measured by LiDCOplus) and systemic vascular resistance (SVR) following the administration of vasopressor. Lines represent the median smooth for each parameter.
Figure 5.4. Scatter plot showing the correlation between the percentage change in peak heart rate with percentage change in peak cardiac output from pre-vasopressor value, after vasopressor administration.

For ephedrine $r = 0.65$; $P$-value = 0.003
For phenylephrine $r = 0.87$, $P$-value < 0.0001

$P$ = Phenylephrine
$E$ = Ephedrine
$CO$ = cardiac output
$HR$ = heart rate
Figure 5.5. Ensembles of percentage changes from pre-vasopressor values in cardiac output as measured with the LiDCOplus and the BioZ monitors

Each ensemble shows the percentage chance for each patient (light gray) and the median smooth for the group (black) for the 150 seconds following administration of either ephedrine or phenylephrine.
Figure 5.6. Mean percentage changes in cardiac output for the 150 seconds following first vasopressor administration in each group as measured by each device

Figure 5.7. shows a between-group comparison of percentage change from pre-vasopressor values of CO and HR in patients receiving vasopressor either pre- or post-delivery. The mean and percentage peak between-group differences in CO and HR for the 150 seconds after vasopressor administration, were not significantly different pre- and post-delivery ($P$-value = 0.55 and 0.67 for mean, and 0.75 and 0.09 for percentage peak change in CO and HR respectively).
Figure 5.7. Between-group comparison of patients receiving vasopressor pre- or post-delivery - Percentage changes from pre-vasopressor values, in cardiac output (LiDCOplus) and heart rate following the administration of vasopressor.

*Lines represent the median smooth for each parameter*

CO = cardiac output
HR = heart rate

The secondary outcome of the effects of SA on haemodynamics during the pre-delivery period, is shown in Figure 5.8. This is presented as a percentage change from baseline at the pre-vasopressor time interval in patients receiving vasopressor pre-delivery, or at the pre-uterine incision time interval for those patients not receiving vasopressor pre-delivery. At the pre-vasopressor time interval CO had increased significantly from baseline values, due to an increase in HR and SV. In patients not requiring vasopressor before the pre-uterine incision time interval, CO had also increased significantly, due to an increase in SV alone.
Figure 5.8. Percentage haemodynamic changes from baseline at the pre-vasopressor time interval in those patients who received vasopressor pre-delivery (n = 20), or at the pre-uterine incision time interval for those patients not receiving vasopressor pre-delivery

95% confidence intervals indicated by the error bars

HR = heart rate
MAP = mean arterial pressure
SV = stroke volume
SVR = systemic vascular resistance
CO (LiDCO) and CO (BioZ) = cardiac output derived using the LiDCO and BioZ monitors respectively

# - p < 0.05 for changes from baseline in the subjects receiving vasopressor only
* - p < 0.05 for changes from baseline for both vasopressor and no vasopressor subjects

Bland and Altman comparison of pulse wave form analysis (LiDCOplus) and bioimpedance changes (BioZ) was performed at 3 measurement periods (baseline, pre-uterine incision, and 40 minutes post induction of SA). The bias at each measurement point was 1.0, 1.0 and 1.6 L/min respectively. The limits of agreement at each measurement point were -1.8 – 3.7, -1.9 – 3.9 and -2.0 – 5.2 L/min respectively.
5.4. Discussion

This prospective randomized comparison of the effects of phenylephrine and ephedrine on maternal haemodynamics during SA for CS, showed that a bolus of 80µg phenylephrine caused a significantly lower maternal CO when compared to a bolus dose of 10mg ephedrine, during the 150 seconds after vasopressor administration. However, the mean post-phenylephrine CO values remained above baseline (Tables 5.3. and 5.4.), since CO values immediately prior to vasopressor administration were higher than baseline.

The two CO monitors used, based upon pulse wave form analysis and transthoracic bioimpedance changes, recorded similar trends in changes in CO after vasopressor administration. The maximum change in HR was also significantly different between groups. There was a strong correlation between HR and CO in both groups, following vasopressor administration.

The peak changes in CO and MAP following phenylephrine occurred significantly earlier than those following ephedrine. SVR changes after the vasopressors suggested a marked rise in afterload after phenylephrine. After ephedrine administration, there was a sequence of a transient increase in afterload, followed by a transient decrease (possibly $\beta_2$ mediated) and then a sustained increase in SVR (probably mediated by noradrenaline release) (Figures 5.2. and 5.3.).

Haemodynamic changes associated with SA for CS are of particular importance to anaesthesiologists, both in terms of patient safety and comfort. Precipitous decreases in maternal CO, particularly when associated with bradycardia, may be life-threatening and place the fetus at risk of hypoxia and a poor neurological outcome. Maternal hypotension is known to be associated with nausea and vomiting, which makes the experience of the delivery unpleasant for the mother. Fluid and vasopressor use should thus be appropriate for the specific haemodynamic disturbance encountered.
Previous studies have employed intermittent measurement of maternal CO, using indicator dilution or suprasternal Doppler flow technology (Ueland et al, 1968; Thomas et al, 1996; Ashpole et al, 2005). In a randomized comparison of the effects of boluses of 5mg ephedrine and 100µg phenylephrine on maternal CO and cord gas values, overall CO changes were not different between groups. These investigators used atropine in 11/19 cases of phenylephrine-associated bradycardia. This makes the interpretation of the mechanism of CO changes difficult. The study was primarily powered to detect differences in umbilical artery pH, and did not examine CO responses to individual boluses of vasopressor as in the current study. In our trial, slowing of the HR following phenylephrine administration was not treated with anticholinergics if blood pressure was maintained or elevated following vasopressor administration.

There is considerable controversy as to the dose equivalence of phenylephrine and ephedrine for vasopressor effect. A recent investigation using continuous infusions found a potency ratio of 83:1 (Saravanan et al, 2006). Published studies have employed ratios varying from 20:1 to 250:1. Consensus was reached amongst the investigators that in our patient population group, a bolus of phenylephrine 80µg was equivalent to ephedrine 10mg, a ratio of 125:1. These were regarded as doses that would restore MAP to within a range of 20% above or below baseline. The effectiveness of the dose may also be related to the time to peak effect. In the current study phenylephrine had a peak pressor effect at 61.8 seconds, which was later than the peak depressant effect on CO (32.2 seconds). The peak pressor effect of ephedrine was at 89.8 seconds while the peak change in CO was also earlier (58.8 seconds) than the peak pressor effect. In the case of phenylephrine, this could be due to a gradual improvement in CO that was seen following the peak depressant effect (Anrep effect, see below). In the case of ephedrine this could be explained by the early $\beta_1$ and $\beta_2$ effects, causing an increase in CO, followed by the indirect effect of release of norepinephrine from the sympathetic nerve terminals, resulting in the peak increase in blood pressure.
An early investigation of intermittent CO measurement during SA for CS, using indicator dilution, showed that maternal CO was significantly depressed in 10/12 patients and greatly improved by a change from the supine to the left lateral position (Ueland et al, 1968). A more recent study employing intermittent suprasternal Doppler flow measurements, showed that SA employing a median dose of 11mg bupivacaine was associated with a decrease in CO of >1 litre/minute in 9/16 patients (Robson et al, 1992). A further trial, employing lower doses of local anaesthetic (7 and 10mg bupivacaine) in conjunction with subarachnoid sufentanil, demonstrated an increase in CO following SA, which was obtunded by the use of an infusion of phenylephrine at 0.25 µg/kg/minute (Langesaeter et al, 2008). In our study, employing 10mg spinal bupivacaine, careful left lateral tilt, and 20 mL/kg crystalloid coload, there was a significant decrease in SVR, and an increase in HR, SV and CO from the baseline value, at the time immediately prior to administration of vasopressor during the pre-delivery period, or in SV and CO at the time of uterine incision, if no vasopressor was required by this time (Figure 5.8.). In an investigation of sympathovagal balance during SA in the non-obstetric population, the maintenance of HR despite sympathetic denervation, has been attributed to concomitant diminished parasympathetic activity to the heart (Introna et al, 1995). In our trial, none of the 43 patients developed precipitous bradycardia in response to SA, and this event, possibly due to reflex activation of the vagus nerve as a result of failure of ventricular filling (Kinsella and Tuckey, 2001), appears relatively uncommon. A recent editorial examining the relative contributions of the venous and arterial circulation to the hypotensive effects of SA, placed equal emphasis on arterial dilatation as on decreased venous return (Sharwood-Smith and Drummond, 2009). In keeping with this view, a post hoc between-group comparison in the current study of the effects of vasopressor administered before or after delivery, suggested that the percentage changes in haemodynamic variables following ephedrine and phenylephrine, were independent of the time of administration (Figure 5.7.).

From these studies it therefore appears that modest hypotension during SA for CS (0 – 20% decrease in baseline blood pressure) is often associated with
a decrease in SVR and a partial compensatory increase in CO, mediated by
an increase in HR and SV. This may be obtunded by the use of either low
dose boluses or a low dose infusion of phenylephrine. Using suprasternal
Doppler flow measurements during SA for CS, a dose dependent reduction in
CO has been demonstrated in parturients receiving an infusion of
phenylephrine at 100µg per minute (Stewart et al, 2008). Thus, these studies
and the current investigation suggest that doses of phenylephrine large
enough to cause marked increases in MAP above baseline, and sinus
bradycardia, would be associated with depression of CO to below baseline
values, and should be avoided. The strong correlation between HR and CO
changes after both ephedrine and phenylephrine administration, suggests that
HR, and not MAP, is the most important surrogate marker of CO during SA for
CS. After an initial depression of CO by bolus phenylephrine in the present
study, a gradual recovery of CO was observed during a period of sustained
increase in MAP and SVR, and decrease in HR (Figure 5.2.). The associated
increase in SV (Figure 5.3.) could represent the Anrep effect, which is a
positive inotropic effect that occurs during an increase in left ventricular
afterload (von Anrep, 1912).

Current literature supports the fact that the use of ephedrine as a vasopressor
during elective CS under SA is associated with significantly more neonatal
acidosis than phenylephrine (Cooper et al, 2002). In keeping with this
literature, umbilical arterial pH was lower, and base excess statistically
significantly lower in patients receiving ephedrine pre-delivery in the current
study (Table 5.2.). The clinical significance remains unknown.

Lithium dilution cardiac output (LiDCO™; LiDCO, Cambridge, United
Kingdom) is a validated minimally invasive indicator dilution technique for the
measurement of CO (Kurita et al, 1997). The LiDCOplus monitor is a beat-to-
beat CO monitor that calculates SV from the arterial pressure waveform using
an autocorrelation algorithm (Chapter 2).

A recent editorial outlines the rationale for the use of this device in obstetric
anaesthesia research (Dyer and James, 2008). In the present study,
specifically designed to examine short term haemodynamic changes during SA for CS, bioimpedance changes were concurrently measured, in order to corroborate the pulse wave form-derived data. Using the Bland and Altman approach, the limits of agreement between absolute values of CO derived from LiDCOplus and BioZ were outside the recommended acceptable 30% (Critchley and Critchley, 1999) in the present study. However, the agreement between the haemodynamic trends demonstrated by both LiDCOplus and BioZ in this study, in response to both vasopressors and oxytocin, provide further evidence of the usefulness of the pulse wave form monitor as a research tool for the study of acute haemodynamic changes during SA. The larger differences between the instruments in Group P (Figure 5.6.), may reflect a tendency of bioimpedance methods to overestimate CO when SVR is high (Critchley et al, 2005). There was a difference between the two monitors in the time to peak effect following the administration of vasopressor. This may be due to the fact that the LiDCOplus derives values from the peripheral arterial trace, while the BioZ uses centrally measured changes in thoracic impedance. The sampling rate of the two devices was also different, with the LiDCOplus sampling every heartbeat, while the BioZ sampled every 10 beats. These two effects probably account adequately for the difference in time intervals.

In conclusion, this study showed that bolus phenylephrine produced an absolute reduction in maternal CO, and decreased CO when compared with ephedrine during elective SA for CS. CO changes correlated strongly with HR changes. HR may therefore be the best surrogate indicator of CO during SA for CS. During SA, haemodynamic changes were characterized by a well-preserved or increased CO and a marked reduction in SVR. This suggests that low dose phenylephrine, insufficient to cause marked MAP increases above baseline associated with sinus bradycardia, may be the most appropriate intervention for the initial management of hypotension in most cases, in order to restore SVR and CO to baseline levels. The results also suggest that ephedrine is the more appropriate vasopressor when hypotension and bradycardia occur, since this combination reflects a decreased maternal cardiac output. The agreement between the trends
shown by the two CO monitors following both vasopressor and oxytocin administration, lends further support to this form of pulse waveform analysis as a research tool.
5.5. Appendix

Figure 5.9. Individual recordings of percentage change in cardiac output during the 150 seconds after either ephedrine or phenylephrine administration

\( E = \text{Ephedrine} \)

\( P = \text{Phenylephrine} \)
Chapter 6

Haemodynamic changes associated with spinal anaesthesia in severe preeclampsia

6.1. Introduction

Many recent studies suggest that SA for CS is safe in patients with severe preeclampsia in the absence of contraindications to regional anaesthesia (Aya et al, 2003; Aya et al, 2005; Clark et al, 2005), Chapter 1. Some studies have shown less hypotension and lower vasopressor requirements than during SA in healthy parturients. One investigation found less hypotension during SA in severe pre-eclamptics than in preterm women in whom fetal weights were similar (Aya et al, 2005). This eliminated the possibility that the more minor degree of hypotension was due to a lesser degree of aortocaval compression in preeclamptic patients. Nevertheless, hypotension and placental underperfusion remain a risk (Karinen et al, 1996), and SA may be associated with more neonatal acidosis than general anaesthesia (see Chapter 8).

