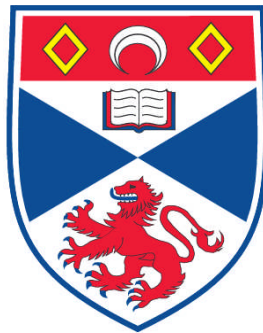


**THE INFERIOR VENA CAVAL COMPRESSION THEORY OF  
HYPOTENSION IN OBSTETRIC SPINAL ANAESTHESIA: STUDIES  
IN NORMAL AND PREECLAMPTIC PREGNANCY, A LITERATURE  
REVIEW AND REVISION OF FUNDAMENTAL CONCEPTS**

**Geoffrey H. Sharwood-Smith**

**A Thesis Submitted for the Degree of MD  
at the  
University of St. Andrews**



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**The inferior vena caval compression theory of hypotension in obstetric spinal  
anaesthesia: studies in normal and preeclamptic pregnancy, a literature review  
and revision of fundamental concepts**

Thesis Submission to the University of St Andrews for the Degree of Doctor of Medicine 2011.

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**Geoffrey H Sharwood-Smith**

**The inferior vena caval compression theory of hypotension in obstetric spinal anaesthesia: studies in normal and preeclamptic pregnancy, a literature review and revision of fundamental concepts**

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## **ABSTRACT**

Three clinical investigations together with a combined editorial and review of the cardiovascular physiology of spinal anaesthesia in normal and preeclamptic pregnancy form the basis of a thesis to be submitted for the degree of Doctor of Medicine at the University of St Andrews. First, the longstanding consensus that spinal anaesthesia could cause severe hypotension in severe preeclampsia was examined using three approaches. The doses of ephedrine required to maintain systolic blood pressure above predetermined limits were first compared in spinal versus epidural anaesthesia. The doses of ephedrine required were then similarly studied during spinal anaesthesia in preeclamptic versus normal control subjects. The principal outcome of these studies, that preeclamptic patients were resistant to hypotension after a spinal anaesthetic, was then further investigated by studying pulse transit time (PTT) changes in normal versus preeclamptic pregnancy. PTT was explored both as beat-to-beat monitor of cardiovascular function and also as an indicator of changes in arterial stiffness. The cardiovascular physiology of obstetric spinal anaesthesia was then reviewed in the light of the three clinical investigations, developments in reproductive vascular biology and the regulation of venous capacitance. It is argued that the theory of a role for vena caval compression as the single cause of spinal anaesthetic induced hypotension in obstetrics should be revised.

## **APPRAISAL 1**

### **Spinal versus epidural anaesthesia in severe preeclampsia**

Linked publication page 53

Sharwood-Smith G, Clark V Watson E. Regional anaesthesia for caesarean section in severe preeclampsia: spinal anaesthesia is the preferred choice. *Int J Obstet Anaesth* 1999; 8: 85-9.

#### **Introduction**

The first appraisal reviews the first investigation and linked publication; it also compares the study design and outcomes with the work of other investigators. It introduces the clinical and physiological concepts to be explored later in the thesis.

#### ***Background***

Between 1992 and 1994 I led a major review of clinical practice in the management of preeclampsia in the large tertiary referral obstetric unit at Edinburgh Royal Infirmary.<sup>1</sup> The areas of concern were the anaesthetic management of preeclamptic patients and the development of multidisciplinary clinical guidelines for use in the labour ward and obstetric high dependency unit. I identified the increasing use of spinal anaesthesia for Caesarean section in severe preeclampsia as an area with considerable potential for clinical research.

#### ***Pre-eclampsia: general and regional anaesthesia***

Preeclampsia is part of a spectrum of pregnancy related hypertensive disorders; it affects 6-8% of all pregnancies and increases the risk of maternal and foetal morbidity and mortality. Anaesthesia in preeclampsia similarly carries a relatively increased risk to mother and foetus, a problem that was recognised some forty years ago.<sup>2</sup> The main anaesthetic issues are related to endotracheal intubation. It can not only be technically difficult due to airway oedema, but may also cause acute reflex hypertension leading to eclampsia. The alternative regional anaesthetic techniques, spinal or epidural, have been known to cause hypotension in normal pregnancy since the 1950's. However, in preeclampsia, autonomic instability and a

relatively reduced plasma volume were more recently thought to contribute to the risk of even more profound hypotension after regional anaesthesia.<sup>3</sup> Also there was thought to be a risk of pulmonary oedema resulting from resuscitation attempts with uncontrolled administration of intravenous fluids and vasopressor drugs.<sup>3, 4</sup> Additionally, it was also suggested that an 'awake' mother could become anxious, thus precipitating hypertension and an eclamptic fit.<sup>3</sup> So there was a physiological ambiguity in interpreting these cardiovascular responses. For example, in the U.K., there was a perception that epidural anaesthesia for labour had relatively little effect in reducing blood pressure in preeclampsia; but, in an apparent paradox, there was also still thought to be a risk of regional anaesthesia causing severe hypotension in Caesarean section.<sup>2</sup> In North America, by contrast, epidural anaesthesia was increasingly being used for Caesarean section in preeclampsia.<sup>5</sup> The slower incremental onset of sensory and autonomic blockade with an epidural was thought to be more controllable and therefore less likely to precipitate hypotension. However, even in North America, spinal anaesthesia was still not recommended.<sup>6</sup> There were no studies cited in support of the view that spinal anaesthesia would cause severe hypotension. Clinical practice was therefore based on a consensus of theoretical considerations and the opinion of leading practitioners in the, still developing, speciality of obstetric anaesthesia.

### ***Evidence on the use of spinal anaesthesia in preeclampsia***

The increasing use of spinal anaesthesia in severe preeclampsia in our unit therefore seemed to go against this prevailing consensus. However there was recent support in the literature. A retrospective study comparing spinal versus epidural anaesthesia in severe preeclampsia had been reported in a conference abstract. Against the consensus, the study suggested that spinals were not more likely to cause hypotension. The study would subsequently be peer reviewed and published formally.<sup>7, 8</sup>



## **Design and Methods**

The simple working hypothesis of our first study, in line with contemporary thinking, was that spinal rather than epidural anaesthesia would be likely to cause hypotension; there would therefore be a consequent difference in ephedrine requirement to maintain blood pressure between the groups. The patients in the planned study would satisfy the following criteria: be non-labouring, have severe hypertensive, proteinuric preeclampsia; further, they would be stabilised on antihypertensive therapy, be scheduled for non-emergency Caesarean section and be suitable for randomisation to either spinal or epidural anaesthesia. The techniques used would be in line with the then standard clinical practice required to achieve adequate anaesthesia, i.e. in terms of the density and segmental height of sensory block for a Caesarean section. In both groups systolic blood pressure, measured non-invasively, would be maintained at above 70% of the baseline pre anaesthesia level by the administration of standardised boluses of ephedrine. This protocol followed a standardised version of normal clinical practice. The mean ephedrine dose required for each group would be compared, and this would be the primary outcome of the study. Secondary outcomes included gestational ages, adverse intra-operative events, neonatal Apgar scores and any continuing relevant health problems one month after delivery. Other than the actual method of anaesthesia all other clinical management including fluid administration and positioning would be standardised in both groups. It was not possible to blind an observer because the differences in the two anaesthetic procedures would be readily identified. Strict criteria were otherwise applied to generate equivalent groups for comparison. Factors such as extremes of height, weight or incidental complicating medical conditions were excluded so that the standardised anaesthetic technique could be used appropriately and safely.

## **Results**

Based on a pilot study it had been planned to power the study at 80% to detect a mean difference of 6mg ephedrine between the two groups. This would have required 40 patients for each arm of the study. However it quickly became clear that some patients required no ephedrine; more importantly, the spinal was delivering a significantly superior quality of anaesthesia in terms breakthrough pain and nausea. This posed a difficult

question. Was it justified to continue randomising patients so that some would receive what appeared to be an inferior technique? Importantly, there was recent evidence to suggest that epidural analgesia could be improved by the addition of an opioid.<sup>9</sup> Although a logical step in these circumstances, it was not our unit clinical practice to add an opioid to the spinal. This change in the protocol i.e. only using an opioid in the epidurals therefore created an element of non standardisation between the two groups, although it was probably clinically unimportant. However, despite the alteration to the technique, the epidural group continued to experience relatively poor anaesthesia. After some consideration, the ethics committee recommended that the study be concluded and the results reported after randomising a total of 28 patients. There was no significant difference in the mean ephedrine doses between the groups (5.2 mg in the spinal and 6.3 mg in the epidural group) and the neonatal Apgar scores were also similar.

## **Discussion**

### ***Defining pre-eclampsia***

The main problem for any study on anaesthesia in preeclampsia was, and remains, one of semantics and classification. Preeclampsia is a heterogeneous condition typically characterised by hypertension developing after the twentieth week of gestation with proteinuria. Various attempts have been made to classify preeclampsia, for example by using categories like mild, moderate and severe. A widely accepted classification defined certain minimum systolic and diastolic pressure limits.<sup>10</sup> Proteinuria was specified in terms of method of measurement and mass of protein excreted over 24 hours. Despite imposing such demanding criteria, the authors conceded that the causes of hypertension in pregnancy were largely unknown at the time. Severe preeclampsia, at various times in its development, can include hepatic, renal, haematological and cerebrovascular pathologies alone or in combination. Hypertension as a consequence of peripheral vascular endothelial pathology appeared to be the critical factor leading to the concerns that arterial pressure would be labile if of spinal anaesthesia was used. Therefore the presentation of 'severe' hypertension developing after the twentieth week of gestation was selected as the main criterion for including patients in our studies. Proteinuria, as strictly defined, was thought at the time to be a requirement

for the category 'severe preeclampsia'. However it was becoming clear that proteinuria can be latent and develop at any stage during the disease i.e. up to or after the point of delivery. It was, and is, also often difficult to measure reliably in a labour ward setting.<sup>11</sup> The differentiation of patients into 'pre-eclampsia' - hypertension with proteinuria, or 'pregnancy induced hypertension (PIH) - hypertension without proteinuria, appeared to represent different pathologies. Therefore there could be 'PIH', with varying degrees of proteinuria, or alternatively 'preeclampsia' with proteinuria, but only as specified. The heterogeneous nature of preeclampsia continues to challenge attempts to classify the pathology.<sup>12</sup>

For this first study the classical presentation of severe preeclampsia as 'severe hypertension and proteinuria 'as defined' was adopted.<sup>10</sup>

### ***Other studies***

In the single relevant previous publication already mentioned, Hood et al had retrospectively compared blood pressure changes and ephedrine doses between two groups: 103 women who had received spinals for Caesarean section and 35 who had been given epidural anaesthesia.<sup>8</sup> This study was useful and informative although physiological data and case selection were determined retrospectively

Fortuitously, when our proposed study was under consideration by the unit ethics committee, a second, but this time prospective, study was published by Wallace et al.<sup>13</sup> This study was a three way comparison between general, epidural and combined spinal epidural anaesthesia in severe preeclampsia. It was not therefore a direct comparison of spinal and epidural anaesthesia. Their approach was very different from that of our protocol. The inclusion criteria were relatively complex and standardisation of anaesthetic procedures was not attempted. Only non emergency cases were studied, however some had been labouring and had therefore received varying doses of oxytocic therapy. Their subjects had various degrees of proteinuria but nevertheless, for the purpose of the study, were classified as 'preeclampsia'. All patients had been given intramuscular magnesium sulphate, an eclampsia prophylactic and hypotensive agent. Rather than a period of blood pressure stabilisation on oral therapy they had been given intermittent ad hoc intravenous hydralazine boluses. The general anaesthetic group received relatively larger intravenous fluid volumes. The primary outcome was the mean arterial pressure of each group derived from non invasive blood pressure

measurements at various key times during the procedures. Secondary outcomes included intravenous fluid volumes administered and the recorded neonatal condition. The latter was assessed by Apgar scores, umbilical artery blood gases, birth weight and gestational age. Ephedrine doses were not reported, only the number of subjects in each group that actually received ephedrine. There were no significant differences between the groups in terms of mean blood pressure at key moments or in the secondary outcomes. The statistical power analysis suggested that the secondary outcomes of 'no differences' between the groups could include a type 2 error. The primary outcome did not appear to have been powered.