Most studies have employed HR and blood pressure measurements as surrogate markers of maternal CO. Although pulse and blood pressure measurements are of value in assessing the safety of an anaesthetic technique, the true goal of SA for CS is to maintain maternal CO and uteroplacental blood flow. In healthy patients the maximum change in CO has been shown to correlate better with uteroplacental blood flow than upper arm blood pressure (Robson et al, 1992). Furthermore, in severe preeclampsia a raised SVR could render blood pressure a poor indicator of CO, but the information available on such patients during SA is scanty. It was therefore decided to investigate CO changes during SA for CS in severe preeclampsia. Our hypothesis was that SA would result in a clinically insignificant change in CO in these patients, other than at the time of oxytocin administration. Also studied were the haemodynamic responses to vasopressors, and to delivery
and oxytocin. In addition, an assessment was made of the haemodynamics of recovery from SA.

Ultimately, a better understanding of the peri-operative haemodynamic changes could contribute to a reduction in peri-operative pulmonary oedema, renal dysfunction, eclampsia and neonatal morbidity.

6.2. Patients and methods

Fifteen patients were recruited to this prospective observational study of the haemodynamics of SA for CS in severe preeclampsia. Preeclampsia was regarded as severe if the systolic blood pressure on admission exceeded 160mmHg and/or the diastolic blood pressure exceeded 110mmHg, obtained on at least two separate occasions, or if the patient had symptoms of imminent eclampsia (namely severe headache, visual disturbance, epigastric pain, hyper-reflexia, dizziness and fainting, or vomiting) and proteinuria on urine dipstix was 3+ or worse. Patients with Haemolysis, Elevated Liver enzymes and Low Platelets (HELLP) syndrome were eligible for inclusion if the platelet count exceeded 75 x10^9/L.

The study commenced after the approval of the Human Research Ethics Committee of the University of Cape Town. Informed written consent for inclusion in the study was taken at the time of decision to proceed to CS. The decision to proceed with operative delivery for either a maternal or a fetal indication, was made by the obstetric team independent of the investigators. Patients with severe PE, with worsening maternal disease, and requiring urgent but not emergency CS, were eligible for recruitment to the study.

Exclusion criteria were: patient refusal, any contra-indication to SA, body mass index greater than 35 kg.m⁻², chronic hypertension, abruptio placentae, placenta praevia, coagulation abnormality, thrombocytopenia (platelet count < 75 x10^9/L), local or generalized sepsis, cord prolapse, <28 weeks’ gestation,
twin pregnancy, active labour, or a non-reassuring fetal heart trace. Should any spinal anaesthetic take longer than 30 minutes to perform, the patient would receive general anaesthesia and be withdrawn from the study.

The antepartum management was according to the established protocol of our institution: on admission, all patients with severe preeclampsia have an intravenous line placed, and receive seizure prophylaxis consisting of magnesium sulphate (MgSO$_4$) as a loading dose of 4g intravenously, followed by 1g hourly. Volume expansion using 300 – 500 mL of hydroxyethyl starch precedes the use of IV dihydralazine, followed by a balanced crystalloid solution administered at <120 mL per hour. Dihydralazine is administered intravenously, either as 2.5 mg boluses or as a continuous infusion. If there is no immediate maternal or fetal indication for delivery, and gestational age is less than 34 weeks, the patient is admitted for in-patient expectant management, until an indication for delivery arises. Oral alpha-methyldopa and/or nifedipine are used for blood pressure control. However if gestational age on admission is more than 34 weeks, delivery is expedited after stabilization of the mother. If CS is anticipated, patients receive 30 mL sodium citrate orally in the operating room.

Non-invasive monitoring consisted of electrocardiograph and pulse oximetry. CO measurements employed a beat to beat CO monitor that calculates SV from the arterial pressure waveform using an autocorrelation algorithm (LiDCOPlus, LiDCO, London, United Kingdom) (Chapter 2). A 20G intra-arterial line was inserted, and calibration of the CO monitor was performed. Due to time constraints, one calibration was performed in 5 cases, and two separate calibrations, 5 minutes apart, in the remaining 10 patients. In these cases, the average calibration factor was calculated and applied to the data. Beat by beat HR, systolic, diastolic and MAP, SV and CO were recorded in an Excel Workbook, from the time of calibration until the time of first request for analgesia. Of primary interest in this study was the change in CO in each individual patient. In order to evaluate the hypothesis that SA caused no clinically significant decrease in CO, a 20% decrease from baseline values was used as the clinical criterion.
Placement of a central venous line is not required clinically in most patients with severe preeclampsia. Therefore, central venous pressure (CVP) was given an arbitrary value of 5mmHg, for the purposes of calculation of SVR. Baseline data were obtained post hoc by averaging all haemodynamic parameters over the 2 – 6 minutes after calibration, with the patient in the left lateral position. The MAP value for the purposes of calculation of target blood pressures for vasopressor administration, was recorded as the mean of three consecutive readings not differing from one another by more than 10 percent, taken in the 3 minutes prior to sitting up for the induction of anaesthesia.

The management of SA was as follows:

Intravenous crystalloid coload (modified ringer’s lactate (10 mL/kg)) was rapidly administered via a 16G peripheral line, initiated after cerebrospinal fluid appeared in the hub of the spinal needle. Thereafter, no further fluids were administered unless excessive haemorrhage occurred. All patients received 2.0mL of hyperbaric 0.5% bupivacaine, plus 10µg of fentanyl, administered at the L3/4 interspace. After 20 seconds in the sitting position, patients were positioned supine, with 20 degrees of left lateral tilt, to minimize aortocaval compression. Block height was assessed using cold sensitivity to ethyl chloride spray. All mothers received 40% oxygen by face-mask until delivery.

Interventions were as follows:

The first choice vasopressor was phenylephrine, administered by the anaesthesiologist in response to HR and blood pressure changes, as is normal clinical practice during SA for CS.

If MAP decreased by 20% from baseline, 50µg phenylephrine was administered every minute until the blood pressure recovered to within 20% of the baseline value. No vasopressor was given if MAP was >110 mmHg. If MAP decreased by 30% from baseline, 100µg phenylephrine was administered every minute until the blood pressure recovered to within 20% of baseline. If CO did not increase by 5% above the pre-treatment level when
the target MAP had been reached, ephedrine boluses of 5 or 10mg were be administered thereafter, according to the same protocol as for phenylephrine, should further hypotension occur. If any patient required more than 50mg ephedrine, this was interpreted as tachyphylaxis, and phenylephrine was used thereafter. If HR were to decrease to less than 55 beats per minute in association with hypotension (MAP decrease by 30% from baseline), Atropine 0.5mg and ephedrine 10mg would be administered, and the haemodynamic response recorded. After delivery, phenylephrine (50 – 100µg), or ephedrine (5 – 10mg) was administered to maintain MAP within 30% of baseline pressure.

Further interventions were as follows:
Thirty seconds after delivery, oxytocin 2.5IU in 10mL water, was administered over a period of 30 seconds. No vasopressor was administered for up to 3 minutes after oxytocin, and no further intraoperative oxytocin was administered until the end of surgery, unless requested by the obstetrician in the case of uterine atony.

Cefazolin 1g was given IV at the end of the surgical procedure. Intraoperative maternal blood loss was estimated from suction bottle measurement and checking of swabs. Neonatal Apgar scores, umbilical arterial and maternal pH and base deficit, and neonatal weights were recorded.

**Statistical Analysis:**
Haemodynamic values were averaged for the following defined time intervals:
- Baseline measurements
- Sitting (time from sitting up for SA until induction of SA)
- Spinal anaesthesia (from induction of SA until the adoption of the supine position)
- Supine (from the return to the supine position until left lateral tilt)
- Left lateral tilt (from tilt until skin incision)
- Skin incision (from skin incision until 30 seconds before uterine incision)
- Uterine incision (30 second time period before uterine incision)
- Post-delivery (the 30 second period from delivery until administration of oxytocin)
- Peak oxytocin effect (from administration of oxytocin until peak effect on CO)
- End of surgery (30 second time period prior to skin closure)
- Recovery from SA (5 minute time period before request for analgesia)

These absolute values were analyzed for differences from baseline using ANOVA for repeated measures with the Dunnett correction for multiple comparisons.

CO was the main outcome variable considered for testing the hypothesis that this haemodynamic variable did not deviate by more than 20% from the baseline value in the individual case. For the testing of this hypothesis, the period of oxytocin administration was excluded. Descriptive statistics of the cardiac variables were calculated for the 11 time periods considered. For CO a regression model was used to estimate the mean change from baseline to each of the follow-up time intervals. This model took into account the repeated measurements within each patient by allowing a general variance-covariance structure to be estimated for this purpose. The 95% confidence intervals for the nine differences were adjusted to ensure an overall type I error rate of 5%. This was done using the Dunnett adjustment for multiple comparisons of P-values and confidence intervals.

The mean changes from baseline values of the other cardiac variables were estimated using the same approach as for CO. The individual CO time profiles were plotted as well as the individual percentage change from baseline. The estimated changes from baseline values at each time interval with the adjusted 95% confidence intervals were also plotted. Fisher's exact test was used to test for an association between the indicator of a decrease of more than 20% in CO at any time point for all patients, and the time indicator variable.
The effects of phenylephrine on each haemodynamic parameter were measured by averaging the effects before and after each dose in each patient, and then averaging between patients. Pre-values were taken as the mean value for the period 30 seconds before phenylephrine administration. Post-values were taken as the mean value for the 5 seconds before and after the highest value recorded in the 3 minutes after vasopressor administration. A similar procedure was followed in order to estimate the haemodynamic changes from baseline that had occurred at the time immediately preceding the first administration of phenylephrine (i.e. at target MAP). The post-phenylephrine values were then compared to the pre-phenylephrine values using repeated measures analysis of variance. Data analysis was performed using SAS version 9 (SAS Institute Inc., Cary, NC, USA).

6.3. Results

Fifteen consecutive patients meeting the entry criteria were recruited over a period of 14 months. Two patients refused consent. Recruitment took place from November 2005 to January 2007, at the Maternity Centre of Groote Schuur Hospital, Cape Town, South Africa. Demographic data, relevant preoperative drug therapy, and MAP used to calculate the target for vasopressor administration, appear in Table 6.1.

Seven patients had had a previous CS, and four had deteriorating renal function evidenced by a raised serum creatinine level. The remainder had worsening maternal disease with difficult control of blood pressure.

Median maximum block height was T3 (range T3-T4), and block height at the time of request for analgesia was T8 (range T5-T10). Mean time (SD) for completion of fluid infusion was 12.5 (2.6) min. In no patient was estimated blood loss greater than 600mL. Mean time (SD) from induction of SA until request for analgesia, was 114.5 (31.1) min. There were no block failures. Only two patients had symptoms during the surgical procedure; one had headache and the other blurred vision and epigastric pain.
### Table 6.1. Demographic data, relevant preoperative drug therapy, and baseline mean arterial pressure

<table>
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<tr>
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<th>G</th>
<th>P</th>
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<th>Ht</th>
<th>GA</th>
<th>Relevant preoperative drugs</th>
<th>MAP</th>
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*G* = gravidity  
*P* = parity  
*Wt* = weight (kg)  
*Ht* = height (cm)  
*GA* = gestational age  
*Mg* = magnesium sulphate  
*MAP* = mean arterial pressure (mmHg) used for calculating target pressure for vasopressor administration (MAP-20%)

Averaged haemodynamic variables at the defined time intervals are shown in Table 6.2.
Table 6.2. Haemodynamic variables with duration of time intervals for all patients (n = 15)