In more recent study Visalyaputra (2005) used another approach with a larger multicentre design comparing spinal versus epidural anaesthesia.<sup>14</sup> A total of 120 severely preeclamptic subjects were studied in five centres. The investigators noted that mean arterial pressure was frequently measured (every 2 minutes) to monitor hypotension although ephedrine was administered on the basis of systolic readings – raising the concerns on diastolic pressure estimation discussed below. 91% of both groups received magnesium sulphate and 34% of epidural and 39% of spinal groups were given intravenous hydralazine according to their protocol. There were varying numbers of twins and triplets delivered in each group. Pre-anaesthetic and intraoperative fluid volume ranges indicated difficulty in controlling these elements of clinical management. However the large number of subjects studied gave some statistical reliability to the principal outcome which supported the use of spinal anaesthesia in severe preeclampsia.

### ***This study***

The main advantages compared to the other studies were of clarity and simplicity; the two anaesthetic techniques, spinal and epidural anaesthesia, were directly compared. Confounding variables were reduced to the minimum that was clinically possible. The principal outcome, the intravenous ephedrine requirement to maintain systolic blood pressure above a defined level, was simple to record accurately for comparison between the groups.

The main disadvantages were that the numbers studied were relatively small, and we too could not exclude a type 2 statistical error; in other words there might in fact be a difference between the groups but we could not demonstrate it. However it can reasonably be argued that the decision, on ethical grounds, i.e. to complete

the study after 24 randomisations due the relatively poor anaesthesia of the epidural technique was of considerable clinical significance. Blood pressure trends were recorded as required for clinical monitoring. Although, with hindsight, additional blood pressure data would have been desirable, it would not however have affected the principal outcome of the study. In practice there are also there are reservations on the fidelity of non invasive of blood pressure diastolic pressure recording and therefore the derived value of mean arterial pressure. This is discussed and referenced in the linked article. The ‘gold standard’ of intra-arterial blood pressure monitoring was considered too invasive, and therefore unethical, unless specifically indicated for an unstable patient. Non invasive blood pressure (NIBP) recordings are difficult to track frequently and reliably in obstetrics due to patient movement and obesity and this issue is dealt with in detail in the third study

### ***Implications***

Our first study added to evidence suggesting that, far from creating hemodynamic instability, severe preeclampsia might exert a relatively protective effect, reducing the risk of hypotension. 36% of spinal and 50% of epidural subjects required ephedrine, in a relatively low dose, to maintain systolic blood pressure. This compared to the higher dose of ephedrine by then known to be required in 80% of normal pregnant women. These findings had been precisely predicted by the small but elegant studies of Assali more than forty years before.<sup>15</sup> He had found that normal pregnant compared to non pregnant women demonstrated a greatly increased sensitivity to hypotension after spinal anaesthesia; contrastingly the presence of severe hypertensive preeclampsia was associated with resistance to hypotension. The administration of an autonomic ganglion blocking drug had produced a similar result in a previous study. All subjects were studied in the supine position. These studies had been effectively lost to the emerging speciality of obstetric anaesthesia in the 1960’s. In consequence the alternative ‘single cause’ theory of hypotension in obstetric spinals has dominated anaesthetic textbooks and teaching for more than forty years.<sup>16, 17</sup> In this theory the gravid uterus was said to trap blood in the legs by compression of the inferior vena cava when the mother is in the supine position.

Further research, at this time, was planned as follows: a study on the apparent effect of preeclampsia in protecting against spinal induced hypotension would form the basis of a follow up investigation; then, any further investigations required and a detailed review of the physiology of obstetric spinal anaesthesia would be planned and undertaken to complete the series.

### **Publication and Impact of Research**

This first study was presented at the Obstetric Anaesthetists Association conference in 1998 and subsequently published the following year. Recent selected references indicate the impact of this study on changes in obstetric anaesthetic practice and education.<sup>18, 19, 20</sup>

## APPRAISAL 2

### Spinal anaesthesia in severe preeclampsia versus normal pregnancy

Linked publication page 58

Clark VA, Sharwood-Smith GH, Stewart AVG. Ephedrine requirements are reduced during spinal anaesthesia for caesarean section in preeclampsia. *Int J Obstet Anesth* 2005; 14: 9-13

#### Introduction

The idea for this study emerged from the earlier practice review, the first investigation and other published articles. It seemed, in line with Assali's studies,<sup>15</sup> that preeclampsia might actually exert a protective effect on the hypotension caused by sympathetic blockade with a spinal anaesthetic. If demonstrated in a study, this blood pressure stabilising effect would contrast with the profound hypotension, when untreated, seen after a spinal in normal pregnancy. The idea for this further study was clearly stated in the discussion section of the first publication.

#### Methods

This was a cohort study design. In other respects the methods used in the previous study were generally repeated to maintain consistency; anaesthetic and intravenous fluid administration were standardised, the preeclamptic patients were non-labouring, suitable for spinal anaesthesia and had already been stabilised haemodynamically. However we did amend the anaesthetic protocol in accordance with changes in our unit's clinical practice. Tighter blood pressure control meant that the trigger for ephedrine bolus administration was a reduction in systolic blood pressure to below 80 %, rather than 70% of the baseline recording. As previously mentioned, there was evidence that the addition of an opioid improved the quality of spinal and epidural anaesthesia; fentanyl was therefore added to the local anaesthetic.<sup>9</sup> Based on published investigations, the study was powered at 90% to show a significant difference of 11 mg in ephedrine requirement between the groups.

## **Results**

In the primary outcome the mean ephedrine requirement of the normal pregnant patients ( $27.9 \pm 11.6$  mg) was significantly greater than that of the pre-eclamptic group ( $16.4 \pm 15$  mg) ( $P < 0.01$ ). As an index of haemodynamic stability, the difference in ephedrine requirement suggested that preeclampsia exerted a protective effect, reducing the risk of hypotension.

## **Discussion**

### ***Foetal weight and vena caval compression***

Was the reduced ephedrine requirement of the pre-eclamptic group simply a matter of foetal 'weight'? Earlier gestation at delivery and foetal growth retardation are features of preeclampsia. A smaller foetus could theoretically cause less vena caval compression and therefore less hypotension during the spinal anaesthetic. The question had already been partly addressed in one study; resistance to 'supine hypotension' due to 'vena caval compression' had been demonstrated in a study of 128 non anaesthetised pre-eclamptic patients.<sup>21</sup> Later, in a more definitive study,<sup>22</sup> Aya et al were to investigate a preterm but otherwise normal control group and compare them to a preeclamptic group; the result again would suggest that the critical difference is related to the presence of preeclampsia, not foetal weight..

### ***NIBP measurement***

As already mentioned, NIBP measurements suitable for detailed analysis are inherently difficult to obtain. Consistently reliable and frequent readings are disturbed by patient movement. Diastole pressure and thus the derived function of mean arterial pressure are not always reliably identified,<sup>23</sup> and haemodynamic changes can be too rapid for the monitor to track. The gold standard of continuous intra-arterial blood pressure monitoring was considered to be too invasive for use in the majority of patients. This issue of beat-to-beat cardiovascular monitoring is difficult and was to be addressed specifically in our third study. In this third study, the subject of Appraisal 3, additional resources meant that continuous pulse pressure transit time data were available and non invasive blood pressure recordings could be made at 2 minute intervals. Although not



a primary outcome of the study, the arterial pressure trends of the two groups closely followed predictions from the first two studies. Reservations on diastolic pressure measurement fidelity remain however, and this is stated in the third publication.

### ***Non-stabilised preeclampsia***

Our two studies concerned women with stabilised hypertensive preeclampsia. Because of limited worldwide resources for antenatal care it is sometimes necessary to anaesthetise unstable preeclamptic patients. It is important to be clear that our findings could not necessarily be extrapolated to this unstable group.

### ***Competing Publication***

The results of a similar research project by Aya et al <sup>24</sup> were published as we revised our own submission in response to a peer review by the same journal. There were very similar inclusion criteria in the competing article and the primary outcome was also the dose of ephedrine needed to maintain blood pressure within defined limits. However there were considerable differences in clinical practice. Hypertension, usually an acute condition in preeclampsia, was only treated when there was ‘evidence of end organ damage’. Both groups were given an intravenous ‘prehydration’ load of 1.5 to 2.0 L. in an attempt to prevent hypotension after the spinal. Some, but not all, patients received magnesium sulphate, an eclampsia prophylactic and vascular smooth muscle relaxant. Blood pressure and heart rate changes were recorded following spinal anaesthesia.

In their study, Aya et al described their proposed physiological basis of both their normal clinical practice and study results as ‘speculative’. Their discussion was useful in that the uncertainty it communicated gave me an opportunity to explore the fundamental conceptions rooted in the early development of obstetric anaesthesia. The discussion, in study 1 as published, introduced the ideas which were further developed as discussion in the second publication. This issue is elaborated yet further in the editorial and review in Appraisal 4. In brief, there was no need to speculate. Critical published evidence supporting a physiological explanation for the differences in response to spinal anaesthesia in preeclamptic compared to otherwise normal pregnancy was already available. Cardiovascular changes in early normal pregnancy result in a generalised vasodilatory state with decreased responses to endogenous and exogenous pressor agents. <sup>25</sup>

Animal and human work had demonstrated the normal sequence of these cardiovascular changes in pregnancy.<sup>26, 27</sup> There is a compensatory increase in renin-aldosterone-angiotensin activity which restores the blood volume. Widespread vascular endothelial damage in pre-eclampsia leads to a failure of this normal vasodilatory response; hypertension may develop with an increased sensitivity to vasopressors and a relative hypovolaemia.<sup>28</sup> Subsequently, more extensive damage to the endothelial mechanism may further increase arterial pressure. Increased excitability or sensitivity to sympathomimetic agents in pre-eclampsia, a hypertensive state, does not necessarily indicate an increased underlying sympathetic neurogenic tone. There is evidence of increased sympathetic basal neuronal activity but, critically, it occurs in normal, not pre-eclamptic pregnancy. This was first demonstrated in animal work and appears to be required for the maintenance of arterial pressure and to prevent orthostatic hypotension.<sup>29</sup> Therefore when a spinal anaesthetic is given in normal pregnancy there is usually a profound hypotensive response, unless treated.<sup>30</sup> The relative part played by aortic and vena caval compression in causing hypotension, a core concept in this thesis, is discussed in Appraisal 4.