<table>
<thead>
<tr>
<th>Time Interval</th>
<th>Mean duration (sec)</th>
<th>HR (beats/min)</th>
<th>MAP (mmHg)</th>
<th>SV (mL/beat)</th>
<th>CO (L/min)</th>
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<tr>
<td>Baseline</td>
<td>120 – 360</td>
<td>82.5 (11.8)</td>
<td>125.8 (14.9)</td>
<td>76.2 (17.8)</td>
<td>6.2 (1.4)</td>
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<td>Sitting</td>
<td>437 (181)</td>
<td>91.2 (14.6)*</td>
<td>132.5 (16.1)*</td>
<td>70.5 (15.4)</td>
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<td>94.1 (19.2) *</td>
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<td>6.3 (1.5)</td>
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<td>Supine</td>
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<td>94.5 (19.8) *</td>
<td>121.7 (15.5)</td>
<td>77.4 (19.1)</td>
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<td>439 (151)</td>
<td>83.5 (15.2)</td>
<td>114.0 (17.6)</td>
<td>81.0 (19.9) *</td>
<td>6.6 (1.5)</td>
</tr>
<tr>
<td>Skin incision</td>
<td>233 (115)</td>
<td>80.9 (15.5)</td>
<td>112.1 (17.2)</td>
<td>81.4 (16.2)</td>
<td>6.5 (1.5)</td>
</tr>
<tr>
<td>Uterine incision</td>
<td>30</td>
<td>81.6 (15.5)</td>
<td>110.8 (21.3)</td>
<td>79.2 (16.1)</td>
<td>6.4 (1.5)</td>
</tr>
<tr>
<td>Post-delivery</td>
<td>30</td>
<td>84.7 (12.6)</td>
<td>114.3 (15.0)</td>
<td>82.9 (15.9) *</td>
<td>7.0 (1.5)  *</td>
</tr>
<tr>
<td>Oxytocin Peak</td>
<td>45 (14)</td>
<td>101.5 (15.9)+</td>
<td>80.6 (15.3)+</td>
<td>89.1 (17.3)</td>
<td>9.1 (2.3)+</td>
</tr>
<tr>
<td>End surgery</td>
<td>30</td>
<td>79.5 (11.3)</td>
<td>102.3 (13.6)</td>
<td>80.1 (17.9)</td>
<td>6.3 (1.3)</td>
</tr>
<tr>
<td>Recovery</td>
<td>300</td>
<td>71.6 (11.2) *</td>
<td>122.1 (10.1)</td>
<td>80.7 (19.3)</td>
<td>5.7 (1.2)  *</td>
</tr>
</tbody>
</table>

* = Significant difference from baseline values (P-value < 0.05)
* = Significant difference from all other time intervals (P-value < 0.01)

** HR = heart rate
** MAP = Mean arterial pressure
** SV = Stroke volume, measured by the LiDCOplus monitor
** CO = Cardiac output
** SVR = Systemic vascular resistance

Data are shown as means (SD). For baseline values, the range of time is shown. Mean duration refers to the duration of the defined time interval. Time intervals defined in the protocol do not have SD indications.

For oxytocin the duration is the mean time from intravenous injection to peak effect on CO. All other haemodynamic indices are calculated at this time point.
CO remained stable throughout CS and until the time of request for analgesia in each patient, except for the period following oxytocin administration (Figure 6.1.).

Figure 6.1. Cardiac output measurements for each patient at each time interval

- Baseline: Baseline measurements averaged following calibration of cardiac output monitor
- Sitting: Time from sitting up for SA until induction of SA
- Spinal: Time from induction of SA until patient supine
- Supine: Time from adoption of supine position until left lateral tilt
- L tilt: Left lateral tilt (from tilt until skin incision)
- Skin: Time from skin incision until 30 seconds before uterine incision
- Uterine: 30 second time period before uterine incision
- Post-delivery: 30 second period from delivery to administration of oxytocin
- Oxytocin Peak: Time from administration of oxytocin until peak effect on cardiac output
- End surg.: 30 second time period prior to skin closure (end of surgery)
- Recovery: 5 minute time period before request for analgesia
Figure 6.2. Illustrates CO percentage changes in individual cases, excluding the peak oxytocin effect. There were a total of 135 time epochs after the baseline period, of which 2 showed a greater than 20% decrease in CO. The two observed decreases were transient and the patients were asymptomatic. CO increased to more than 20% above baseline values in several cases at various time intervals. Assuming that the 135 time periods at which CO was measured were independent measurements, and considering the test for the association between the indicator for a CO decrease of more than 20% from baseline, and the time indicator, a Fisher’s exact test indicated no significant association ($P$-value = 1.000).

![Figure 6.2: Percentage cardiac output change from baseline for individual patients, at defined time intervals, as for Figure 6.1.](image)

Reference lines have been drawn at + and – 20%

CO = cardiac output
Mean changes from baseline values in HR, MAP, SV, CO and SVR, together with 95% confidence intervals at all time intervals, for the cohort of 15 patients, are shown in Figures 6.3.A-E.

A

B
Figure 6.3A-E. Mean absolute changes from baseline values for all haemodynamic variables at defined time intervals, as in Figure 6.1.

A: Heart rate (HR)
B: Mean arterial pressure (MAP)
C: Stroke volume (SV)
D: Cardiac output (CO)
E: Systemic vascular resistance (SVR)

Error bars indicate 95% confidence intervals
*P-value < 0.05.

A total of ten patients received phenylephrine, 8 before and 6 after delivery. The median (range) doses before and after delivery, were 50µg (0 – 150µg), and 0µg (0 – 150µg) respectively. Seven patients required ephedrine, and one developed tachyphylaxis, necessitating a change to phenylephrine, as dictated by the protocol. The median (range) dose of ephedrine was 0 (0 - 45) mg. Vasopressor use is summarized in Table 6.3.
Immediately prior to the first administration of phenylephrine, i.e. when MAP was 20% below baseline values, SVR was significantly lower than baseline measurements. CO and HR were not different from baseline at this time (Table 6.4.).

### Table 6.3. Vasopressor administration pre- and post- delivery

<table>
<thead>
<tr>
<th>Patient number</th>
<th>Phenylephrine pre-delivery (µg)</th>
<th>Phenylephrine post-delivery (µg)</th>
<th>Ephedrine pre-delivery (mg)</th>
<th>Ephedrine post-delivery (mg)</th>
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<tr>
<td>1</td>
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<td>150</td>
<td>0</td>
<td>0</td>
</tr>
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<td>15</td>
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Table 6.4. Haemodynamic data at baseline and prior to first administration of phenylephrine in those patients who received the vasopressor (n=10)

<table>
<thead>
<tr>
<th></th>
<th>Baseline mean (SD)</th>
<th>Pre P1 mean (SD)</th>
<th>Difference between means</th>
<th>99% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>CO (L/min)</td>
<td>6.1 (1.7)</td>
<td>6.3 (1.5)</td>
<td>0.2</td>
<td>-1.0 to 1.4</td>
</tr>
<tr>
<td>SVR (dyne.sec.cm⁻⁵)</td>
<td>1616 (362)</td>
<td>1198 (330)</td>
<td>-418</td>
<td>-628 to -208</td>
</tr>
<tr>
<td>MAP (mmHg)</td>
<td>122 (17)</td>
<td>95 (13)</td>
<td>-27</td>
<td>-34 to -21</td>
</tr>
<tr>
<td>SV (mL/beat)</td>
<td>76.9 (19.5)</td>
<td>76.0 (19.7)</td>
<td>-0.9</td>
<td>-7.8 to 6.0</td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td>80.4 (11.6)</td>
<td>84.0 (16.1)</td>
<td>4.4</td>
<td>-7.2 to 16.0</td>
</tr>
</tbody>
</table>

Pre P1 = values prior to the first dose of phenylephrine
CO = cardiac output
HR = heart rate
MAP = mean arterial pressure
SV = stroke volume, derived from the LiDCOplus monitor
SVR = systemic vascular resistance

99% confidence intervals (99% CI) were used to adjust for multiplicity. There were significant decreases in SVR and MAP.

The administration of phenylephrine was associated with a significant increase in MAP and SVR, and a significant decrease in HR, but SV and CO were not significantly changed from values immediately prior to phenylephrine use (Table 6.5.). There was a trend towards a decrease in CO. The mean (SD) times to peak effect of the first, second and third doses, were 28.3 (4.2), 39.6 (30.0) and 24.6 (3.2) seconds respectively. The infrequent use of ephedrine precluded a detailed analysis of the use of this vasopressor.
Table 6.5. Effects of phenylephrine on haemodynamic parameters using data from all doses of phenylephrine (n = 20)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Pre mean (SD)</th>
<th>Post mean (SD)</th>
<th>Difference between means</th>
<th>99% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>CO (L/min)</td>
<td>6.3 (1.5)</td>
<td>5.8 (1.6)</td>
<td>- 0.5</td>
<td>-1.1 to 0.2</td>
</tr>
<tr>
<td>SVR (dyne.sec.cm⁻⁵)</td>
<td>1155 (297)</td>
<td>1507 (469)</td>
<td>352</td>
<td>59 to 645</td>
</tr>
<tr>
<td>MAP (mmHg)</td>
<td>91 (13)</td>
<td>108 (15)</td>
<td>17</td>
<td>8 to 24</td>
</tr>
<tr>
<td>SV (mL/beat)</td>
<td>75.9 (18.7)</td>
<td>78.7 (20.5)</td>
<td>2.8</td>
<td>-2.4 to 8.1</td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td>84.2 (15.1)</td>
<td>74.9 (10.8)</td>
<td>- 9.3</td>
<td>-17.2 to -1.4</td>
</tr>
</tbody>
</table>

Pre = averaged values prior to phenylephrine
Post = averaged values following phenylephrine
CO = cardiac output
HR = heart rate
MAP = mean arterial pressure
SV = stroke volume, derived from the LiDCOplus monitor
SVR = systemic vascular resistance
HR decreased significantly
MAP and SVR increased significantly following phenylephrine administration

Data relevant to the neonate include the following:

The uterine incision to delivery time [mean (SD)] was 54.4 (29.2) sec. The [mean (SD)] neonatal weight was 1697 (520) gm. The [median (range)] Apgar score at 1 minute was 9 (7 – 9) and at 5 minutes was 9 (9 – 10). The median (range) umbilical arterial pH and mean (SD) base deficit were 7.28 (7.19 – 7.31) and -3.1 (1.9) mmol/L respectively.
6.4. Discussion

This observational study describes the maternal haemodynamic response to SA for CS in 15 patients with severe preeclampsia, using phenylephrine as the first choice vasopressor, as is the current practice in healthy patients during SA for CS (Ngan Kee et al, 2005; Ngan Kee and Khaw, 2006). SA was associated with haemodynamic stability in the 15 patients studied (Figure 5.1.A.); this study therefore confirms the hypothesis that CO decreases were clinically insignificant during the procedure. During only two time intervals out of a total of 135 comparisons with baseline values, in two different patients, did CO decrease by more than the clinically relevant value of 20% of baseline measurements (Figure 6.2. and 6.3D.). The mean baseline SVR was above normal despite antihypertensive therapy, and mean baseline CO is in the normal range (Table 6.2.), in keeping with previous literature relating to the haemodynamics of treated patients with severe preeclampsia (Young and Johanson, 2001). Induction of SA was followed by significant decreases in MAP and SVR, which persisted until the end of surgery. In many patients, CO increased to more than 20% above baseline values at several time intervals other than at the time of peak oxytocin effect (Figure 6.2.). Thus the main haemodynamic effect of SA was modest afterload reduction. The use of phenylephrine was associated with a trend toward a decrease in CO. Although CVP was not measured, the magnitude of the arterial pressure changes suggest that an increase in afterload contributed to the mechanism (Table 6.5.).

The requirement for vasopressors was low, in keeping with the existing literature, which suggests a lower requirement than in normal parturients (Aya et al, 2003; Aya et al, 2005; Clark et al, 2005). Some recent publications have recommended that phenylephrine be infused in normal parturients during SA for CS at a rate which maintains baseline MAP (Ngan Kee et al, 2004a; Ngan Kee et al, 2005). This technique was however associated with a significant incidence of maternal hypertension. In the present study, when target values of MAP for vasopressor administration (a 20% decrease in blood pressure)
were reached, CO had not decreased significantly, and in many cases had increased (Table 6.4.). This suggests that maintaining blood pressure at the baseline level in this patient population during SA may not be optimal practice, especially considering the risk of worsening hypertension in patients with severe preeclampsia. Furthermore phenylephrine, administered in response to a 20% decrease in baseline MAP, did not increase CO. In several cases, CO decreased (Table 6.5). The mean change in CO was not significant but this could reflect problems of statistical power.

In a recent study employing whole body impedance cardiography during SA for CS, the authors reported on 10 preeclamptic women, of whom 6 had severe disease. Comparative haemodynamic data from healthy women were obtained from historical rather than contemporaneous studies (Tihtonen et al, 2006). Patients received a preload of 10 mL/kg of 6% hydroxyethyl starch, and 10 mL/kg/hour thereafter. Fluid preloading increased CO in the preeclamptic group, but not in healthy patients. The use of ephedrine increased both MAP and SVR. At delivery, increases in the CO of preeclamptic patients were due only to increases in HR; SV did not increase, in contrast with the healthy patients. The effects of oxytocin were not described. Of particular clinical relevance was the finding that in the healthy patients, haemodynamic values returned to baseline levels after recovery from SA, whereas the stroke index and cardiac index in the preeclamptic group were significantly lower than pre-surgery levels. The authors speculate that the inability to increase SV at delivery in the preeclamptic group could be due either to the existence of a lower preload after delivery than in healthy patients, or to diastolic dysfunction resulting in an inadequate adaptation to volume load at delivery. Such changes could predispose these patients to life-threatening pulmonary oedema in the early puerperium. In the present study, delivery and oxytocin administration were associated with CO changes that were predominantly HR mediated (Chapter 7). At the time of recovery from SA, CO was significantly lower than baseline values. However the magnitude of the effect was only 0.49L, which is well below criteria for a clinically relevant decrease, namely 20% of baseline values, or 1.23L. This
decrease in CO is most likely attributable to the significant decrease in HR at this time (Figure 6.3A.).

Since CVP was not measured in this study, a default CVP of 5mmHg was chosen, for the purposes of calculation of SVR. Since right atrial pressure is very much lower than systemic pressure, this does not impact significantly on the calculation of SVR. Furthermore, in a previous study employing CVP measurements before and during SA for CS in preeclampsia, a preload of 1 litre of crystalloid induced a transient mean increase of less than 5mmHg, and CVP values returned towards baseline after induction of SA. Modest crystalloid cohydration was employed in the present study, since there may be advantages in administering fluids immediately after induction of SA, thus limiting acute CVP increases and the effects of rapid redistribution of crystalloid fluid (Ngan Kee et al, 2005).

More than 800 patients with severe preeclampsia were admitted during the time period of recruitment to the study (14 months). The slow recruitment was due to two factors. Firstly, obstetricians in our institution favour induction of labour at 34 weeks’ gestation, in the absence of a prior maternal or fetal indication for CS. Thus a relatively small percentage of patients undergo CS for a maternal indication. Secondly, in the great majority of patients with severe preeclampsia requiring CS in our institution, the indication is a non-reassuring fetal heart trace. The delays in establishing and calibrating non-invasive CO monitoring would not be ethically justifiable in these patients. In view of the fact that only approximately 50% of patients require a vasopressor before delivery, a large cohort of patients and a prolonged time period of investigation would be required for adequate power in a randomized trial on the effects of phenylephrine and ephedrine on maternal and fetal outcome.

In conclusion, this observational study in 15 patients with severe preeclampsia, showed that SA was associated with modest afterload reduction and minimal CO changes. Phenylephrine did not improve CO, and further work is required to establish whether a mixed α, β-agonist is the
preferred vasopressor, both from the maternal and fetal point of view, since no observations were made in the present study concerning uteroplacental perfusion. SV was well preserved at the time of recovery from SA, and there was a clinically insignificant decrease in CO at this time. Combined spinal-epidural anaesthesia has been successfully used for CS in patients with severe preeclampsia (Ramanathan et al, 2001; Teoh and Sia, 2006) and may confer benefits in terms of postoperative analgesia, but our data suggest that adequate haemodynamic stability, as assessed by CO changes, is provided by single shot SA.
Chapter 7

Haemodynamic effects of oxytocin during spinal anaesthesia for caesarean section

7.1. Introduction

Oxytocin is recognised as an essential drug for administration at delivery, and is the first line agent in establishing adequate uterine contraction and in so doing, preventing postpartum haemorrhage. However, as described in Chapter 1, oxytocin may cause unpleasant maternal side effects, which spoil the experience of the delivery in the awake patient. Furthermore, this agent causes significant haemodynamic instability. In circumstances of limited cardiac reserve, for example impaired ventricular function or significant valvular stenosis, precipitous decrease in systemic vascular resistance and the accompanying hypotension may be associated with an inadequate response in CO to restore normotension, and place the mother at risk. Quantification of these effects is thus important, in order to determine the optimal dose and method of administration, so that side effects can be minimised.

As a secondary outcome in two studies described in this thesis (Chapters 5 and 6), the haemodynamic effects of oxytocin were described in healthy patients and in patients with severe preeclampsia.
Chapter 7

7.2. Haemodynamic effects of oxytocin in healthy parturients

7.2.1. Patients and methods

As part of a randomised study comparing the haemodynamic effects of ephedrine and phenylephrine during SA for CS (See Chapter 5 for detailed methodology), the haemodynamic effects of a bolus of 2.5IU oxytocin were described. The co-administration of phenylephrine was also studied in 20 patients. The aim was to obtund the haemodynamic responses to oxytocin. Since the data from one patient was lost, 32 patients received oxytocin alone. CO changes were assessed by both pulse wave form analysis (LiDCOplus) and transthoracic bioimpedance changes (BioZ) in each patient.

A total of 43 patients were recruited. Thirty seconds after delivery, 2.5IU of oxytocin in 10mL water, was administered IV over a period of 30 seconds, to all patients receiving ephedrine prior to delivery, and to all other patients except for a subgroup of 20 consecutive patients not having received ephedrine prior to delivery. These 20 patients were randomized to receive IV either 2.5IU of oxytocin, or 2.5IU of oxytocin, mixed with 80µg phenylephrine in 10mL water, over a period of 30 seconds, starting 30 seconds after delivery. For this purpose, a sealed envelope pre-prepared by the statistician was opened immediately prior to delivery. The anaesthesiologist administering oxytocin was blinded as to the treatment group. No further vasopressor was administered for up to 3 minutes after oxytocin administration. The obstetrician was asked to grade uterine contraction as good, adequate, or inadequate and requiring further oxytocin, and this was recorded.

The response to oxytocin was analyzed as follows: hemodynamic data were averaged for 30 seconds prior to the administration of oxytocin. The data for the 150 seconds following oxytocin administration were plotted against time to ascertain the time to maximum effect of oxytocin (taken as the highest value of CO), and the maximum response to oxytocin was estimated by averaging the data for 5 seconds before and after this point. In the 20 patients
randomized to receive either oxytocin or the oxytocin-phenylephrine mixture, the change in hemodynamic variables was compared. A sample size of 5 patients in each group would have 90% power to detect a difference in mean CO of 25% assuming that the common standard deviation is 10%, using a two group t-test with a 0.05 two-sided significance level. Therefore 10 patients were included in each group. The 2-sample t-test was used for comparison of all the hemodynamic parameters. The estimated mean difference and the 95% confidence intervals were reported. To account for the multiple testing performed in the study, the false discovery rate was controlled by applying the method of Benjamini and Hochberg (Benjamini and Hochberg, 1995). The required $P$-value limit was calculated for the main and the sub-study and these bounds are indicated in the legend of the Table 7.1, which reports the inference results. To depict the summary profile of the response to oxytocin administration in the two groups, a median smooth was used. This approach gave an estimate that was robust to extreme values and sensitive to acute changes in hemodynamic variables. These were presented as graphic ensembles.

7.2.2. Results

Figure 7.1 shows ensembles of responses to oxytocin (percentage change in CO and SVR from the pre-oxytocin values) in the 32 patients receiving oxytocin alone, derived from the LiDCOplus monitor, and comparative CO data from the BioZ monitor.
Figure 7.1. Ensembles of changes in cardiac output as shown with each monitor in all patients receiving oxytocin alone (n = 32)

Each ensemble shows the percentage change for each patient (light gray) and the median smooth for the group (black) for the 150 seconds following administration of oxytocin. The percentage change in CO at peak effect was 32.7 (32.8) vs. 27.8 (18.9) % in the LiDCOplus and BioZ machines respectively.

Figure 7.2. shows ensembles of the CO changes in patients randomised to oxytocin or a mixture of oxytocin and phenylephrine.
Figure 7.2. Ensembles of cardiac output changes from pre-oxytocin values as measured with the LiDCOplus and the BioZ monitors

Figure 7.3 shows ensembles of the responses (percentage change in HR, MAP, SV and SVR from pre-oxytocin values) of the 20 patients randomized to receive either oxytocin alone, or a mixture of oxytocin and phenylephrine.
Figure 7.3A-D. Ensembles of percentage changes from pre-oxytocin values in heart rate (HR – 7A), mean arterial pressure (MAP – 7B), stroke volume (SV – 7C), systemic vascular resistance (SVR – 7D)
Table 7.1. Haemodynamic data pre- and post oxytocin or mixture of oxytocin and phenylephrine

<table>
<thead>
<tr>
<th></th>
<th>Oxytocin (n = 10)</th>
<th>Oxytocin plus phenylephrine (n = 10)</th>
<th>95% Confidence Interval</th>
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<td>Mean</td>
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<td>HR</td>
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<td>CO(BioZ)</td>
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<tr>
<td></td>
<td>percent-peak</td>
<td>45.3</td>
<td>41.57</td>
</tr>
<tr>
<td></td>
<td>time to peak</td>
<td>62.9</td>
<td>36.31</td>
</tr>
<tr>
<td>CO(BioZ)</td>
<td>peak</td>
<td>6.4</td>
<td>1.64</td>
</tr>
<tr>
<td></td>
<td>percent-peak</td>
<td>23.7</td>
<td>18.39</td>
</tr>
<tr>
<td></td>
<td>time to peak</td>
<td>64.9</td>
<td>29.32</td>
</tr>
</tbody>
</table>

* = false discovery rate bound is 0.0057
HR = heart rate
MAP = mean arterial pressure
SV = stroke volume
SVR = systemic vascular resistance
CO = cardiac output
CO (LiDCO) and CO (BioZ) = cardiac output derived using the LiDCO and BioZ monitors respectively
Peak = maximum absolute response to oxytocin or oxytocin plus phenylephrine
Percent-peak = percentage change in variable from pre-oxytocin value at peak value

Table 7.1. shows a detailed between-group comparison of hemodynamic parameters pre- and post- administration of oxytocin or the oxytocin/phenylephrine mixture. Absolute peak HR was lower, and SVR and MAP significantly higher in the group receiving the mixture. Percentage changes in these parameters, as well as CO as measured by the LiDCOplus monitor, were also significantly different in the two groups. Times to peak changes were also different, with the exception of SV and CO changes. The BioZ monitor showed a similar trend in CO change, but between-group differences were not significant. In all patients, uterine contraction was assessed by the obstetrician as good.
7.2.3. Discussion

CO was significantly increased following 2.5IU oxytocin in the 32 patients receiving oxytocin alone. The two monitors indicated similar trends, adding to existing evidence suggesting that the LiDCOplus device is a useful beat by beat trend monitor in the setting of rapid changes in systemic vascular resistance in obstetric anaesthesia (Dyer and James, 2008). These findings were consistent with previous papers investigating the haemodynamic effects of bolus oxytocin (Pinder et al, 2002; Langesaeter et al, 2006).

In the twenty patients randomized to receive oxytocin or a mixture of oxytocin and 80µg phenylephrine, the hemodynamic responses to oxytocin were obtunded but not abolished (Table 7.1, Figures 7.2 and 7.3). The fact that the onset of the hemodynamic effects of oxytocin was not prevented, together with the transient delayed depression of HR and CO following the administration of the mixture, suggest that the timing of the use of phenylephrine to obtund the hemodynamic effects of oxytocin, could be improved. SV remained stable when the mixture was used, suggesting the Anrep effect, a positive inotropic effect which occurs in the presence of a sustained increase in afterload (von Anrep, 1912). This preliminary data suggest that further studies are required to establish the most effective doses and timing of combinations of oxytocin and phenylephrine in order to eliminate the unwanted cardiovascular effects of oxytocin. This could include the prior administration of phenylephrine.
7.3. Haemodynamic effects of oxytocin in preeclamptic patients

7.3.1. Patients and Methods

One aspect of a study examining the haemodynamic effects of SA in 15 patients with severe preeclampsia (Chapter 6), was the haemodynamic effects of oxytocin. For this purpose, the LiDCOplus system was used.

Thirty seconds after delivery, oxytocin 2.5 IU in 10mL water, was administered over a period of 30 seconds. No vasopressor was administered for up to 3 minutes after oxytocin, and no further intraoperative oxytocin was administered until the end of surgery, unless requested by the obstetrician in the case of uterine atony. The response to oxytocin was analyzed as follows: hemodynamic data were averaged for 30 seconds prior to the administration of oxytocin. The subsequent data were plotted against time to ascertain the time to maximum effect of oxytocin (taken as the highest value of CO), and the maximum response to oxytocin was estimated by averaging the data for 5 seconds before and after this point. This value was then compared to the pre-oxytocin value using analysis of variance for repeated measures.

7.3.2. Results

Figure 7.4. shows ensembles of the responses of the 15 patients to oxytocin (HR, MAP, SV, CO and SVR). Individual responses are shown as thin grey lines, and the ensemble average is depicted as a superimposed thick black line.
A

Oxytocin

B

Oxytocin
Figure 7.4A-E. Ensemble of haemodynamic changes following the administration of oxytocin

A. HR - Heart rate. At peak effect, HR increased from 84.7 (12.6) to 101.5 (15.9)* beats/min
B. MAP - Mean arterial pressure. At peak effect, MAP decreased from 114.3 (15.0) to 80.6 (15.3)* mmHg
C. SV - Stroke volume. At peak effect, SV increased from 82.9 (15.9) to 89.1 (17.3) (ns)
D. CO - Cardiac output. At peak effect, CO increased from 7.0 (1.5) to 9.1 (2.3)* L/min
E. SVR - Systemic vascular resistance. At peak effect, SVR decreased from 1295 (252) to 718 (282)* dyne.sec.cm^-5

* = value significantly different from baseline and post-delivery
P-value < 0.01
7.3.3. Discussion

A small dose of oxytocin administered 30 seconds after delivery, was associated with significant hypotension, and increases in HR and CO (Figure 7.4.). These transient haemodynamic effects were greater in these patients with severe preeclampsia than in those following the sympathectomy associated with SA (Chapter 5). SV did not increase significantly following oxytocin. By contrast, there were significant increases in both HR and SV following the administration of oxytocin in healthy patients (Chapter 7.2.2). This may reflect diastolic dysfunction in patients with severe preeclampsia, and the findings are in agreement with a recent publication examining CO changes during caesarean delivery in patients with severe preeclampsia, using whole body bioimpedance technology (Tihtonen et al, 2006). In patients not at risk for uterine atony, the ED90 for oxytocin has been found to be 0.35IU (Carvalho et al, 2004). A repeat of this study would be useful in high risk patients such as those with severe preeclampsia. In the interim, the data suggest that oxytocin is probably best administered by slow infusion in these patients during SA.
8.1. Introduction

Spinal anaesthesia for caesarean section in patients with severe preeclampsia is now widely accepted in the absence of contraindications, since maternal haemodynamic stability has been satisfactorily demonstrated in several studies (Chapters 1 and 6). The effect of spinal anaesthesia on short term neonatal outcome in healthy parturients, is also summarised in Chapter 1 of this thesis.