A further issue and a difference in our unit's clinical practice compared was the use of intravenous fluid in a so called prehydration, load. 'Prehydration' in non pre-eclamptic subjects had already been found to be relatively ineffective in maintaining blood pressure after spinal anaesthesia.<sup>31</sup> Attempts, on theoretical grounds, to forcibly hydrate, or prehydrate, a severely preeclamptic patient carries the risk of pulmonary oedema, a problem that developed when non pregnancy related critical care physiology was applied to pre-eclamptic patients.<sup>4</sup> This was an important concern in the triennial Confidential Enquiry in Maternal Deaths at the time.<sup>32</sup>

### **Publication and Impact of research**

The second study was presented as an abstract in 2001 and published after some delay in January 2005. Together with our first study the article is cited, among others, in the relevant Cochrane database review The recent impact is linked to that of study 1 and was discussed and referenced in Appraisal 1.

## APPRAISAL 3

### **The use of pulse transit time to assess cardiovascular changes in spinal anaesthesia: preeclampsia versus normal pregnancy**

Linked publications pages 63-71

Bruce J, Sharwood-Smith G, Drummond G. Pulse transit time: a new approach to haemodynamic monitoring in obstetric spinal anaesthesia. *Int J Obstet Anaesth* 2002; 11, Supplement 1, 1-38

Sharwood-Smith G, Drummond G, Bruce J. Pulse transit time confirms altered haemodynamic response to spinal anaesthesia in pregnancy induced hypertension. *Hypertension in Pregnancy* 2002; 21 suppl 1: 31

*Sharwood-Smith G, Drummond G, Bruce J. Pulse transit time confirms altered response to spinal anaesthesia in pregnancy induced hypertension. (poster annex to the above abstract).*

Sharwood-Smith G, Bruce J and Drummond G. Assessment of pulse transit time to indicate cardiovascular changes during obstetric spinal anaesthesia. *Br J Anaesth* 2006; 96: 100-5

## **Introduction**

### ***Outstanding issues in 2000- 2001***

There were two outstanding issues at the time. Doubts, expressed editorially, about the stability of severely pre-eclamptic patients after spinal anaesthesia continued to appear in the literature.<sup>33, 34</sup> Also, improved non invasive beat to beat cardiovascular monitoring was a desirable requirement for routine use in obstetric spinal anaesthesia. If such a hypothetical monitoring technique was found to be practicable, it seemed that it might also have the potential for use in more definitive investigations in normal and pre-eclamptic pregnancy.

### ***Cardiovascular monitoring***

We had already used ephedrine requirements as a surrogate for cardiovascular stability following spinal anaesthesia. Clinically, heart rate and NIBP were monitored during these studies. While other investigators had reported and evaluated them we had provided only limited data. However, clinically, it was very

important to avoid episodes of maternal hypotension and bradycardia; if prolonged these might reduce placental perfusion and therefore risk foetal asphyxia. In pre-eclampsia the advantage of accurate cardiovascular data recording would be that different rates of change, peaks and troughs in cardiovascular measurements, could be demonstrated. This would still apply, notwithstanding the standardised limits of systolic blood pressure change that were applied in our studies to determine the requirement for ephedrine administration. The difficulty, as previously discussed, was the relative unreliability of NIBP diastolic measurements. A technique that provided a non invasive beat-to-beat index of cardiovascular response to spinal anaesthesia and quantified arterial wall stiffness could be useful both for physiological research and also for development as a routine anaesthetic monitor. The significance of arterial stiffness is the issue of changes in vascular wall physical properties. This amounts firstly to structural changes: the relationship of vascular compliance to actin-myosin ratio and collagen properties. Animal studies of these structural vascular changes have utilised large vessels, for practical reasons, although the haemodynamic consequences appear to be in resistance vessels.<sup>35</sup> Increased vessel stiffness also relates to important functional changes driven by vascular endothelial cells.<sup>36</sup> In practice, for a study, there were three structural and functional states to consider: normal vascular function, pregnancy changes and those of preeclampsia. Of various potential approaches becoming available at the time the measurement of pulse wave velocity seemed to offer the greatest potential as an investigative tool.

### ***Pulse Wave Velocity (PWV)***

PWV is useful because it depends primarily on arterial wall stiffness. PWV increases with ageing due to increased stiffness of the vascular tree, a principle that was established nearly ninety years ago<sup>37</sup> Measurement of PWV simply requires the recording of two pressure waveform measurements separated by a known distance. This measurement is the pulse transit time (PTT) which is inversely related to the PWV.

Arterial stiffness can be described in several ways.<sup>38</sup> Compliance, familiar to anaesthetists in pulmonary physiology, is a volume, diameter or area change for a given pressure change. Elastance, the inverse of compliance, is relatively intuitive since as stiffness decreases so does elastance and therefore PWV.

There was one relevant study in the literature. PTT changes above and below the segmental level of an epidural block a regional block had been compared.<sup>39</sup> The investigators were interested in vascular wall tone differences due to a sympathetic block that was confined to the lower trunk and legs. PTT in the arm was used as a control. In a discussion more generally about vascular stiffness they noted that the function of smaller peripheral resistance arteries were affected by the structural wall changes; in particular the ratios of collagen, elastin and smooth muscle were important. They had not considered obstetric anaesthesia but the relevance and potential application in the study of pregnancy and pre-eclampsia were clear.

In 2000, fortuitously, an analogue computer from Leiden University capable of transferring electrocardiogram (ECG) data and photoplethysmography signals from routine monitoring equipment was on loan to a colleague working with non-obstetric patients. The time interval between the peak of the ECG 'R' wave and the maximum rate of the plethysmograph upswing could be measured using this equipment. The beat-to-beat PTT could then be computed, displayed and recorded in real time together with heart rate and systolic and diastolic blood pressure. Responding to a request for ideas with the potential for pulse transit time studies, I identified spinal anaesthesia in normal and pre-eclamptic subjects as a suitable 'case' for study. We therefore established a collaborative project and successfully applied for a grant from the Obstetric Anaesthetists Association. The grant subsequently funded additional equipment and a research assistant for six months. There were three principal questions to answer:

1. Could PTT reliably track beat to beat changes during obstetric spinal anaesthesia?
2. What would the relationship be of PTT to be to mean arterial pressure (as measured non-invasively)?
3. Would PTT changes demonstrate the predicted differences in arterial stiffness in pre-eclampsia?

In order to maximise the chances of obtaining a grant, and after negotiating a collaborative approach with both physiological and obstetric perspectives, we had opted to study PTT as a means of beat-to-beat cardiovascular monitoring in spinal anaesthesia as the primary outcome. The study of pre-eclamptic subjects was to be a secondary outcome but, apart from my own research interest, was also important for two reasons. If arterial structural and functional changes caused increased arterial stiffness in pre-eclampsia, PTT changes should reflect this. There should be a relative difference observed in both baseline PTT and also the rate of

change of PTT following spinal anaesthesia. If confirmed in a study it would support validation of the PTT technique for the intended purposes. In addition it would corroborate the primary outcomes in our first two studies on spinals in pre-eclampsia, and also in other related investigations as they were being reported in the literature.

## **Methods**

We had taken two years each to complete the previous two studies but, for this more demanding study that would require a dedicated research assistant, there was only six months funding available. We therefore recruited normal and pre-eclamptic subjects with varying degrees of proteinuria (therefore the subjects were referred to as having 'PIH'). The use of a dedicated research assistant to oversee physiological monitoring improved the accuracy of cardiovascular data acquisition and recording. Although it was by necessity an observational study, a critical element was the willingness of anaesthetic colleagues to delay the administration of a vasopressor until clinically required. In other words, as part of their routine practice, they did not always use a vasopressor prophylactically. This meant that PTT, heart rate and NIBP could be recorded before, during and after the administration of the spinal anaesthetic up to a specified key time. This time was called either the first intervention (of a vasopressor and/or a vagal blocking drug) or alternatively the peak PTT recorded if there was no intervention. For the purpose of the study, the interval between spinal administration and the peak PTT recording or anaesthetic intervention therefore represented the maximum change in recorded cardiovascular response to the spinal. The inference, again for the purpose of the study, was that this represented the maximum vasodilatation caused by sympathetic blockade. The rate of change of PTT could then be measured and compared between the two groups.

## Results

In an observational study of 73 patients 15 had severe pregnancy induced hypertension (as defined). In answer to the questions posed when the study was designed:

1. Beat-to-beat PTT was consistently displayed and recorded using input from standard anaesthetic monitors during spinal anaesthesia.
2. In the relationship between PTT and mean arterial pressure there was a significant correlation ( $r^2=0.55$   $P<0.0001$ ) before and after anaesthesia
3. The interval representing the greatest change in PTT or the time to first intervention occurred 2.4 minutes after spinal anaesthesia in the normotensive group and 5.0 minutes in the hypertensive group. Looking at the rate of change, PTT increased more rapidly in the normotensive group compared to the hypertensive group by a factor of 4.

## Discussion

Of the 73 patients investigated. 15 severely hypertensive patients were the maximum number of non emergency subjects that could be recruited within the time frame of 6 months, even in a large 6,000 delivery tertiary referral maternity unit. A condition of publication was that we calculate the sensitivity and specificity of changes in PTT to indicate the onset of hypotension. From the ROC curves, for a decrease in mean arterial pressure of, more than 10%, an increase in PTT of 20% was 74% sensitive and 70% specific. However there were reservations on interpreting this particular statistical exercise, particularly if PTT is being considered as a surrogate for arterial pressure. Arterial pressure itself causes increase in arterial stiffness; but arterial wall tissues have visco-elastic properties and the relationship to PTT is non linear at high and low pressures arterial pressures. Patient size, measurement artefacts and other variations in vessel wall characteristics can influence the relationship between arterial pressure and PTT. As has been discussed, NIBP is not the gold standard or benchmark of arterial pressure measurements. In theory there was therefore also an argument for turning the editorial question the other way round. Could NIBP changes reliably track PTT changes? NIBP

measurements were at best available every two minutes. Conceivably there could be a delay of four minutes before a blood pressure recording became available. Obstetric anaesthetists in routine practice therefore often rely on symptoms such as dizziness, nausea and vomiting to indicate the acute onset of hypotension. Blood pressure measurements: systolic, diastolic and the derived mean, only give a dimension of cardiovascular function. Although there is a useful relationship between PTT and NIBP changes, PTT is clearly another dimension of cardiovascular function. More research is needed to establish the role of beat to beat PTT as a monitor of cardiovascular function in these circumstances. Whether this happens depends on developments in the technology and physiology in other areas of continuous non invasive cardiovascular monitoring.

### **Publication and Impact of Research**

The data was presented as conference abstracts separately for each part of the study i.e. first as a study of arterial stiffness in the two groups, then as a study of the relationship between PTT and arterial pressure and finally an assessment of PTT as a non invasive monitor of cardiovascular changes. The study had 22 Medline citations by September 2010. The significance of the study specifically for the thesis was for the purpose of understanding and studying the concept of changes in vascular properties during normal and preeclamptic pregnancy. This was important for interpreting the outcomes of the first two studies and other related publications in the literature. Together with a literature search, it therefore also formed an important background for studying and understanding an important element of the pathophysiology. Thus there were also implications for writing the editorial, the literature review and the thesis conclusion. The changes in systolic, mean and diastolic arterial pressure trends supported the outcomes from studies 1 and 2. These incidental findings were not specifically reported but are available in summary form (Table 1 of the published article).