The first prospective randomised comparison of regional and general anaesthesia for caesarean section in preeclampsia was performed as recently as 1995. Three groups of patients with severe preeclampsia were randomised to receive epidural, combined spinal-epidural or general anaesthesia for caesarean section, with similar haemodynamic stability (as assessed by heart rate and blood pressure) and fetal outcome in each group (Wallace et al, 1995). However, patients with non-reassuring fetal heart traces were excluded from this study. No studies have prospectively addressed the problem as to whether fetal outcome is influenced by the method of anaesthesia in preeclamptic patients requiring emergency caesarean section for a non-reassuring fetal heart trace. It was therefore decided to test the hypothesis that the mode of anaesthesia influenced markers of neonatal hypoxia. Patients with preeclampsia and a non-reassuring fetal heart trace were randomised into 2 groups receiving either spinal or general anaesthesia for caesarean section. A study to examine neonatal outcome would require a prohibitively large numbers of patients. Therefore surrogate markers of neonatal outcome, primarily umbilical arterial base deficit, as well as umbilical arterial pH, Apgar scores, requirements for resuscitation, and complications were assessed. As further secondary
outcome measures, maternal haemodynamics, namely pulse rate and non-invasive blood pressure data, were also collected.

8.2. Patients and methods

Preeclampsia was diagnosed if the diastolic blood pressure after 20 weeks’ gestational age was greater than or equal to 90 mmHg on two separate occasions at least 4 hours apart, and proteinuria was found of greater than or equal to 1 gram or 2+ on urine dipstick in two clean midstream samples taken at least 4 hours apart, or greater than or equal to 300mg protein per 24 hours. Preeclampsia was regarded as severe if the systolic blood pressure exceeded 160 mmHg and/or the diastolic blood pressure exceeded 110 mmHg, obtained on at least two separate occasions, or if the patient had symptoms of imminent eclampsia (namely severe headache, visual disturbance, epigastric pain, hyper-reflexia, dizziness and fainting, or vomiting) and proteinuria on urine dipstick was 3+ or worse.

Patients with preeclampsia and a non-reassuring fetal heart trace were randomised by sealed envelopes into 2 groups of 35, for either spinal or general anaesthesia for caesarean section. Informed written consent was taken at the time of decision to proceed to caesarean section. The study commenced after the approval of the Ethics Committee of the University of Cape Town.

Exclusion criteria were patient refusal, or any other relative contra-indication to either general or spinal anaesthesia, in particular oral intake other than clear fluids within 4 hours of the intended surgery, body mass index greater than 35 kg/m², Mallampati score greater than 2, clinical signs of hypovolaemia, abruptio placentae, placenta praevia, coagulation abnormality, thrombocytopenia (platelet count < 75x10⁹/L), local or generalised sepsis, spinal deformity, cord prolapse, < 30 weeks’ gestation, or twin pregnancy.
Should any spinal anaesthetic take longer than 15 minutes to perform, the patient would receive general anaesthesia, and the data would be recorded as a failure of the technique. The data from these subjects would be assessed as a separate sub-group.

The antepartum management was according to the established protocol of our institution: If the patient was in established labour, an intravenous line was inserted, and a balanced crystalloid solution administered at 120 mL per hour. Patients not in labour were allowed free oral fluids. Seizure prophylaxis was administered to patients with severe preeclampsia, and consisted of magnesium sulphate (MgSO₄), administered as a loading dose of 4g intravenously, followed by 1g hourly intravenously. Dihydralazine was administered intravenously as a vasodilator, for additional blood pressure control against a standardized protocol that was identical in both groups. Prior use of other agents (α-methyldopa, morphine and dexamethasone) was recorded.

In the absence of labour, a baseline fetal heart rate of less than 100 or greater than 150 beats per minute, decreased or absent fetal heart rate variability (< 5 beats per minute) of 60 minutes’ duration, and the presence of repetitive decelerations were considered to be indications for delivery by caesarean section. Intrapartum abnormalities of the fetal heart rate that indicated caesarean section were, in addition to the above, the presence of late decelerations and variable decelerations greater than 60 beats per minute (Table 8.1.).
Table 8.1. Fetal heart rate abnormalities indicating caesarean section

<table>
<thead>
<tr>
<th>Fetal Heart Rate abnormalities</th>
<th>Intrapartum FHR abnormality</th>
<th>Antepartum FHR abnormality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Loss of STV</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Loss of STV, and bradycardia</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Loss of STV, early decelerations</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Late decelerations</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Variable decelerations</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Recurrent decelerations, not in labour</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Loss of STV and decelerations</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>TOTAL (n)</td>
<td>10</td>
<td>10</td>
</tr>
</tbody>
</table>

FHR = Fetal heart rate  
STV = Short term variability  
N/A = Not applicable, since defined fetal heart rate abnormalities are specific to the presence or absence of active labour

The decision to proceed with operative delivery was made by the obstetric team independent of the investigators. After a non-reassuring fetal heart trace had been identified, all patients were placed in the lateral position before transfer to theatre, and received 40% oxygen by face-mask.

Both groups of patients received 30 mL sodium citrate orally in theatre. Non-invasive monitoring consisted of electrocardiograph, blood pressure and pulse oximetry in both groups, as well as capnography in the general anaesthesia group.

Both groups had crystalloid infusions established prior to transfer to theatre. A total further fluid load of modified Ringer’s lactate (<750 mL) was given in the peri-induction period. Induction was not delayed in either group for the specific purpose of fluid administration, in keeping with published guidelines for normal parturients (Rout et al, 1993b).
After adequate pre-oxygenation, induction of general anaesthesia was with thiopentone 5 mg/kg, followed by an appropriate dose of intravenous magnesium sulphate (MgSO$_4$) for control of the pressor response to tracheal intubation. The dose of MgSO$_4$ was 45 mg/kg if there had been no prior administration of MgSO$_4$, and 30 mg/kg if the patient was currently receiving the drug. Muscle relaxation was achieved with suxamethonium 1.5 mg/kg, and 1 minute after administration, a rapid sequence intubation was performed. Maintenance of anaesthesia was with 50% nitrous oxide in oxygen, and 0.75 - 1.5% end-tidal isoflurane, and patients were ventilated to a target end-tidal carbon dioxide concentration of 30 - 34 mmHg, using a circle system, employing fresh gas flows of 5 litres per minute until delivery. A maternal arterial blood gas measurement was taken immediately post-delivery. Neuromuscular blockade was maintained using an infusion of suxamethonium (200mg / 200mL Plasmalyte B at 4mg per minute), monitored by a peripheral nerve stimulator. Oxytocin 5 IU, and morphine 0.05 mg/kg, were administered intravenously at delivery. Thereafter a continuous infusion of oxytocin was administered (20 IU/L, at 60 - 100 mL per hour). A further 0.05 mg/kg morphine was administered intravenously prior to extubation if the haemodynamic and respiratory status allowed it. Patients were extubated awake.

Recordings of heart rate, and non-invasive measurements of systolic, diastolic and mean blood pressure (Dinamap, Critikon, Florida) were made at the following time points:

Blood pressure was recorded pre-induction (starting systolic, diastolic and mean blood pressures were taken as the mean of two consecutive readings taken in the 3 minutes prior to induction of anaesthesia), immediately before intubation, and at 1 minute intervals after intubation for 10 minutes, and thereafter every 5 minutes until arrival in recovery room.
The management of patients in the spinal anaesthesia group was as follows:

All patients received 1.8 mL of hyperbaric 0.5% bupivacaine, with 10µg of fentanyl, administered at the L3/4 interspace in the absence of uterine contractions. After 20 seconds in the sitting position, patients were positioned supine, with 20 degrees of left lateral tilt, to minimize aortocaval compression. Block height was assessed using cold sensitivity to ethyl chloride spray. All mothers received 40% oxygen by face-mask. Oxytocin therapy after delivery was as for the general anaesthesia group. Heart rate and blood pressure were measured pre-induction of spinal anaesthesia in the same manner as in the general anaesthesia group, at 1 minute intervals post-induction for the next 10 minutes, and thereafter every 5 minutes until arrival in recovery room. Hypotension in either group, defined as a decrease in systolic blood pressure of more than 25% below the pre-induction value, was treated with ephedrine (5 mg boluses), given every minute until the blood pressure recovered to within 25% of the starting value. However, no ephedrine was given to patients with a mean arterial pressure greater than 100 mmHg. The total dose of ephedrine was recorded. A maternal arterial blood gas measurement was taken immediately post-delivery.

Further important time intervals were recorded:

- Time from arrival in theatre until induction of anaesthesia
- Induction to skin incision time
- Induction to uterine incision time
- Uterine incision to delivery time

All maternal medication received in the 24 hours prior to anaesthesia was carefully noted. Severity of disease (as assessed by the degree of hypertension and the requirement for vasodilator and/or seizure prophylaxis therapy, and degree of proteinuria) and presence or absence of labour was also recorded. In some patients antenatal fetal assessment was performed (umbilical artery Doppler and amniotic fluid index) at the discretion of the attending obstetrician. Resistance index was calculated from Doppler
measures of umbilical arteries using peak systolic velocity (S) and the end diastolic velocity (D) (Resistance index = S-D/S). Amniotic fluid index is the sum total of the deepest vertical pool of amniotic fluid in 4 quadrants (normal range 5 - 25 cm). Where available, these data were recorded. Intra-operative maternal blood loss was estimated from suction bottle measurement and weighing of swabs.

Neonatal outcome was assessed by a paediatrician dedicated to the study, and blinded to the method of anaesthesia. Assessment criteria were as follows:

A. At birth:
Neonatal weight, gender, gestational age (Ballard score), one and five minute Apgar score, arterial cord blood gas, and degree of resuscitation (face mask ventilation, intubation and ventilation, cardiopulmonary resuscitation) were recorded.

B. In the nursery:
Signs of respiratory distress using clinical and radiological diagnosis, and the need for respiratory support in the form of head box oxygen, nasal continuous positive airway pressure, intermittent positive-pressure ventilation, high frequency oscillatory ventilation or surfactant replacement therapy, was recorded.

A hypoxic-ischaemic encephalopathy score (Thompson et al, 1997) was performed in all babies with a 5 minute Apgar score of below 6 or with a cord pH of less than 7.1 and a base deficit of more than 10 mEq/L, daily for 5 days. An ultrasound scan of the head was done on day 5 in all preterm babies with a birth weight of below 1500 gram. Mortality at discharge was recorded. All the neonatal recordings were normal practice in the neonatal nursery and intensive care unit, and no additional blood sampling was performed solely for the purpose of the study.
Statistical Analysis:

Sample size was calculated as follows:

Previous studies have reported a normal value for umbilical arterial base deficit following elective caesarean section of the order of $5 \pm 3$ mEq/L (Ratcliffe and Evans, 1993; Krishnan et al, 1995). It was hypothesized that a mean base deficit of 8 mEq/L or more would, therefore, represent a clinically relevant level of acidosis. Assuming a standard deviation of 7.5, the study would have a minimum power of 90% to detect this magnitude of difference with 66 subjects (33 in each group). We therefore studied 70 patients. The Null hypothesis was that the method of anaesthesia (spinal or general) would make no difference to neonatal umbilical arterial base deficit in patients with preeclampsia and a non-reassuring fetal heart trace undergoing caesarean section.