## **APPRAISAL 4**

### **A reappraisal of the concept of hypotension following obstetric spinal anaesthesia**

Linked publication page 72

Sharwood-Smith G, Drummond G B. Hypotension in obstetric spinal anaesthesia: a lesson from pre-eclampsia. *Br J Anaesth* 2009; 102: 291-4.

#### **Introduction to the Appraisal**

This appraisal comprises three elements: a summary outline of the editorial, an expanded review to develop the editorial themes and a conclusion to the completed thesis.

#### **The Editorial**

##### **Introduction to the Editorial**

The objective of the editorial was to reappraise the concepts ‘supine hypotensive syndrome’ and ‘inferior vena caval compression’ in the light of the response of patients with severe preeclampsia to spinal anaesthesia. The reappraisal forms part of a logical argument flowing directly from the outcomes of studies 1, 2 and 3 in this thesis. The desired outcome was, at minimum, to initiate a more general reappraisal and influence the future direction of clinical practice, teaching and research.

#### ***Background***

As a consequence of studies 1 and 2, together with the similar outcomes from other research, it has now generally been accepted that spinal anaesthesia does not normally cause severe hypotension in severe preeclampsia (subjects with severe hypertensive preeclampsia in the clinical circumstances of the studies specified). Study 3 included an assessment of arterial stiffness that corroborated the findings of the other studies using a novel approach. The main finding was that of a relatively delayed and quantitatively reduced vasomotor relaxation following sympathetic blockade with a spinal anaesthetic. The structural and functional cardiovascular changes of normal and preeclamptic pregnancy had been the subject of intensive research over the previous twenty five years. These developments provided the pathophysiological basis for

understanding the observations made in studies 1, 2 and now 3. Critically, from a historical perspective, these advances in understanding could have been predicted. Outcomes of Assali's studies of some sixty years ago did exactly this. Assali's observations on hypotension following spinal anaesthesia in normal and preeclamptic pregnancy contrasted with the subsequent obstetric anaesthetic consensus which favoured a single cause caval vena compression theory of hypotension after spinal anaesthesia in normal pregnancy. With hindsight, Assali's research methods had some limitations, which are discussed in the review to follow. However his work had important implications both at the time and currently. The historical significance of these studies has been omitted from the teaching, research and clinical practice of obstetric anaesthesia.

It had originally been my intention to write an editorial to follow the three studies. My colleague, and co-author of both study 3 and of the editorial, Dr Gordon Drummond whose main subspecialty interest for this purpose is physiology rather than obstetric anaesthesia, had also independently perceived a problem in the original vena cava compression theory. Rather than in the area of reproductive vascular biology, this was more specifically in the initial interpretation of Guyton's work: on the relationships between 'cardiac output, 'right atrial pressure' and the concept of 'venous return'. I was also interested in the significance of recent concepts of venous capacitance. The advantage of a collaborative editorial was that ideas originating in different subspecialist areas of anaesthesia, obstetrics and physiology, could be exchanged and combined; the interpretation of clinical and scientific evidence as perceived by one author could be analysed and challenged by the other. If there was any disadvantage to such a collaboration it was that the two perspectives and priorities involved some final compromise; also that the review element of an editorial, the method chosen for communication, was of necessity very concise. The second part of this appraisal, a review, is intended to address this issue from my own perspective as the author of the thesis, in addition to its more general role as a component of the thesis and a lead-in to the conclusion.

## **Summary of the editorial argument**

***Relatively severe hypotension occurs following spinal anaesthesia in normal pregnancy compared to non pregnant and preeclamptic subjects.***

This is assumed – the statement is based on outcomes of the preceding studies in the thesis and is also extensively supported by other studies. It is also a premise of the relevant Cochrane Collaboration review. These factors have been discussed in Appraisals 1-3.

***The vena caval compression theory of hypotension in obstetric spinal anaesthesia is a concept with several limitations***

The history of this concept and its relationship to the ‘supine hypotensive syndrome’ is examined. The series of case reports and studies which formed the basis for the vena cava compression theory are re-examined. The method by the theory was modified to accommodate apparently contradictory evidence is examined. The outcome of methods of prevention and treatment based on predictions from the theory are assessed.

***The ‘pregnancy’ theory of severe hypotension after spinal anaesthesia in obstetric anaesthesia is revisited.***

A series of studies by Assali are reassessed. Assali’s argument, on the basis of outcomes from the studies, that the relative sensitivity to sympathetic blockade leading to severe hypotension was a characteristic feature of normal pregnancy is reappraised.

***Developments in cardiovascular physiology are important in reinterpreting earlier investigations***

The implications of contemporary and later developments in cardiovascular physiology for two rival theories are assessed. In particular the concepts of cardiac output and venous return in the context of the time and also more recently are considered. Significant developments in the concept of venous capacitance and its regulation are also discussed.

***Developments in reproductive vascular biology support Assali's 'pregnancy' theory.***

The significance for the two theories of hypotension following obstetric anaesthesia of international research and development in this field are assessed. The ways in which these developments support Assali's 'pregnancy' theory of hypotension are discussed.

***Editorial conclusion: the single cause theory of hypotension following spinal anaesthesia, inferior vena cava compression due to the supine hypotensive syndrome, is not supported.***

**Editorial Outcome.**

A final answer on whether the intended outcome of the editorial has been achieved can only be assessed after a period of several years. The initial aim has been achieved; this was to publish the editorial in a major international journal of anaesthesia with a high impact factor. Medical academic and professional institutions tend to operate their teaching and research programs within the boundaries of a conceptual framework, an almost self evident fact that applies to science in general. The institutional pressures that can, and often do, constrain the development of such a core conceptual framework have been studied extensively.<sup>40</sup> Change and development ideally result from the accumulation of contradictory evidence. This is not usually a revolutionary process but more often occurs as a result of a process of amendment. Alternatively core frameworks can become completely redundant when the evidence in support of new conceptual structures becomes overwhelming. This change or development is clearly fundamental to progress in science. Academic discourse and the exchange of new ideas are basic requirements for this process to take place. The arguments developed in the editorial and also in the thesis more generally are intended to contribute to the discourse required for a change in the relevant concepts with important implications for teaching and research.

## **Hypotension after obstetric spinal anaesthesia: a review of physiological concepts, their history and development and the impact of advances in vascular biology**

### **Methods**

The literature search was essentially the same as that applied to the thesis as a whole. During the full period of research, twenty years if the initial audit is included, there have been considerable developments in information technology. These have been utilised as they have become available. Medical information and research databases continue to accumulate publications from earlier decades. Initially it was necessary to hand search journals and cross reference citations in reviews, research reports, studies and textbook chapters, particularly when searching original articles published before 1960. Most recent searches have used Medline, EMBASE, individual journal online databases and evidence based medicine resources such as the Cochrane Reviews.

### **Hindsight and the quality of research**

It is important to appreciate that in the pioneering era of obstetric anaesthesia, fifty to seventy years ago, clinical practice and teaching were dominated by personal experience and opinion, often strongly expressed; as for evidence, many studies were individual case reports or small series with data gathered retrospectively. If prospective studies were performed the potential for selection bias was frequently characterised by a lack of randomisation and control groups. The more recently established discipline, 'Evidence Based Medicine' (EBM) was a distant prospect. However the underlying philosophy of EBM predates the acronym and is not confined to systematic reviews or randomised trials.<sup>41</sup> It would therefore be wrong to underestimate the extraordinary efforts of the early physicians working in conditions very different from those of today. Some collaborative studies were in fact carefully designed and used relatively sophisticated technology and interpretation methods. The struggles and successes of these early pioneers to establish safer practice using specialist skills and knowledge in a context of limited resources and rivalry between specialist disciplines

should not be underestimated. To be able to analyse and reassess this early research with the benefit of hindsight is a particular luxury.

### **Inferior Vena Cava Compression and Spinal shock**

In the 1950's there was a very high anaesthetic mortality associated with spinal anaesthesia for Caesarean section. Termed 'spinal shock', and characterised by a severe hypotensive reaction, there was a direct mortality rate of 1%. Holmes, an Edinburgh anaesthetist, reported on this medical disaster in 1957.<sup>42</sup> He was aware that, during pregnancy, the recumbent supine position sometimes appeared to cause compression of the inferior vena cava by the gravid uterus. In his view this phenomenon, part of the so called 'supine hypotensive syndrome', was causally linked to 'spinal shock'.<sup>43</sup> The first description of supine hypotension in pregnancy has been attributed to Gideon Ahltop; the case was reported in 1932.<sup>44</sup> He later found that 30% of 650 women avoided the supine position and 6% found it impossible due to severe symptoms.<sup>45</sup> Ahltop suggested three possible causes, favouring the first: inferior vena cava occlusion, a utero-cardiac reflex or pathological elevation of the diaphragm. It was noted that both aorta and inferior vena cava could be compressed in the pathophysiology of this syndrome. Many reports and studies of supine hypotension in pregnancy were subsequently reported. These reports were analysed in detail and reviewed by Kinsella and Lohmann (1994).<sup>46</sup> Severe hypotension was reported in 2.5% to 20% of these patients. In some patients, hypotension only occurred after twenty minutes in the supine position and it was even reported following delivery. The words used to describe the phenomenon reflected uncertainty of the aetiology. Ahltop in 1932 referred to 'cardiac insufficiency in the dorsal position in pregnancy',<sup>45</sup> while other terms applied in the 1940-50 period included 'fainting in pregnancy' or 'a vaso-vagal fainting reaction' and 'postural shock in pregnancy'. The final and perhaps appropriate title for this heterogeneous spectrum of signs, symptoms and potential causes, 'supine hypotensive syndrome', was coined by Howard et al in 1953.<sup>47</sup> The heterogeneity of this syndrome is of particular importance in reassessing its relationship to severe hypotension following spinal anaesthesia.

In his 1957 report on the cause and prevention of 'spinal shock', Holmes gave brief details of eleven publications in the literature.<sup>42</sup> It is not clear as to the total number of individual case histories described

within these publications, one of which is stated to refer to seventeen individual patients. In his conclusion he stated that, in his opinion, the cause of death was related to occlusion of the inferior vena cava and a reduction of peripheral vascular resistance. He dismissed several unspecified alternative theories. He also quoted in his article from Sir Robert Macintosh, a pioneer in the audit of anaesthetic deaths, '..... that pregnancy itself could not predispose to hypotension after spinal anaesthesia, on common sense grounds'. In retrospect and in the light of Assali's work this might justifiably be considered a controversial view. It was subsequently further endorsed in a standard textbook on spinal anaesthesia (Lee and Atkinson 1978).<sup>48</sup>

Concluding his report Holmes made three basic recommendations to prevent death from 'spinal shock'. He recommended, in his personal opinion, that the susceptibility to hypotension be predicted from the patient's history. He also said that, to avoid hypotension, the height of block should be limited to segmental level T10. If hypotension still occurred, he recommended turning the patient on her side and raising her legs. In the 1960 article referred to earlier, Holmes extended his concept by publishing two illustrative case reports of hypotension after spinal anaesthesia. The choice of title is significant, '*The supine hypotensive syndrome: its importance to the anaesthetist*'.<sup>43</sup> In the same year he contributed his own study of the supine hypotensive syndrome in late pregnancy (not involving anaesthesia).<sup>49</sup> It was a clinical study of 500 patients and case reports. In this study 2% of 500 patients experienced 'severe' hypotension associated with the supine position. In Holmes' opinion the low incidence of severe hypotension in this non anaesthetised series was entirely compatible with the hypothesis that spinal shock was due to inferior vena caval compression. The explanation was as follows: the spinal anaesthetic removed the reflex vasoconstrictor tone in the legs and then 'revealed' the vena caval compression.