Haemodynamic data were analysed within groups by analysis of variance (ANOVA) for repeated measures, and between groups by multiple dependent (group and time) ANOVA using the 95% confidence interval method for post hoc detection of significant differences. Qualitative data were assessed using appropriate non-parametric tests including the Fisher exact test, chi-square and the Kruskal-Wallis analysis of variance for multiple comparisons. Correlation between the use of ephedrine and neonatal base deficit was performed using regression analysis. Non-normally distributed data were compared between groups using the Mann-Whitney U-test. Regression analysis was also performed on maternal and neonatal umbilical arterial base deficit. All statistical analysis was performed using the Statistica Version 6 statistical package (StatSoft Inc, Tulsa, OK, USA).
8.3. Results

Table 8.1. shows the similar fetal heart rate abnormalities that indicated caesarean section in the two groups. Demographic data are presented in Table 8.2. The two groups of 35 patients were similar. There were no differences between groups in the use of non-study medications (alpha-methyldopa, dihydralazine, morphine or dexamethasone). Similar numbers of patients in each group were in active labour, and the severity of preeclampsia (as judged by the requirement for magnesium sulphate therapy, diastolic blood pressure >110 mmHg, dihydralazine therapy, both in terms of numbers receiving the drug and total dose, and proteinuria) was similar in the two groups, as were the gestational ages. In those patients in whom antenatal fetal assessment (umbilical artery Doppler and amniotic fluid index) was performed, there were no statistically significant between-group differences. No patient was excluded because the allowed time for spinal anaesthesia was exceeded, and no patients required conversion from spinal to general anaesthesia. The range of block height obtained was between T2 – T6, with 19 patients having a sensory level of T4. No patient complained of pain or required supplemental analgesia.
Table 8.2. Demographic data

<table>
<thead>
<tr>
<th>Maternal</th>
<th>General n = 35</th>
<th>Spinal n = 35</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years) (mean ± SD)</td>
<td>26 ± 6</td>
<td>25 ± 7</td>
</tr>
<tr>
<td>Weight (kg) (mean ± SD)</td>
<td>74 ± 11</td>
<td>75 ± 13</td>
</tr>
<tr>
<td>Height (cm) (mean ± SD)</td>
<td>157 ± 13</td>
<td>157 ± 12</td>
</tr>
<tr>
<td>Pre-induction systolic blood pressure (mmHg)</td>
<td>159 ± 30</td>
<td>155 ± 30</td>
</tr>
<tr>
<td>Pre-induction diastolic blood pressure (mmHg)</td>
<td>98 ± 20</td>
<td>97 ± 21</td>
</tr>
<tr>
<td>Pre-induction mean blood pressure (mmHg)</td>
<td>120 ± 22</td>
<td>121 ± 24</td>
</tr>
<tr>
<td>Gravidity (median (range))</td>
<td>1.5 (1-4)</td>
<td>1 (1-6)</td>
</tr>
<tr>
<td>Parity (median (range))</td>
<td>0.5 (0-3)</td>
<td>0 (0-5)</td>
</tr>
<tr>
<td>Active labour (n)</td>
<td>11</td>
<td>10</td>
</tr>
<tr>
<td>Induced, not in labour (n)</td>
<td>6</td>
<td>11</td>
</tr>
<tr>
<td>Not induced, no labour (n)</td>
<td>18</td>
<td>14</td>
</tr>
<tr>
<td>Diastolic blood pressure &gt; 110 mmHg</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>MgSO4 therapy (n)</td>
<td>19</td>
<td>20</td>
</tr>
<tr>
<td>Dihydralazine therapy (n)</td>
<td>9</td>
<td>13</td>
</tr>
<tr>
<td>Proteinuria 1-2+ (n)</td>
<td>13</td>
<td>12</td>
</tr>
<tr>
<td>Proteinuria 3-4+ (n)</td>
<td>22</td>
<td>23</td>
</tr>
<tr>
<td>Gestational age (weeks)</td>
<td>35.1 (3.2)</td>
<td>34.9 (2.6)</td>
</tr>
<tr>
<td>Gestational age &lt; 35 weeks (n)</td>
<td>18</td>
<td>15</td>
</tr>
<tr>
<td>Gestational age &lt; 34 weeks (n)</td>
<td>11</td>
<td>11</td>
</tr>
<tr>
<td>Gestational age 30 weeks (n)</td>
<td>3</td>
<td>1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Fetal / neonatal</th>
<th>General n = 35</th>
<th>Spinal n = 35</th>
</tr>
</thead>
<tbody>
<tr>
<td>Umbilical artery Doppler (Resistance Index):</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal (n)</td>
<td>12</td>
<td>10</td>
</tr>
<tr>
<td>Absent end-diastolic flow (n)</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Amniotic Fluid Index (Normal 5-25 cm)</td>
<td>9 (1-16)</td>
<td>6.5 (1-18)</td>
</tr>
<tr>
<td>Gestational age &lt; 35 weeks (n)</td>
<td>18</td>
<td>15</td>
</tr>
<tr>
<td>Gestational age &lt; 34 weeks (n)</td>
<td>11</td>
<td>11</td>
</tr>
<tr>
<td>Gestational age 30 weeks (n)</td>
<td>3</td>
<td>1</td>
</tr>
</tbody>
</table>

One severe pre-eclamptic in the general anaesthesia group was inappropriately recruited to the study, since she had a normal fetal heart trace. She was included in the data analysis. There were no differences in the outcome variables when the data analysis was performed with and without this patient. A further patient in the general anaesthesia group had an undiagnosed abruptio placentae, which resulted in a stillbirth; maternal data for this patient were analysed, but there were no neonatal data.
Consequently, 70 mothers were included in the data analysis, but only 69 neonates. There was a single case of sudden infant death syndrome in the spinal anaesthesia group on day 5 post-delivery.

Anaesthesia parameters and blood gas values are presented in Tables 8.3 and 8.4. The spinal anaesthesia group received significantly more fluid before induction of anaesthesia. Induction to skin incision times were longer by a mean of 2.1 minutes in the spinal group, and induction to uterine incision times were longer by 2.5 minutes. There was significantly more blood loss in the general anaesthesia group (446 vs. 393 mL); however no patient was regarded as having more than normal haemorrhage associated with caesarean section, and no patient required transfusion.

Maternal PaCO$_2$ values were significantly lower in the spontaneously breathing spinal anaesthesia group patients than in the general anaesthesia group patients whose PaCO$_2$ was controlled by the anaesthesiologist (28.9 vs. 32.4 mmHg).

Considering the primary outcome variable, the mean base deficit in the spinal anaesthesia group was significantly higher than in the general anaesthesia group (7.13 vs. 4.68 mEq/L).

The neonatal pH data were found to be non-normally distributed. Median umbilical arterial pH and mean standard bicarbonate values were significantly lower in the spinal anaesthesia group (7.20 vs. 7.23, and 18.4 vs. 20.4 mEq/L respectively; Table 8.4).
Table 8.3. Anaesthesia data, including maternal and neonatal measures

<table>
<thead>
<tr>
<th>Fluid management</th>
<th>General</th>
<th>Spinal</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preload (mL)</td>
<td>393 ± 114</td>
<td>454 ± 110</td>
<td>0.025</td>
</tr>
<tr>
<td>Total fluid (mL)</td>
<td>1053 ± 421</td>
<td>1131 ± 357</td>
<td>0.4</td>
</tr>
<tr>
<td>Blood loss (mL)</td>
<td>446 ± 126</td>
<td>394 ± 64</td>
<td>0.036</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Time points</th>
<th>General</th>
<th>Spinal</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>TTIA (min)</td>
<td>9.7 ± 3.9</td>
<td>11.1 ± 5.7</td>
<td>0.24</td>
</tr>
<tr>
<td>TISI (min)</td>
<td>4.2 ± 2.6</td>
<td>6.3 ± 2.6</td>
<td>0.001</td>
</tr>
<tr>
<td>TIUI (min)</td>
<td>7.1 ± 3.3</td>
<td>9.6 ± 2.9</td>
<td>0.002</td>
</tr>
<tr>
<td>TUID (min)</td>
<td>1.1 ± 0.6</td>
<td>1.2 ± 0.8</td>
<td>0.82</td>
</tr>
<tr>
<td>Duration of Surgery (min)</td>
<td>36.5 ± 13.1</td>
<td>37.3 ± 13.4</td>
<td>0.80</td>
</tr>
<tr>
<td>Ephedrine total dose (mg)</td>
<td>2.7 ± 8.9</td>
<td>13.7 ± 17.5</td>
<td>0.002</td>
</tr>
</tbody>
</table>

Data are presented as mean ± SD

TTIA = Time from arrival in operating theatre until induction of anaesthesia
TISI = Time from induction to skin incision
TIUI = Time from induction to uterine incision
TUID = Time from uterine incision to delivery

Table 8.4. Blood gas data in both mothers and neonates

<table>
<thead>
<tr>
<th>Maternal</th>
<th>General</th>
<th>Spinal</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>pH</td>
<td>7.35 ± 0.07</td>
<td>7.37 ± 0.04</td>
<td>0.064</td>
</tr>
<tr>
<td>PCO₂ (mmHg)</td>
<td>32.4 ± 5.1</td>
<td>28.9 ± 3.7</td>
<td>0.002</td>
</tr>
<tr>
<td>PO₂ (mmHg)</td>
<td>165.7 ± 52.5</td>
<td>172.5 ± 47.2</td>
<td>0.48</td>
</tr>
<tr>
<td>Base deficit (mEq/L)</td>
<td>6.6 ± 2.8</td>
<td>6.5 ± 2.7</td>
<td>0.69</td>
</tr>
<tr>
<td>Standard bicarbonate (mEq/L)</td>
<td>19.5 ± 2.3</td>
<td>20.0 ± 1.9</td>
<td>0.35</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Neonatal umbilical arterial</th>
<th>General</th>
<th>Spinal</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>pH (median and range)</td>
<td>7.23 (7.05-7.4)</td>
<td>7.20 (6.93-7.34)</td>
<td>0.046</td>
</tr>
<tr>
<td>PCO₂ (mmHg)</td>
<td>50.2 ± 10.5</td>
<td>48.7 ± 12.0</td>
<td>0.44</td>
</tr>
<tr>
<td>PO₂ (mmHg)</td>
<td>22.5 ± 18.7</td>
<td>21.0 ± 19.5</td>
<td>0.67</td>
</tr>
<tr>
<td>Base deficit (mEq/L)</td>
<td>4.68 ± 3.3</td>
<td>7.13 ± 4.0</td>
<td>0.02</td>
</tr>
<tr>
<td>Standard bicarbonate (mEq/L)</td>
<td>20.4 ± 3.0</td>
<td>18.4 ± 3.3</td>
<td>0.04</td>
</tr>
</tbody>
</table>

Data are presented as mean ± SD, unless stated

Median 1 minute Apgar scores were significantly lower in the general anaesthesia group (Figure 8.1.). There were no significant differences in the 5 minute scores (Figure 8.1.), and no correlation between Apgar scores and neonatal umbilical arterial base deficit.
Figure 8.1. Apgar scores at one and five minutes in the spinal (SP) (n=35) and general anaesthesia (GA) (n=34) groups

* Significant differences between groups
P-value < 0.05

Considering categorical data (Table 8.5), there were 22 neonates with a cord pH < 7.2, of whom 14 were in the spinal anaesthesia group and 8 were in the general anaesthesia group. Of the 5 neonates with a cord pH < 7.1, 4 were in the spinal anaesthesia group and 1 in the general anaesthesia group. Of the 7 infants with a base deficit of 8 - 10 mEq/L, 3 were in the spinal anaesthesia group and 3 were in the general anaesthesia group, while of the 9 with base deficits > 10mEq/L, 3 were in the general anaesthesia group and 6 in the spinal anaesthesia group.
### Table 8.5. Markers for fetal hypoxia

<table>
<thead>
<tr>
<th></th>
<th>General</th>
<th>Spinal</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Apgar score</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 Minute Apgar &lt;7 (n = 27)</td>
<td>14</td>
<td>13</td>
<td>1</td>
</tr>
<tr>
<td>5 Minute Apgar &lt;7 (n = 1)</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td><strong>Neonatal acidosis</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Umbilical arterial pH</td>
<td>n</td>
<td>n</td>
<td></td>
</tr>
<tr>
<td>pH &lt; 7.2 (n = 22)</td>
<td>8</td>
<td>14</td>
<td>0.20</td>
</tr>
<tr>
<td>pH &lt; 7.1 (n = 5)</td>
<td>1</td>
<td>4</td>
<td>0.20</td>
</tr>
<tr>
<td><strong>Neonates requiring resuscitation</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Face-mask oxygen (n = 30)</td>
<td>18</td>
<td>12</td>
<td>0.20</td>
</tr>
<tr>
<td>Intubation (n = 5)</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>CPR + Drugs (n = 2)</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Total requiring resuscitation</td>
<td>22</td>
<td>15</td>
<td>0.07</td>
</tr>
<tr>
<td><strong>Complications</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Respiratory Distress</td>
<td>n</td>
<td>n</td>
<td></td>
</tr>
<tr>
<td>Total = 8</td>
<td>5</td>
<td>3</td>
<td>0.6</td>
</tr>
<tr>
<td>Requiring IPPV</td>
<td>2</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Hypoxic Ischaemic Encephalopathy:</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

_Umbilical arterial base deficit_

- **Base deficit 5 - 7.9 mEq/L (n = 23)**
  - n
  - 17
  - 0.02
- **Base deficit 8 - 10 mEq/L (n = 6)**
  - n
  - n
- **Base deficit >10 mEq/L (n = 9)**
  - n
  - 6
  - 0.49

Neonatal blood gases could not be obtained in 2 patients from the general anaesthesia group and 1 patient from the spinal anaesthesia group. There were no significant between group differences apart from a higher incidence of mild base deficit in the spinal anaesthesia group (5 - 7.9 mEq/L). The requirements for in-theatre or nursery resuscitation were similar.
There was a weak correlation ($r = 0.36$) between maternal base deficit and neonatal base deficit (Figure 8.2).