### **The 'pregnancy' theory of hypotension after spinal anaesthesia**

In the late 1940's Assali, the Professor of Obstetrics and Gynecology at Cincinnati University and his colleague Prystowsky were investigating cardiovascular changes in 'toxaemia' of pregnancy (severe preeclampsia) with standardised selective (sensory and autonomic blockade) continuous spinal anaesthesia using Procaine 0.2%. They demonstrated profound falls in blood pressure after spinal anaesthesia in normal term pregnancy but negligible falls in preeclamptic and non pregnant controls using the supine position.<sup>15</sup> They had already obtained similar results with a systemic sympathetic blocking pharmacological agent. By

comparison with other studies of the time, these prospective controlled studies were elegant and well designed. The weaknesses, by contemporary standards, were the limited number of subjects studied and the fact that all pregnant subjects were supine and included both ante and post partum cases. However data was carefully compared between each study group. It is also difficult to imagine an ethics committee approving such a volunteer study some fifty or sixty years later, although this reservation also applies to research published by many of the relevant investigators of the time. The most significant feature, in the light of later developments in reproductive vascular biology, was the remarkable foresight of Assali who proposed a humoral mechanism for the maintenance of blood pressure after spinal anaesthesia in preeclampsia and further suggested that increased sympathetic tone supported the blood pressure in normal pregnancy.

Assali's studies appear never to have been cited in the reports by Holmes or other investigators of inferior vena cava compression and its relationship to spinal anaesthesia. They have only rarely been cited in the anaesthetic literature since then, and in particular I have found no citation in any reviews or articles on the history spinal anaesthesia in pregnancy. However a chance discovery during a recent literature search did reveal convincing evidence of an academic dispute between protagonists of the two theories. It took the form of a practice review (1958) of spinal anaesthesia in pregnancy by Williams, a UK obstetrician-anaesthetist.<sup>50</sup> Publication was followed by a vigorous dispute and an exchange of correspondence with Holmes.<sup>51</sup>

### **Investigation of the Inferior Vena Caval Compression Theory**

There were three approaches: the measurement of pressure in the lower inferior vena cava and femoral veins, the radiological demonstration of compression of the inferior vena cava together with the linked collateral vena azygos circulation, the demonstration of reduced cardiac output in the supine position.

The measurement of pressure in the 'lower' inferior vena cava was studied by Scott (1968) in subjects under general anaesthesia while awaiting caesarean section.<sup>52</sup> It demonstrated increased pressure in the femoral veins at the bifurcation of the inferior vena cava in the supine position. In the lateral position venous pressure was less, but still not as low as non-pregnant levels. Pressure swings with respiration were transmitted to the femoral veins relatively less than in non-pregnant subjects.



Kerr, Scott and Samuel (1964) used angiography to demonstrate complete supine occlusion of the inferior vena cava with distension of the collateral vena azygos circulation in twelve patients having Caesarean section under general anaesthesia for various indications.<sup>53</sup> Partial caval occlusion was also demonstrated in the lateral position.

Lees, Scott, Kerr and Taylor (1966) studied cardiac output in eight conscious patients using a dye dilution technique.<sup>54</sup> Mean cardiac output was twelve per cent less in the supine compared to the lateral position. However in three subjects within the group the mean reduction was only six per cent. An associated feature in these subjects was said to be the engagement of the foetal head. The interpretation was that relief of vena caval compression was a consequence of that particular foetal position. In two subjects there were profound reductions in arterial pressure and cardiac output (>50%) with bradycardia, suggesting a reflex response. Interpretation of the results by the investigators was cautious, pointing out that the mechanism of haemodynamic changes from the supine position in late pregnancy is varied and differs from patient to patient i.e. no that pattern or single mechanism could be implicated. Scott additionally noted that in contrast to the consequence of vena caval pressure at the pelvic outlet, a profound reduction in cardiac output occurred when the obstruction was placed at the level of the hepatic vein. Significantly, with this observation, he recognised the potential importance of the splanchnic circulation. He also suggested, based on his observations, that a vasopressor could not restore cardiac output and therefore should not be given. In later studies the cardiac output changes were less; for example Newman (1983) studied thirty subjects and a control group using transcutaneous Doppler.<sup>55</sup> The maximum six per cent change in cardiac output occurred on moving from supine to a left fifteen degree tilt, and there was no difference when the foetal head was engaged.

Finally, and significantly, none of the investigations were performed during spinal anaesthesia.

### **The inferior vena cava compression theory is refined: preventive therapy is predicted and applied**

The key features of the inferior vena cava compression theory were developed from Holmes' work. His interpretation was that the supine hypotensive syndrome and inferior vena cava compression represented a

single entity.<sup>42, 43</sup> As discussed, engagement of the foetal head was thought to relieve venous compression. This was based on data from three patients in the Lees' 1966 cardiac output study. For the purpose of the theory, this observation effectively pinpointed the site of maximum physiological effect at or just above the bifurcation of the inferior vena cava. In another illustrative case history Marx (1969) developed key features of the theory, including the trapping of venous blood in the legs.<sup>56</sup> Based on the concept as elaborated, Marx developed the preventive techniques of lateral tilt and 'acute hydration' in which 1-2 Litres of crystalloid or colloid were administered before the spinal anaesthetic.<sup>57</sup> The dramatic results of the early acute hydration studies were never repeated; however the basic technique remained apparently unquestioned and was still a standard practice some thirty years later.<sup>58</sup> Finally, in an editorial, Rout and Rocke (1999) addressed the results of many studies which indicated the effective failure of the technique and, by implication, the basic concept as originally proposed.<sup>59</sup> They also addressed the methodological problems of the early studies.

### **Spinal anaesthesia in obstetric clinical practice 1960 – 1990**

The situation of spinal anaesthesia in obstetrics in the 1960's, particularly for Caesarean section, was reflected in the approach taken by Selwyn Crawford, one of the leading UK obstetric anaesthetists, in a standard textbook.<sup>60</sup> He reported an 82% incidence of hypotension. He also indicated a lack of personal experience with the technique by citing 'authorities such as Marx' who had advised the use of an intravenous crystalloid preload and large (20 mg) boluses of ephedrine. He recommended, in line with Holmes' earlier advice, limiting the height of block to T10. Nausea and pain therefore caused a significant morbidity and he recommended 'a large dose of tranquilliser'; for example the administration of intravenous Diazepam 10 mg and Pethidine 50 mg at the beginning and end of the procedure. As to the cause of hypotension he commented that there had been little attempt to discriminate between the respective contributions of sympathetic block and caval compression. Interestingly, in their reluctance to use spinal anaesthesia for Caesarean section, neither Selwyn Crawford nor Moir, author of another contemporary textbook,<sup>61</sup> mentioned the risk of litigation following contamination of equipment as specific contraindications to spinals, or the incidence of post dural puncture headache.

In view of these reservations, spinal anaesthesia was very rarely administered in the UK in the subsequent two decades. A three year survey of practice published in 1982 indicated only 3% of elective and 1% of emergency Caesarean sections were performed under spinal anaesthesia.<sup>61</sup> Ten years later, increasing experience in the USA with improved haemodynamic control using vasopressor drugs, and possibly better quality spinal needles, had begun to reverse the situation. By 1992 in the UK, 52% of elective and 16 % emergency Caesarean sections were performed under spinal anaesthesia (epidurals 19% and 30% respectively).<sup>62</sup>

### **Attempts to improve the therapies originally predicted to be effective by the theory**

It is useful to consider the extensive resources that were applied over several decades in attempts to improve and refine the limited efficacy of the predicted therapies. Particularly this applied to ‘acute hydration’ but also to lateral positioning and various forms of leg compression. In a recent Cochrane Collaboration Review, a total of 75 studies performed between 1992 and 1995 were selected for analysis according to the stated evidence based criteria. 23 studies were of intravenous fluid therapy, 31 of drugs (largely vasopressor) and 21 of physical methods (tilt and leg compression).<sup>18</sup> Many other (unselected) studies were also published during this time and even more over the two previous decades. Additionally for each single published study there are normally several investigations presented at international conferences. Although relief of aortic and vena caval compression is suggested to benefit from lateral positioning, no method or combinations of preventive strategies have been found to reduce the need to treat hypotension with a vasopressor drug. By contrast with the recommendation of early investigators, safe contemporary anaesthetic practice is based on the administration of one or more vasopressor drugs, often by continuous intravenous infusion during the procedure.<sup>63</sup> An important additional theoretical prediction has also been challenged. It had been taught for many years that multiple compared to singleton pregnancy leads to increased vena caval compression and hypotension, particularly following a spinal anaesthetic. This has been confounded by a recent large controlled study.<sup>64</sup> Even without this recent study it might seem surprising that the fundamental basis of the concept was not reviewed at an earlier stage.

### **Haemodynamic changes in pregnancy: implications for the interpretation of theories of hypotension after spinal anaesthesia**

The vigorous debate between Holmes and Williams in 1958 indicated that the rival theories of 'spinal shock' were originally seen as mutually exclusive. Holmes' theory, as developed by Marx, became dominant; however Assali's theory, which was based on earlier studies, is now supported by important later developments in vascular biology.

A basic understanding of the physiological changes of pregnancy had preceded Assali's work. Burwell et al (1938) in animal and human work studied the increased cardiac output and oxygen consumption.<sup>65</sup> They also developed a concept of the placental intervillous space as an arteriovenous anastomosis. More recently, outcomes from primate and human studies (1987, 1988) provided confirmation of the decrease in vascular resistance of normal early pregnancy.<sup>25, 26</sup> Other studies indicated that from the tenth week of gestation in normal pregnancy there is a decrease in endogenous pressor responsiveness (especially to angiotensin II) due to an endothelium dependant alteration of vascular smooth muscle, an increased synthesis of vasodilator prostaglandins and an increased rate of nitric oxide synthesis leading to an increase in vasodilator tone.<sup>27</sup> In response, according to the Guyton model, the renin-angiotensin system increased extracellular fluid and hence blood volume. Consequent to these structural and functional vascular changes there is an increased dependence on sympathetic vasoconstriction for the control of vascular tone.<sup>29</sup> Thus the use of vasopressors to sustain arterial pressure and also, possibly, to control venous capacitance have become the most important strategy for safe spinal anaesthesia in contemporary practice.

By contrast, in pre-eclampsia the vascular endothelium is damaged, probably in a mechanism involving placenta derived proteins Flt2 and soluble endoglin which inhibit the functions of two angiogenic growth factors, vascular endothelial growth factor VRGF and transforming growth factor beta.<sup>66</sup> The normal vascular changes of pregnancy are thus reduced or absent; vasodilatation after spinal anaesthesia is thus also reduced or prevented.<sup>67, 68, 69</sup> There is therefore less or no need for vasopressor support.