Figure 8.2. Correlation between maternal and neonatal base deficit (BD) in the entire study cohort, showing regression line and 95% confidence intervals of the mean

Maternal BD: Neonatal BD: $R = 0.36$, $P$-value = 0.003
Neonatal BD = 2.73 + 0.50$x$
This correlation was stronger in the spinal anaesthesia group ($r = 0.47$; Figure 8.3.) than in the general anaesthesia group ($r = 0.29$; Figure 8.4.):

![Graph showing correlation between maternal and neonatal base deficit (BD).](image)

**Figure 8.3.** Correlation between maternal and neonatal base deficit (BD) in the spinal anaesthesia group, showing regression line and 95% confidence intervals of the mean

*Maternal BD: Neonatal BD: $R = 0.47$*  
*P-value = 0.005*  
*Neonatal BD = 2.79 + 0.67 \times X*
Haemodynamic data for the pre-anaesthetic measurement, the subsequent 10 minutes, and the immediate postoperative measurement are presented in Figure 8.5. At several time points the heart rate, and the systolic, diastolic and mean blood pressures were significantly lower in the spinal anaesthesia group. There was no significant correlation between the number of minutes spent at more than 25% below the baseline mean arterial blood pressure and the neonatal base deficit in either group (r = 0.23 for the general anaesthesia group, and -0.14 for the spinal anaesthesia group). There was also no significant correlation between absolute changes in mean arterial pressure and neonatal base deficit in either group (r = 0.09 for the general anaesthesia group, and -0.09 for the spinal anaesthesia group). There was no significant between-group difference in the duration of time spent at blood pressures <25% baseline. Significantly more ephedrine was required in the spinal
anaesthesia group (13.7 vs. 2.7 mg; Table 8.3), but there was no correlation between ephedrine utilization and neonatal base deficit in either group.

Figure 8.5. Changes in heart rate and mean arterial pressure in the general anaesthesia (GA) and spinal anaesthesia (SP) groups (mean ± SD)

* Significant differences between groups
P-value < 0.05
Time points refer to minutes post induction of anaesthesia
Prean = Pre-anaesthetic measurement
End = Immediate post surgery measurement
8.4. Discussion

There have been no previous published prospective randomised trials comparing spinal and general anaesthesia for caesarean section in severe pre-eclampsia, where the indication for operative intervention is a non-reassuring fetal heart trace. The present study addressed the issue of neonatal outcome while also comparing haemodynamic data in the two groups. The primary outcome measure was mean neonatal umbilical arterial base deficit, since variations in maternal ventilation will alter umbilical arterial pH, and therefore umbilical arterial base deficit is a more specific index of the metabolic component of acid-base balance (Reynolds et al, 2002). Spinal anaesthesia was associated with a significantly greater mean umbilical arterial base deficit and a lower median umbilical arterial pH than general anaesthesia. One minute Apgar scores were lower after general anaesthesia. Pulse rate and blood pressure measurements were acceptable in these two groups presenting for urgent caesarean section.

It is likely that there are many influences on neonatal outcome following caesarean section in preeclampsia. These include severity of the maternal and fetal condition, anaesthesia and surgical management. Fetal development is related to gestational age, and to chronic utero-placental insufficiency, which results in intrauterine growth restriction. In addition, any acute maternal deterioration may impact unfavourably on fetal outcome. The equivalence between the two study groups in terms of maternal and neonatal demographic and clinical data, in particular the severity of maternal disease, the presence or absence of active labour, and the gestational age, allowed the influence of anaesthesia to be assessed independently.

To identify perinatal morbidity, the positive predictive value of an antepartum fetal heart rate non-stress test in high risk pregnancy is approximately 55% (Lenstrup and Haase, 1985), while the positive predictive value of late decelerations during labour, for fetal acidaemia is 30 – 40% (Spencer, 1993). In the present study, the neonates clearly represented a high risk group, since
in addition to the abnormal fetal heart trace, a large proportion of the mothers had severe preeclampsia, and most had a compensated metabolic acidosis, probably indicating poor tissue perfusion; furthermore, a large proportion of the neonates were pre-term. Fetal scalp blood sampling could not be performed due to the possibility of an increased risk of vertical transmission of the Human Immunodeficiency Virus.

In our study, considering the data pertaining to anaesthesia, the time from induction of anaesthesia to skin incision was statistically but probably not clinically significantly shorter in the general anaesthesia group. Thus, potentially harmful delays attributable to spinal anaesthesia (Wainwright, 1996) did not apply in this study. The significantly lower Apgar scores at one minute in the general anaesthesia group is in keeping with previous studies (Ratcliffe and Evans, 1993; Roberts et al, 1995; Mueller et al, 1997), and probably represents transient sedation of the neonate from the anaesthetic agents.

In elective, uncomplicated term pregnancies, one major retrospective study indicated a significantly increased degree of neonatal acidosis (umbilical arterial pH), in parturients receiving either spinal or epidural anaesthesia when compared with general anaesthesia (Roberts et al, 1995). The acidosis was attributed in part to an increased umbilical arterial PaCO\(_2\) due to maternal hypoventilation during regional anaesthesia. There was also a higher incidence of maternal hypotension in patients having regional anaesthesia in this study. The significantly lower maternal PaCO\(_2\) in the spinal anaesthesia group in the present study probably reflects a respiratory compensation in a patient with a metabolic acidosis. The resultant mild hypocarbia may have adversely influenced uterine perfusion, although a previous study suggests that more severe hypocarbia than that seen in the current investigation may be required to decrease uterine perfusion significantly (Levinson et al, 1974). No study has examined the influence of maternal ventilation on utero-placental perfusion in patients with preeclampsia. A recent meta-analysis examined the effects of regional versus general anaesthesia for caesarean section on fetal acid-base balance, predominantly in healthy parturients. This
paper suggested that mean values for umbilical arterial base deficit are higher in patients receiving spinal than epidural or general anaesthesia, and that this was independent of the use of ephedrine (Chapter 1) (Reynolds and Seed, 2005). In the current prospective, randomised study, the significantly greater mean neonatal umbilical arterial base deficit and lower median umbilical arterial pH in the spinal anaesthesia group requires explanation. Investigations of the use of ephedrine as the vasopressor in spinal anaesthesia for caesarean section in healthy parturients have shown that ephedrine is associated with more neonatal acidosis than phenylephrine (Lee et al, 2002). An increased umbilical arteriovenous CO₂ difference has been demonstrated in a comparison between ephedrine and phenylephrine, implying an increased fetal metabolic rate secondary to ephedrine-induced β-adrenergic stimulation (Cooper et al, 2002), Chapter1. In the current study, significantly less ephedrine was used in the general anaesthesia group. However, the median pre-delivery dose of ephedrine in the spinal anaesthesia group was zero. There was no correlation between ephedrine utilization and neonatal base deficit in the spinal anaesthesia group overall, and in particular in the case of neonates with severe acidosis (base deficit >10 mEq/L). Thus the significantly higher base deficit in the spinal anaesthesia group did not appear to be attributable to a few patients with severe hypotension.

After the difference in base deficit was discovered, post-hoc analysis was performed to examine the influence of disease severity (maternal diastolic blood pressure > 110 mmHg) (Table 8.6.).
Table 8.6. Influence of maternal disease severity on maternal base deficit

<table>
<thead>
<tr>
<th>Between-group analysis</th>
<th>General</th>
<th>Spinal</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>DBP &lt;110mmHg (n)</td>
<td>15</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>NN Base deficit</td>
<td>4.4 ± 3.1</td>
<td>5.2 ± 3.1</td>
<td>0.49</td>
</tr>
<tr>
<td>DBP &gt;110mmHg (n)</td>
<td>20</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>NN Base deficit</td>
<td>5.0 ± 3.4</td>
<td>8.7 ± 4.0</td>
<td>0.007</td>
</tr>
</tbody>
</table>

**Neonatal acidosis**

<table>
<thead>
<tr>
<th>General</th>
<th>Spinal</th>
</tr>
</thead>
<tbody>
<tr>
<td>DBP &lt;110mmHg (n)</td>
<td>15</td>
</tr>
<tr>
<td>NN Base deficit</td>
<td>4.4 ± 3.1</td>
</tr>
<tr>
<td>DBP &gt;110mmHg (n)</td>
<td>20</td>
</tr>
<tr>
<td>NN Base deficit</td>
<td>5.0 ± 3.4</td>
</tr>
<tr>
<td>P-value</td>
<td>0.6</td>
</tr>
</tbody>
</table>

*DBP = Diastolic Blood Pressure*

*NN = Neonatal*

This showed that, in the absence of a diastolic blood pressure > 110 mmHg, there was no difference in mean neonatal base deficit between groups. However, in those mothers with a diastolic blood pressure > 110 mmHg, the spinal anaesthesia group had a significantly greater neonatal base deficit than the general anaesthesia group (Table 8.6., upper panel). Furthermore, when this criterion was applied within groups, there was no difference in neonatal base deficit in the general anaesthesia group, but in the spinal anaesthesia group those neonates whose mothers had a diastolic blood pressure > 110 mmHg had significantly higher base deficit values than neonates whose mothers did not show this degree of hypertension (Table 8.6., lower panel). This observation should be interpreted with caution, in view of the fact that the original hypothesis was not designed to test differences between groups based on maternal disease severity.

It should be noted that following uncomplicated vaginal delivery, umbilical arterial base deficit is between 4 and 10 mmol/L (Reynolds et al, 2002). Therefore, the range of base deficit found in this study is relatively reassuring. Although the degree of acidosis was worse in the spinal anaesthesia group, the median value for 1 minute Apgar scores was lower in the general anaesthesia group. A published study concluding that Apgar scores are a
better predictor of neonatal outcome than fetal pH, suggests that the small differences in the base deficit are clinically unimportant given the similar five-minute Apgar scores in this study (Casey et al, 2001).

Considering the categorical neonatal data, statistical significance was only achieved when comparing the incidence of base deficit in the range 5 to 7.9 mEq/L, where the incidence was higher in the spinal anaesthesia group. The level of fetal acidaemia that correlates with an increasing risk of neurological deficit has been found to be a pH of less than 7.0 and a base deficit of more than 16meq/L (MacLennan, 1999). The increased numbers in the spinal group in the categories of pH <7.20 and base deficit >10 mEq/L suggest that in a much larger study powered to detect differences in these distributive data, there might have been a low, but significantly increased incidence of clinically important acidosis in the spinal group. There was a trend towards an increased requirement for resuscitative measures in the general anaesthesia group (Table 8.5.). Retrospective analysis suggests that the data had 90% power to detect differences in this variable.

There were two neonatal deaths in this study. The one neonatal death in the general anaesthesia group was due to undiagnosed abruptio placentae, which resulted in a stillbirth, and could not be attributed to the anaesthetic technique. The single case of sudden infant death syndrome at 5 days of age in the spinal anaesthesia group, was also unlikely to be attributable to the method of anaesthesia.

One early study performed in the absence of acute fetal compromise, demonstrated that the differences between base deficit values between women with preeclampsia and their fetuses was greater than in healthy parturients (simultaneous blood micro-samples were taken from the maternal ear and uterine cervix and the fetus) (Tervila and Vartiainen, 1975). In the present study, the correlation (r = 0.36) between maternal base deficit and neonatal base deficit, which was stronger in the spinal anaesthesia group (r = 0.47) than in the general anaesthesia group (r = 0.29), suggests some association between preeclampsia and poor placental perfusion, although the
relationship is weak. Measuring the maternal base deficit may therefore help identify infants at greatest risk.

One early investigation comparing general and epidural anaesthesia for caesarean section in preeclampsia showed considerable haemodynamic instability in the general anaesthesia group, including marked systemic and pulmonary hypertension on intubation. However, the sample sizes were small (a total of 17 patients were studied), and no pharmacological measures were employed to obtund the intubation response (Hodgkinson et al, 1980). In the current study involving urgent caesarean section, a previously validated method of controlling intubation response was employed (Ashton et al, 1991) and haemodynamic responses were acceptable. Similar haemodynamic responses were achieved in the spinal anaesthesia group, although the blood pressures were significantly lower in this group at several time points. It should however be recognized that cardiac output may correlate better than upper limb blood pressure with fetal acidosis (Robson et al, 1992). In a previous study involving a group of 12 preeclamptic patients undergoing spinal anaesthesia for elective caesarean section, in whom the placental uterine artery circulation was studied using a pulsed colour Doppler technique, a marked increase in uterine artery pulsatility index as a sign of increased vascular resistance was seen in only one patient during a period of severe maternal hypotension (Karinen et al, 1996). In the current study, blood pressure changes of the magnitude measured in the spinal anaesthesia group might well have had no clinically detrimental effect on the fetus in normal parturients. However, in the setting of emergency caesarean section in severe preeclampsia with fetal compromise, and in combination with mild hypocarbia induced by maternal hyperventilation, even a modest lowering of the blood pressure could have contributed to decreased placental perfusion. This could explain the increased umbilical arterial base deficit demonstrated in the spinal group.
This study shows that spinal anaesthesia for caesarean section in preeclamptic patients with a non-reassuring fetal heart trace may be associated with a higher mean neonatal umbilical arterial base deficit and a lower median umbilical arterial pH than general anaesthesia. The clinical significance remains to be established.
Chapter 9
Conclusions and recommendations for the practice of spinal anaesthesia for caesarean section

9.1. Introduction

The literature pertaining to the haemodynamics of spinal anaesthesia for non-emergency caesarean section was extensively reviewed (Chapter 1). A validation study was performed employing recently developed minimally invasive cardiac output technology based upon pulse wave form analysis. Further studies described in this thesis have addressed several unresolved important clinical aspects in this field. These were: the haemodynamic effects of spinal anaesthesia per se, and of fluid, vasopressor and oxytocin therapy in healthy parturients. Also studied were the effects of spinal anaesthesia and vasopressor therapy in patients with severe preeclampsia, and short term neonatal outcome after spinal anaesthesia in preeclamptic patients.