## **Venous Capacitance**

While the focus has been on changes in the more easily studied peripheral arterial resistance, the contribution of venous function, particularly venous capacitance and its regulation in responses to spinal anaesthesia may ultimately prove to be very significant. Mobilisation of blood volume by vasoconstriction is largely a function of the splanchnic veins. In the non pregnant state the splanchnic circulation contains twenty per cent of the blood volume and receives twenty five per cent of the cardiac output. There is evidence to support a similar situation in pregnancy.<sup>70</sup> The importance of this concept relates to the regulation of what has been termed ‘venous return’ and hence cardiac output and arterial pressure. Gelman (2008) reviewed a hydrodynamic model developed to illustrate the relationships between venous capacity and compliance.<sup>71</sup> The concepts of mean circulatory filling pressure, stressed and unstressed volumes are used to predict the response of regulatory mechanisms under different conditions. Of most significance is the fact that splanchnic and cutaneous capacitance veins are under a high degree of sympathetically controlled regulation and are thus relatively densely supplied with adrenergic receptors. The potential consequences of sympathetic blockade following spinal anaesthesia are clear. Lending support to the significant contribution of the splanchnic circulation to venous capacitance, Jones et al explored the pro-vasodilatory state of mesenteric veins in normal pregnancy.<sup>72</sup> Clearly, increased venous capacitance in normal pregnancy is relevant to the failure of efforts to prevent spinal induced hypotension by administering large intravenous volumes of crystalloid or colloid. Conversely, there is evidence to support parallel (to arterial) pathological changes in venous function due to preeclampsia.<sup>73</sup> In this situation the normal pregnancy driven increase in blood volume does not take place. However there is still a lack of studies on this aspect of venous function during pregnancy.

## **The cardiovascular system: dealing with complexity**

The heterogeneity of response to the supine position in late pregnancy was noted by the early investigators. Despite these observations it may have been the apparent and misleading functional simplicity of the human cardiovascular system that influenced development of the inferior vena cava compression theory in the 1960’s. A four chamber heart comprising two pumps in series but cycling synchronously is relatively easy to understand. However the fact that the pulmonary and systemic circulations operate as different, low and

high, pressure systems together with the need to maintain a functional cardiopulmonary circulation under many different conditions begins to introduce complexity. The role of the Frank-Starling mechanism in balancing the pulmonary and systemic circulations was well established by the 1930's. So too was the relationship between arterial pressure, flow and peripheral resistance and its analogy to Ohm's law. This physiological concept was coincidentally under development by Guyton and others (1959) at the same time as Holmes began his investigation into spinal shock.<sup>74</sup> Of interest is the fact that another of the early investigators (Scott 1964) considered that vasopressors should not be given to manage the supine hypotensive syndrome when associated with anaesthesia.<sup>53</sup> The reasoning was that since the cause of hypotension was due to blood being trapped in the legs, cardiac output could not be increased by using this therapy. Investigators, including Scott, had commented on the possible importance of the splanchnic circulation; but the option of developing this idea was limited by the, then current, concept of cardiac output and its relationship with venous and arterial function.

It is helpful, in analysing the development of the two theories of spinal induced hypotension, to examine the more general way this complexity has been dealt with. Standard cardiovascular physiology textbooks outline these basic principles and describe the haemodynamic system as a complex system with multiple layers and feedback loops.<sup>75</sup> Fast extrinsic regulation, for example by the sympathetic system is complemented by slower intrinsic autoregulatory vascular reflexes dependant, among other factors, on local metabolic conditions and the basic myogenic response. Structural and functional haemodynamic changes are then superimposed on this underlying system during pregnancy. The consequences of administering a spinal or epidural are therefore not simply restricted to the immediate direct effects of the central neural, including sympathetic, blockade. There are clear implications for understanding the more complex evolving haemodynamic responses to regional anaesthesia in many key clinical situations in the labour ward and operating theatre.

Further complexity is added by the heterogeneity of human physiological responses. This heterogeneity was particularly noted in the 1960's by some investigators of the supine hypotensive syndrome in its relationship to 'spinal shock'.<sup>54</sup> A useful illustration of the way this affects cardiopulmonary responses has been studied in a hypoxic environment.<sup>76</sup> It is, in part, associated with the evolution of organ systems and the 5%, between individuals, variation of the human genome. For example although the protein encoding genes are shared in common, there are copy number variations and differences in gene expression. There are also differences in numbers of polymorphisms in the protein coding control and transcription elements. Other more obvious possible causes of heterogeneity are related to anatomical differences and the presence of incidental pathology. The observation that up to 20% of normal parturients do *not* experience profound hypotension is very relevant for future research in obstetric spinal anaesthesia is. A possible normal variation in pregnancy induced vascular changes, the presence of occult preeclampsia and anatomical differences are potential hypotheses to explore.

Physiologists have introduced a variety of models to accommodate complexity and predict responses. Electronic circuitry, hydrodynamics, mathematics and computer systems are the most familiar models. The theoretical basis for this kind of modelling can prove baffling to the clinician. However the advantage is that relatively simple predictions can be derived from the models and applied therapeutically in clinical practice. The cardiac function curve (Guyton 1973) which describes the relationship between cardiac output, venous return and right atrial pressure is probably the most familiar for anaesthetists working in the operating theatre, maternity or intensive care unit.<sup>74</sup> The important issue is that the abstract nature of the models and the apparent simplicity of the clinically applied predictions can obscure the limitations of the model. Over time, such a model, often after being taught to trainees didactically and reproduced in textbooks, can become perceived as a permanent reality. However in the field of applied physiology these models are not set in stone but are constantly subject to reappraisal, modification and occasionally abandonment as physiological research and clinical observation generate contradictory or confirmatory evidence. An example illustrated by Malpas, Montani and Osborn (2009) is that of the Guyton computer based model which has been updated to deal with the relationships between blood volume regulation, arterial pressure and the renin-angiotensin

system.<sup>78</sup> Changes in blood volume-arterial pressure relationships and possible insights into acute versus long term responses in pregnancy are of interest; for example in the interpretation of the failed 'acute hydration' prophylactic therapy. Updating the model is a therefore dynamic, not a static process. This illustrates a particular problem for clinical specialisation. In this situation, for example, subspecialties can operate in relative isolation. Obstetric anaesthesia was institutionalised in the UK and USA in the 1970's. The first president of the Obstetric Anaesthetists Association understandably made it clear that the emphasis had been on safety, rather than science, in what is largely practical subspecialty.<sup>3</sup> This remains the situation some forty years later. Recent textbooks of anaesthesia reflect the failure to update the concept of inferior vena cava compression in obstetric spinal anaesthesia.<sup>17</sup>



## CONCLUSION

An audit of clinical practice followed by two prospective studies challenged the prevailing concept that spinal anaesthesia, by comparison with general or epidural anaesthesia, causes potentially dangerous hypotension in severe preeclampsia. The first study compared spinal versus epidural anaesthesia and suggested that both techniques were relatively safe in terms of hypotension. The second tested the hypothesis that the presence of preeclampsia in otherwise stable patients was associated with resistance to severe hypotension. These investigations compared the requirement for vasopressor drugs to sustain arterial pressure within predetermined limits. A third study used a different approach; pulse transit time measurement offered a novel technique for studying beat to beat cardiovascular monitoring. It also compared arterial stiffness between normal and preeclamptic subjects. Arterial stiffness differs between normal, normal pregnant and preeclamptic subjects due to the different structural and functional vascular properties characteristic of each group. Additional cardiovascular data from study 3 also corroborated the study 1 and 2 outcomes.

Preeclampsia is known to reduce or prevent the development of cardiovascular changes in normal pregnancy; this raised the possibility that the cardiovascular changes of normal pregnancy are an important factor in the development of severe hypotension after spinal anaesthesia. Since the second study suggested that the presence of severe preeclampsia was associated with resistance to hypotension it became important to reassess the original underlying concept; this was based on the theory that inferior vena caval compression, when associated with the spinal induced sympathetic blockade, was the single cause of severe hypotension normally experienced following obstetric spinal anaesthesia. The third study gave additional indirect support to Assali's alternative hypothesis, that the structural and functional vascular changes of normal pregnancy are a cause of hypotension following a spinal anaesthetic.

The final part of the thesis followed logically from the outcomes of studies 1, 2 and 3 and also from other supporting studies. In this section the concepts 'supine hypotensive syndrome' and 'inferior vena caval compression' and their role in explaining the aetiology of severe hypotension following spinal anaesthesia in normal pregnancy were reappraised. A published editorial introduced the arguments for the reappraisal.

These arguments were extended, in the thesis, by a more comprehensive literature review. The series of case reports and studies which formed the basis for the vena cava compression theory were appraised. Several prophylactic measures based on physiological responses predicted by the vena cava compression theory were also examined. An essential part of the original theory had been the precise location of effective inferior vena caval compression at the pelvic brim. In the theory, trapping of venous blood in the legs was said be aggravated by administration of a spinal anaesthetic; the mechanism was its action in blocking the normal autonomic vasopressor reflex. There were several limitations to the concept. The supine hypotensive syndrome was known at the time to have more than one possible cause i.e. not only vena cava compression. Early cardiac output studies showed a 12% reduction in the supine position and angiography did demonstrate supine compression of the inferior vena cava and aorta. However later investigations showed a smaller reduction and failed to confirm the hypothesis that the engaged foetal head relieved the compression. The latter being the basis for fixing the site of vena caval compression. The studies did not differentiate between the relative effects of aortic and vena cava compression. There were other reservations: none of the investigations were undertaken during spinal or even epidural anaesthesia and no study demonstrated trapping of venous blood in the legs. Early investigators did acknowledge that the function of the splanchnic circulation might be important after spinal anaesthesia but the idea was not developed further. More recently there have been significant developments in the concept of venous capacitance and its regulation, which is under autonomic control. Therapeutic measures were based on predictions derived from the theory of venous trapping and included the prophylactic administration of 1-2 L of intravenous crystalloid or colloid, the use of lateral positioning and various methods of leg compression. Lateral positioning or tilt was a logical manoeuvre in view of the aortic and vena caval compression that had been demonstrated. However none of the methods individually or in combination have been shown to reliably prevent the need to treat hypotension with vasopressor drugs.

An alternative theory based on earlier studies by Assali was reassessed. Assali's argument, on the basis of outcomes from his studies, was that the relative sensitivity to sympathetic blockade leading to severe hypotension was a characteristic feature of normal pregnancy. This theory is supported by outcomes of

studies 1,2 and 3 in the thesis and also by other published investigations. It is also supported on theoretical grounds by more recent developments in reproductive vascular biology.

The original theory underestimated the heterogeneity of cardiovascular responses to supine and other positions in late pregnancy. Several later developments have contributed to the need for a reassessment: the relative complexity of cardiovascular physiology, the potential significance of venous capacitance and its regulation and the impact of pregnancy induced vascular changes. Physiological models designed to accommodate this complexity and make therapeutic predictions are normally modified or abandoned over time, as investigations confirm or refute previous observations or assumptions. The basic concepts underlying hypotension in obstetric spinal anaesthesia must similarly be updated. For this purpose it is important to engage in the relevant multidisciplinary exchange of ideas and research outcomes. In this way obstetric anaesthetic teaching, clinical practice and research can be better directed. The pioneer obstetric anaesthetists who developed the original ideas and investigations would have expected no less.

## RESEARCH CONTRIBUTIONS

I developed the original ideas for the first two studies when reviewing anaesthetic practice in our unit. The study designs resulted from collaborations with Dr Vicki Clark who co-ordinated data collection procedures. Dr Clark and I performed most of the clinical studies. In the first study we were assisted by Dr Elaine Watson who also presented data in abstract at the Obstetric Anaesthetists Association (OAA) Annual Conference in 1998. In the second study we were assisted by Dr Alexandra Stewart. Dr Clark presented the conference abstract at the OAA in 2001. I performed the statistical analysis on the second study with assistance from Dr Bernhard Heidemann. I drafted and coordinated the editing of both manuscripts for peer review and final publication.