It must be emphasised that the conclusions drawn from this research are applicable to the cohort of patients studied, namely women from an urban, low resource, and culturally heterogeneous community, who were referred for delivery to secondary or tertiary level care maternity centres in the public health sector of South Africa.

9.2. Conclusions

The LiDCO\textit{plus} monitor, calibrated with lithium dilution, showed acceptable agreement with thermodilution in patients with postpartum complications of preeclampsia, suggesting that this form of minimally invasive monitoring could have valuable applications in the management of critically ill obstetric patients.
From the point of view of obstetric anaesthesia research, the results suggest adequate accuracy for measurement of absolute values of CO (Chapter 3).

Although existing literature shows that colloids administered as a preload are undoubtedly superior to crystalloid in reducing spinal hypotension, rapid crystalloid coload was shown to have a benefit in terms of reducing ephedrine requirements pre-delivery during SA for CS, when compared with crystalloid preload (Chapter 4).

Meticulous positioning of the patient in order to minimise aortocaval compression, together with effective fluid management and choice of dose local anaesthetic and combination with opiate, as practiced in the studies described in this thesis, have reduced, but not eliminated hypotension during spinal anaesthesia for caesarean section.

Spinal anaesthesia in healthy parturients, employing careful left lateral tilt and crystalloid coload, induced a marked decrease in systemic vascular resistance. There was a partial compensatory increase in maternal cardiac output, on the basis of increases in both heart rate and stroke volume in cases in whom significant hypotension occurred (Chapter 5). This finding, in keeping with recent literature, suggests that a considerable component of spinal hypotension may be attributable to the effects of SA-induced sympathectomy on the arterial circulation. In patients with treated severe preeclampsia and baseline SVR at the upper limit of normal, spinal anaesthesia was associated with a stable cardiac output, and modest afterload reduction (Chapter 6). This suggests that single shot spinal anaesthesia is the method of choice for caesarean section in these patients, in the absence of contraindications. The finding that spinal anaesthesia is associated with more neonatal acidosis than general anaesthesia (Chapter 8), indicates that even minor degrees of hypotension may cause fetal compromise in this high risk group, even if CO is well maintained. This is in agreement with the early literature on the healthy obstetric population, which
shows that flow in the widely dilated uterine artery is largely pressure dependent (Greiss, 1966).

The LiDCO plus monitor was found to be a useful research tool in the setting of rapid changes in haemodynamic indices, in particular SVR. Following the administration of vasopressors, trends in CO change observed with the bioimpedance monitor were in the same direction as with the pulse wave form monitor (Chapters 5 and 7). In healthy patients, phenylephrine was found to increase SVR and reduce CO in absolute terms, and in comparison with ephedrine. Furthermore, the rapid onset of the pressor effect of phenylephrine coincided with the effect on CO, while in the case of ephedrine, the pressor effect occurred after CO had increased (Chapter 5). This suggests that not only is phenylephrine more effective in small doses in restoring baseline SVR and CO, but the rapid pressor effect could also contribute to avoidance of nausea and vomiting. However, the strong correlation between heart rate changes and CO, indicates that should phenylephrine be used in doses associated with hypertension and bradycardia, this would result in significant decreases in maternal CO. In patients with severe preeclampsia, a small bolus dose of phenylephrine caused a return of the SVR to baseline values, reduced HR, and tended to reduce CO (Chapter 6).

A small bolus of oxytocin caused a marked decrease in SVR, accompanied by hypotension, tachycardia and a compensatory increase in CO. In healthy patients this compensation was due to an increase in HR and SV, while in preeclamptic patients the compensation was largely heart rate mediated (Chapter 7).
9.3. Recommendations

9.3.1 Recommendations for health service delivery

In making recommendations for the safe practice of spinal anaesthesia, one should consider the widely diverse settings in which mothers are delivered. Particularly in busy obstetric units, obstetricians often work under considerable pressure, and the medical assessment of patients is sometimes not ideal. Some units in South Africa are positioned in remote locations with minimal specialist input. Of special concern are fluid balance and undiagnosed co-morbidities such as valvular heart disease and abnormal ventricular function, on the basis of either chronic hypertension or cardiomyopathy. It thus behoves the anaesthesia provider, who is often not a specialist, to assess the maternal medical condition carefully, and ensure that above all, patients do not receive single shot spinal anaesthesia when there are contraindications. When spinal anaesthesia is selected as the method for caesarean section, it is important for all practitioners, particularly inexperienced non-physician anaesthesia providers, to understand the haemodynamic effects of spinal anaesthesia, and to have clear guidelines for the safe use of fluids and vasopressors in each clinical setting.

Although colloids have proven benefits over crystalloid preload, crystalloid coloading is an alternative in elective cases, provided it is clearly understood that the benefit is short-lived in terms of intravascular half-life. The added expense of colloids in high turnover maternity units probably does not justify their routine administration. Thus a rapid crystalloid coload of 20 mL/kg is recommended as the initial fluid intervention in healthy patients. Should further fluids be required, either due to underestimation of the fluid deficit, or to blood loss, rapid administration of a colloid solution is recommended while blood products are awaited.

The research presented in this dissertation relating to haemodynamic changes associated with induction of spinal anaesthesia, shows that afterload reduction is the most important effect, and that CO is well preserved.
Hypotension during spinal anaesthesia for caesarean section can be categorised as part of three main clinical scenarios:

1. Hypotension and an increased heart rate:
This was the typical response in the studies described in this thesis in healthy patients, and maternal CO was increased relative to baseline levels, in partial compensation for the decreased SVR and hypotension. Phenylephrine is recommended in this situation, to restore SVR and baseline CO. Prophylactic phenylephrine is not recommended, and may cause unnecessary hypertension. A bolus dose of 80µg in response to a 20% decrease in MAP restored SVR and CO to baseline values (Chapter 5). This could be followed by low dose continuous infusion (25 – 50 µg/min) or intermittent boluses as necessary, should blood pressure again decrease. In patients with preeclampsia, a 50µg bolus of phenylephrine effectively restored SVR, after a 20% decrease in MAP (Chapter 6). The close correlation between heart rate and CO changes after the administration of either vasopressor, indicates that heart rate is the most important surrogate marker for maternal CO in normal clinical practice. In general, doses of phenylephrine which cause bradycardia and hypertension, result in clinically significant reduction in maternal CO and cannot be recommended. In addition, in busy maternity units with limited resources, in which a small unknown proportion of patients may have impaired ventricular function, high doses of phenylephrine are particularly undesirable, since a sudden rise in SVR could be poorly tolerated in this situation.

2. Hypotension and bradycardia:
This is an uncommon situation (no cases in the 44 recruitments to the study described in Chapter 5), but potentially life-threatening. It has been attributed to the activation of cardiac reflexes in response to sudden decreased venous return and left ventricular end-diastolic volume. One possibility is the Bezold-Jarisch reflex, in which sudden underfilling of the left ventricle induces activation of C-fibres in the left ventricle, with subsequent increased vagal output from the medulla, accompanied by decreased noradrenaline release in
the sympathetic nerve terminals and increased activity in the sympathetic vasodilator fibres in the muscle beds (Kinsella and Tuckey, 2001; Campagna and Carter, 2003). This results in a profound decrease in CO. An alternative aetiology may be rapid firing of venous baroreceptors (Dickinson, 1993). Although not formally studied, the final common pathway includes increased vagal output, and logical therapy includes increased uterine displacement, together with anticholinergics, preferably atropine if bradycardia is severe, followed by ephedrine and/or phenylephrine as necessary, and colloid therapy.

3. Persistent severe hypotension, any heart rate:
Although rare, undiagnosed abnormal ventricular function may require urgent intervention with ephedrine, followed by adrenaline.

The use of bolus oxytocin was associated with considerable transient haemodynamic instability in healthy and preeclamptic patients. Co-administration of phenylephrine obtunded these changes, but there was some “overshoot” of the effects of phenylephrine, suggesting that the timing and dose of phenylephrine could be improved, in circumstances in which a bolus of oxytocin is regarded as necessary (Chapter 7). If not, slow infusion of oxytocin 2.5 – 5.0 IU over 5 minutes is adequate in most cases, since the ED90 is 0.35 IU in patients not at increased risk of uterine atony (Carvalho et al, 2004), and 3.0IU in patients with labour arrest (Balki et al, 2006).

Spinal anaesthesia appears to be associated with more neonatal acidosis than general anaesthesia for caesarean section, as summarised in a recent meta-analysis (Reynolds and Seed, 2005). The same applies in preeclampsia, as shown in Chapter 8. However, the resurgence of the use of phenylephrine as a vasopressor for spinal hypotension, is likely to reduce this difference, and spinal anaesthesia remains the method of choice in the absence of contraindications, in view of the risks associated with tracheal intubation. This is of particular importance in preeclampsia, where intubation still carries a risk of mortality (CEMACH, 2007), despite established pharmacotherapy to obtund the intubation response (Ashton et al, 1991).
Pulse wave form analysis (LiDCOplus) was shown to be a useful research tool in obstetric anaesthesia. In particular, the demonstration of the exact short term haemodynamic changes following the administration of the vasopressors ephedrine and phenylephrine, will assist anaesthesiologists in their choice of vasopressor during SA for CS (Chapter 5).

The effective use of LiDCOplus to measure CO in patients with complications of severe preeclampsia, suggests that thermodilution may be supplanted in this area by this minimally invasive device. In healthy non-pregnant volunteers there is poor correlation between pulmonary capillary wedge pressure and left ventricular filling volume (Kumar et al, 2004). This, together with the poor correlation between central venous pressure and wedge pressure in patients with preeclampsia (Young and Johanson, 2001), suggests that the measurement of filling pressures may be unnecessary. Instead, all clinical indicators of intravascular volume and fluid responsiveness should be used, including passive leg raising (Teboul and Monnet, 2008) and measures such as systolic pressure variation, pulse pressure variation, and stroke volume variation (Monnet and Teboul, 2007; Belloni et al, 2008).

9.3.2. Recommendations for future research

In the course of performance of the research for this dissertation, several important new topics for study became apparent. These studies could contribute to safe practice of spinal anaesthesia and critical care management.

- Prevention is better than cure. Studies are required to predict which patients are likely to become hypotensive during SA for CS. In this regard, heart rate variability has shown great promise. Assessment of preoperative sympathovagal balance is of some value (Hanss et al, 2006), as is the supine stress test (Dahlgren et al, 2007). In addition, there is a need for the development of practical in-theatre predictors for hypotension, such as the recently examined “point correlation dimension”, a measure of heart rate variability (Chamchad et al, 2004).
Devices such as LiDCOplus may be used to investigate systolic pressure variation, pulse pressure variation and stroke volume variation. These measures of fluid responsiveness would be useful to study the venous circulation during spinal anaesthesia, and complement the work on the arterial circulation published in this thesis. Such studies would require the improvement of existing algorithms to allow for the measurement of these indices in spontaneously breathing patients (Teboul and Monnet, 2008).

Similar work in patients with severe preeclampsia could contribute to fluid management in untreated hypertensive patients, as well as patients with complications such as pulmonary oedema.

In view of the absence of data on uteroplacental perfusion in the studies on spinal anaesthesia in preeclampsia, future research remains to demonstrate the optimal use of vasopressors in this clinical setting.

Future studies are required of the optimal method of administration of oxytocin during SA for CS. These should examine not only haemodynamic effects, but also the effects on uterine tone of the exact method employed. This is particularly important in view of the potential for receptor down-regulation after repeated doses or prolonged infusion (Balki et al, 2009).

The haemodynamic effects of long-acting oxytocin, carbetocin, require study.

Ergometrine remains an important second line agent for the treatment of uterine atony during caesarean section. The haemodynamics of ergometrine during spinal anaesthesia requires further study, in view of the known vasoconstrictive side effects.
The goal of future research will be both to improve maternal comfort and overall experience of the delivery, and to impact upon the high maternal and neonatal mortality in poorly resourced and under-privileged population groups (Dyer et al, 2009).
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Publications and Presentations

Publications utilising data included in the dissertation


International Conference Presentations related to the Dissertation