I developed the initial idea for the third (PTT) study as an obstetric application of a technique already in use by Dr Gordon Drummond. The subsequent design was a collaboration with Dr Drummond. Our research assistant, Jean Bruce, coordinated studies and made the initial analysis of cardiovascular and other patient data. I performed a number of the patient studies when Jean Bruce was unavailable. Jean Bruce and I presented the data in abstract at the OAA and the International Society for the Study of Hypertension in Pregnancy (2002). I made the initial draft for publication after which it was jointly edited with Dr Drummond who performed the statistical analysis and coordinated responses to peer reviewers and journal editor.

The editorial was an idea that I began to develop after the second study. Dr Drummond had also independently developed some ideas on related aspects of cardiovascular physiology. The final result was a collaboration in which ideas were exchanged and discussed extensively before finalising a draft for publication.

The original ideas for a unitary theme for the thesis, the appraisals, the literature review and the conclusion are otherwise entirely my own contribution.

## **ACKNOWLEDGEMENTS**

These studies could not have been completed and published without the enthusiastic support and collaboration of Dr Vicki Clark and Dr Gordon Drummond. Jean Bruce, who incidentally won the free paper prize when she presented the PTT study at the OAA meeting in Nottingham, was engaged in the project on a full time basis for six months. My consultant obstetric anaesthetic colleagues patiently supported the studies as did our obstetric medical colleagues and the midwifery and operating theatre staff in the Simpson Maternity Unit. Dr Anne McCrae and Dr Bernhard Heidemann contributed more informally as ideas developed over many years. Finally, the projects could not have been completed without the interest and support of our patients. Professor A Dahan, University of Leiden, loaned the analogue computer for processing ECG and optical plethysmograph signals in the PTT study. The third study was also supported by a grant from the OAA.

## **COMPETING INTERESTS**

There was a grant from the OAA to support the PTT investigation. Jean Bruce and I received discretionary grants from NHS Lothian to travel to the 2002 International Society for the Study of Hypertension in Pregnancy Conference in Toronto where we both gave presentations (two oral and one poster). Travel and subsistence grants were awarded by NHS Lothian and the Department of Anaesthetics for abstract presentations of all the other studies at OAA conferences. There are no competing commercial interests.

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# THESIS ALGORITHM

Thesis page 52

Audit of delivery unit management of severe preeclampsia (SPE) finds that experienced anaesthetists are administering spinal anaesthesia (SA) for Caesarean Section against a 40 year old consensus and clinical guideline

## Study 1

Test the hypothesis that SA is relatively haemodynamically safe compared to epidural in SPE

Study outcome suggests that SA with its rapid onset of sympathetic block is relatively safe. Study data also raises two questions.

1. Does SPE confer resistance to the hypotension seen after SA in normal pregnancy?
2. If so, does this challenge the fundamental theory of caval compression as the single cause of severe hypotension following SA in normal pregnancy? (the vascular changes of normal pregnancy that are suppressed in SPE may be an important cause of hypotension)

## Study 2

Test the hypothesis that SPE confers resistance to the hypotension experienced after SA in normal pregnancy

Journal editorials indicate persisting reservations on the outcomes of studies 1, 2 and similar studies from other centres

## Study 3

Test the hypothesis of increased arterial stiffness and delayed relaxation in SPE using study pulse transit time (PTT) changes

Study 2 suggests patients with SPE are resistant to severe hypotension after SA. Study 3 (PTT) in one outcome corroborates this. Outcomes from other centres confirm. The longstanding consensus that the severe hypotension in normal pregnancy seen following SA due to a single cause – compression of the inferior vena cava (IVC) by the gravid uterus – is also thus challenged.

## Editorial Published

### Objective

(Extended by a literature review in the thesis)

- ☐ To update the concept of hypotension after obstetric SA.
- ☐ To review the implications of studies 1, 2 and 3 and relevant studies from other centres.
- ☐ To review the history and evolution of the single cause IVC compression theory, its basis in cardiovascular physiology and its predictions on prophylactic therapy to manage the hypotension.
- ☐ To recover and review Assali's alternative (vascular changes in pregnancy) theory

**CONCLUSION**

## ORIGINAL ARTICLE

## Regional anaesthesia for caesarean section in severe preeclampsia: spinal anaesthesia is the preferred choice

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**SUMMARY.** Standard textbooks advocate epidural rather than spinal anaesthesia for caesarean section in severe preeclampsia. The basis for this recommendation is the theoretical risk of severe hypotension but no published scientific studies have been identified to support this assertion. We therefore designed a prospective study to compare spinal versus epidural anaesthesia in severely pre-eclamptic patients requiring hypotensive therapy. Following ethics committee approval, 28 women with preeclampsia requiring hypotensive medication who were scheduled for urgent (not emergency) or elective caesarean section consented to receive epidural or spinal anaesthesia by random assignment. Seven patients were excluded due to protocol violations. Four of these were in the epidural group of which two were excluded due to inadequate analgesia. No spinal patient was excluded because of inadequate analgesia. Mean ephedrine dosage was 5.2 mg (range 0–24 mg) in the spinal group and 6.3 mg (range 0–27 mg) in the epidural group. Six of the 11 patients in the spinal group required no ephedrine as did five of 10 in the epidural group. One patient in the spinal group suffered from mild intraoperative pain. By contrast in the epidural group three patients had mild pain and four others had pain severe enough to warrant intraoperative analgesia. There were no differences in neonatal outcomes. These findings support recent studies suggesting the safety and efficacy of spinal anaesthesia in this group of patients.

### INTRODUCTION

Controversy has surrounded the choice of anaesthesia in severe preeclampsia.<sup>1</sup> The concern has been that the placental circulation may be compromised by severe hypotension following regional techniques.<sup>2</sup> Epidural anaesthesia is now generally accepted for these patients but spinal anaesthesia is sometimes considered to be contraindicated.<sup>3</sup> In contrast to the prevailing view an internal audit in our own unit revealed an increasing tendency by anaesthetists to use spinal anaesthesia, finding improvement in both quality of block and onset time but without observing severe hypotension. A retrospective study published in 1992

supported this change in practice.<sup>4</sup> We therefore set out to compare haemodynamic stability and quality of analgesia prospectively in spinal and epidural analgesia for severe hypertensive preeclampsia.

### METHOD

We recruited 28 women with severe preeclampsia requiring anti-hypertensive therapy who were scheduled for elective or urgent but not emergency delivery, i.e. non-labouring patients who were suitable for either technique of regional anaesthesia. The diagnosis of preeclampsia was made by obstetric medical staff following the onset of hypertension and proteinuria after 20 weeks gestation. Standard criteria<sup>5</sup> are applied in our unit as follows: proteinuria is present as 2+ test strip albuminuria in a mid stream specimen of urine, hypertension is defined as a diastolic pressure of more than 110 mm Hg on any one occasion or more than 90 mm Hg on two or more occasions at least 4 h apart. Patients were recruited on the basis of a sustained hypertension of more than 110 mm Hg denoting severe preeclampsia. They were treated with labetalol  $\pm$  nifedipine as indicated according to our

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unit protocol. The study exclusion criteria were as follows: eclampsia, anti-convulsant therapy, coagulopathy, patient refusal of regional blockade and patients who were outside 1.53–1.7 m in height or over 100 kg weight. Written, informed consent was obtained and the patients were randomized to receive either spinal or epidural anaesthesia.

Ranitidine was given preoperatively either orally in a dose of 150 mg or 50 mg i.m. or i.v. according to the degree of urgency of the delivery. sodium citrate 0.3 M 30 ml was administered orally in the anaesthetic room. Baseline systolic blood pressure was measured 5 min after arrival in the anaesthetic room and before instituting any invasive procedures. A blood pressure 30% below baseline systolic was set as the level for intention to treat.

The regional block was sited in the left lateral position at the second or third lumbar interspace. The patient was then turned supine with a wedge under the right buttock to avoid aorto-caval compression. Spinal anaesthesia was instituted with a 24 gauge Sprotte needle and 2.75 ml of heavy 0.5% bupivacaine. Epidural anaesthesia was performed with a 16 gauge Tuohy needle through which 3 cm of a lateral eyed catheter was placed in the epidural space. Four ml of 2% lignocaine was given as a test dose and if negative after 5 min was followed by 16 ml of plain 0.5% bupivacaine. The blocks were tested at 5 min intervals and when analgesia to pinprick with a 27 gauge dental needle reached T5 bilaterally (T5 being the first unblocked segment), surgery was allowed to proceed. In the epidural group, supplementary 0.5% bupivacaine, 1.5 ml per unblocked segment, was given until analgesia to T5 was achieved. After 11 patients had been randomised there was concern as to the relatively poor quality of epidural block and fentanyl 75 µg was added to the epidural solutions.

Apart from 250 ml i.v. Hartmann's solution while instituting the block, we restricted perioperative fluids to 80 ml/h plus losses. In keeping with experience reported by other units<sup>6</sup> we base the management of these patients on a protocol comprising guidelines on fluid restriction and blood pressure control. Our internal audit confirms a reduction in complications with this simplified regime.<sup>7</sup>

The patients were monitored with ECG, pulse oximetry and automated non-invasive blood pressure recordings at 2 min intervals. Oxygen was given at 4 L/min via a Hudson mask until delivery when 10 units of synthetic oxytocin (Syntocinon) was given i.v.

If discomfort or pain was felt during surgery Entonox and/or morphine was given as required. If these measures were not effective or if the initial block failed to reach the specified T5 height the patient

was withdrawn from the study and an alternative anaesthetic administered as appropriate.

Ephedrine in 6 mg increments was given at 2 min intervals if the patient exhibited symptoms associated with hypotension (nausea, vomiting or dizziness) or if the systolic blood pressure fell below 30% of the baseline. Intraoperative blood loss was replaced with Hartmann's solution or blood as judged clinically appropriate. The presence of nausea, vomiting or bradycardia was recorded.

Neonatal Apgar scores were recorded at 1 and 5 min by a paediatrician blinded to the anaesthetic technique. Further neonatal outcome was obtained from the paediatric casenotes.

Postoperatively mothers were monitored in our high dependency unit for a minimum of 24 h where intravenous PCA morphine was administered. Fluid administration followed the unit protocol. A questionnaire was sent to the mothers approximately 1 month after delivery to determine their health status.

## RESULTS

The mean age of the women was 29.7 years (range 23–39) in the spinal and 27.3 years (range 20–35) in the epidural group. The mean gestational age of babies was 33.8 weeks (range 29–39) in the spinal and 35.0 weeks (range 26–41) in the epidural group.

Of the 28 women recruited, seven were excluded because of protocol violations. Of the three exclusions in the spinal group none were excluded due to failure of analgesia. In one, the spinal was not performed as stipulated in the protocol, in another, more than 250 ml of Hartman's solution was given pre-operatively and the third patient was found to be below the range stipulated for height. Of the four exclusions in the epidural group two were for inadequate analgesia. One of these epidurals was converted to general anaesthesia and the other to spinal. The other two epidural exclusions were unrelated to analgesia. One patient was found to be above the stipulated weight range and the other had a period of hypotension but was not given ephedrine according to the protocol. This left 21 women for analysis, 11 in the spinal and 10 in the epidural group.

Only one patient in the spinal group had discomfort during surgery but no treatment was required. By contrast seven out of the 10 women who had epidurals complained of pain during surgery. Three epidural patients required intraoperative morphine. This occurred despite earlier supplementary local anaesthetic top-ups to achieve pinprick analgesia to T5 (Table 1). The poor quality of analgesia in the epidural group, including the two exclusions converted to



**Table 1. Epidural data**

case number	age (years)	epidural volume*	adverse intraoperative events	ephedrine usage (mg)	problems at one month	gestational age (weeks)	Apgar at 1/5 min
2	20	4+16	nil	0	nil	37	7/9
3	31	4+16	pain (morphine) nausea + vomiting	12	nil	33	5/9
6	30	4+16+7.5	pain (Entonox) nausea	6	nil	26	5/9
8	33	4+16+6	pain (morphine)	6	nil	32	8/9
12	24	4+16+4.5+F	slight pain (no Rx)	0	DNRQ	34	9/9
17	22	4+16+F	slight pain (no treatment), nausea	12	DNRQ	35	9/9
19	23	4+16+6+F	nil	0	renal hypertension	37	8/9
20	35	4+16+F	pain (Entonox + morphine) nausea + vomiting	0	nil	41	9/9
22	24	4+4+16+F	repeat test dose	27	nil	40	8/8
23	31	4+16+3+F	slight pain (no Rx)	0	essential hypertension	35	9/9

\*2% lignocaine + 0.5% bupivacaine (ml)

F = Epidural fentanyl

DNRQ = Did not return questionnaire

**Table 2. Spinal data**

case no	age (years)	adverse intraoperative events	ephedrine usage (mg)	problems at 1/12	gestational age (weeks)	Apgar at 1/5 min
7	33	nil	3	DNRQ	36	9/9
9	23	nil	24	nil	33	9/9
11	33	nil	0	nil	34	9/9
14	33	bradycardia, light-headed	6	nil	35	8/9
16	28	pain (no treatment) nausea	0	BP still high	36	9/9
18	30	nil	12	DNRQ	36	9/9
21	23	nausea	0	nil	33	5/7
24	39	nil	0	nil	30	8/9
25	32	nil	0	nil	39	9/9
27	30	nausea	0	DNRQ	31	9/9
28	23	nil	12	DNRQ	29	8/9

DNRQ = Did not return questionnaire

spinal and general anaesthesia, posed an ethical dilemma. A pilot study had suggested that 80 patients would have been required for an 80% power to detect a significant difference of 6 mg ephedrine between the groups. However, this analysis became of secondary importance following our findings of relatively ineffective analgesia in the epidural group. The study was therefore referred for consultation with senior colleagues and the ethics committee chairman; it was agreed that it would be appropriate to conclude any further randomisation to the epidural group after studying 28 patients and to report the results. The data for these patients are presented in Tables 1 and 2.

The ephedrine requirements of the two groups were remarkably similar. The spinal group had a mean ephedrine requirement of 5.2 mg (range 0–24 mg) and the epidural group 6.3 mg (range 0–27 mg). No ephedrine was required for six out of the 11 women in the spinal group and five out of the 10 in the epidural

group. Neonatal Apgar scores were similar for the two groups. All babies survived at the 1 month follow-up.

In our unit the indications for invasive haemodynamic monitoring are major haemorrhage, pulmonary oedema and acute renal failure. No patients in the study required this form of monitoring.

Fifteen women returned the questionnaire sent 1 month postpartum. Of these, one woman in the spinal group had persistently high blood pressure. Persistent hypertension also occurred in two women in the epidural group; a renal cause was found in one.

## DISCUSSION

Preeclampsia affects 6–8% of all pregnancies. The precise cause remains to be elucidated but when severe there is vasoconstriction involving both resistance (arterial) and capacitance (venous) sides of the

circulation with an associated hypovolaemia.<sup>8</sup> There is widespread maternal vascular endothelial damage, increased sensitivity to endogenous vasopressors and a functional imbalance between prostacyclin and thromboxane A<sub>2</sub>. Nitric oxide is normally synthesised in the intact vascular endothelium and is thought to play a fundamental role as a vasodilator in the circulatory adaptation of normal pregnancy.<sup>9</sup> Clinical experience of the relative resistance to hypotension following central neural blockade lends support to this peripheral circulatory mechanism. Additionally, it has also been observed that untreated pre-eclamptic patients are resistant to supine hypotension.<sup>10</sup>

A literature search for scientific evidence to support the recommendation that spinal anaesthesia be avoided in severe preeclampsia proved fruitless. The only explanation would appear to be anxiety that the hypotension typical of non pre-eclamptic parturients would also occur in these patients thus reducing an already compromised placental circulation.<sup>11,12</sup> More recently, epidural anaesthesia has come to be accepted as suitable for severe preeclampsia but the more profound and rapid sympathetic block induced by spinal anaesthesia in non-preeclamptic patients has meant a continuing rejection of this technique by some anaesthetists.<sup>13</sup> Three recent studies have cast doubt on the view that spinal anaesthesia leads to severe hypotension in these patients.<sup>4,6,14</sup> Following one of these studies, a retrospective review of 48 caesarean sections in severely preeclamptic patients, it was suggested that the dogma that spinal anaesthesia is contraindicated in the severely pre-eclamptic patient should be reassessed.<sup>4</sup>

There have been, to our knowledge, no previous prospective studies of the relative merits of spinal and epidural anaesthesia in this group of patients. The explanation is almost certainly due to the difficulties inherent in such a study. Despite a generally accepted classification of this multi-system disorder<sup>5</sup> there are still semantic difficulties. Hypertension without proteinuria arising after 20 weeks gestation is referred to as pregnancy induced hypertension. Essential hypertension arising coincidentally may only be identified at the postpartum stage. It is also important to appreciate that severe preeclampsia may present with a hepatic or haematological disorder rather than hypertension.<sup>8</sup> The investigation was specifically concerned with our most commonly presenting group: patients with classical signs of severe hypertensive preeclampsia who have been stabilized according to our unit protocol. Despite the number of tertiary referrals available to our large obstetric unit these problems meant that the study took 24 months to complete. The seven excluded patients reflect the difficulty of attempting to study comparable groups.

Poor analgesia in the epidural group prompted the decision to add epidural fentanyl 75 µg after the eleventh randomization. This may seem inconsistent with what was otherwise a rigorously applied protocol; however four out of the six patients to whom epidural fentanyl was administered experienced pain of some degree suggesting that this alteration to the protocol made little material difference to the outcome. There are several possible explanations for the inadequate analgesia provided in the epidural group. It is possible that pathological changes in preeclampsia such as oedema may affect the uptake of anaesthetic agent within the epidural space. We also considered the possibility that an alternative epidural technique might have improved the efficacy of blocks. Nevertheless, 0.5% bupivacaine with 75 µg of fentanyl in the appropriate volume is considered a standard and effective method in the UK and elsewhere. Lignocaine 2% with the addition of epinephrine 1:200 000 was a possible equivalent choice; however, we do not add epinephrine to regional analgesia in preeclampsia because of the risk of inadvertent intravenous injection. Warming the solution<sup>15</sup> and adding bicarbonate have been shown to speed the onset of the block but not to improve efficacy.<sup>16</sup>

Another consideration is our method of sensory testing. It has been argued that the segmental level at which touch rather than pinprick sensation is lost will better predict the adequacy of a regional block. Since the spinal group demonstrated a uniformly high quality of block and loss of pinprick sensation to at least T5 was required in both groups this should, in theory, not be an issue. In practice, as Russell has suggested, a spinal often seems to provide a superior block compared with an epidural for a given level of anaesthesia.<sup>17</sup> Bourne et al. have pointed to what may actually be the critical factor: epidural anaesthesia may leave unblocked segments within the main area blocked or in the most caudal dermatomes.<sup>18</sup> Increasing experience of spinal anaesthesia for elective caesarean section in non preeclamptic parturients gives further support to a preference for this method. In a study comparing spinal (n=47) versus epidural (n=47) anaesthesia, Riley et al. found that 38% of the epidural group required supplementary analgesia compared to 17% of the spinal group. The time efficiency and quality of analgesia provided by spinal blockade appeared to set a gold standard which was superior to that provided by epidural anaesthesia.<sup>19</sup> In view of the number of patients in our study we can not completely exclude the possibility that the difference was due to chance. However, after 28 randomizations there was clearly an ethical issue and, in accordance with the uncertainty principle, we were no longer 'substantially uncertain' as to which of the two techniques were suitable for the patients under study.<sup>20</sup>

A salutary discovery in our literature search was the study by Assali et al. in 1950.<sup>21</sup> They set out to resolve conflicting evidence as to the effect of sympathetic blockade in normal and 'toxemic' (severe hypertensive pre-eclamptic) pregnancy. Ethical considerations would preclude undertaking such a study now and, although a statistical test was applied, the numbers were small. It was, however, an elegantly designed study which included a comparison of the effects of high spinal sensory blockade pre- and post-partum on 10 normal pregnant women and 12 pregnant toxemic women. There were five non-pregnant controls. Profound falls in blood pressure occurred in the normal pregnant women whereas the toxemic patients were only minimally affected. Apart from the fact that this study appears to have been forgotten, it is also notable for the remarkable foresight of the authors who suggested that blood pressure in toxemic pregnancy was maintained by a humoral rather than neurogenic mechanism. Clinical support for these findings was reported in a retrospective review of obstetric spinal anaesthesia 12 years later.<sup>22</sup>

Our study has added to a body of evidence which indicates that spinal and epidural anaesthesia do not cause profound hypotension in severe hypertensive preeclampsia. When vasopressor support was required for either technique the dose of ephedrine was small compared to that reported in normal parturients.<sup>23</sup> Spinal anaesthesia is to be preferred in terms of quality of analgesia and efficient use of theatre time. There appears to be no difference in neonatal outcome for the two techniques. Further studies are required to evaluate and confirm the findings presented here. We are currently prospectively comparing haemodynamic stability in spinal anaesthesia for otherwise normal parturients presenting for elective caesarean section with severely hypertensive pre-eclamptic patients.

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ORIGINAL ARTICLE

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# Ephedrine requirements are reduced during spinal anaesthesia for caesarean section in preeclampsia

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**Background:** Despite controversy over the haemodynamically safest blockade for caesarean section in women with severe preeclampsia, an increasing number of anaesthetists now opt for spinal anaesthesia. In a previous study we found that spinal compared to epidural anaesthesia offered an equally safe but more effective option for these patients. The current study was designed to compare the hypotension induced by spinal anaesthesia, as measured by ephedrine requirement, between 20 normotensive and 20 severely preeclamptic but haemodynamically stabilised women.

**Method:** Standardised spinal anaesthesia was instituted and ephedrine was given in boluses of 6 mg if the systolic pressure fell >20% from the baseline, or if the patient exhibited symptoms of hypotension.

**Results:** The mean ephedrine requirement of the normotensive group ( $27.9 \pm 11.6$  mg) was significantly greater ( $P < 0.01$ ) than that of the preeclamptic group ( $16.4 \pm 15.0$  mg).

**Conclusion:** This suggests that the hypotension induced by spinal anaesthesia in women with severe but haemodynamically stabilised preeclampsia, is less than that of normotensive patients.

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**Keywords:** Anaesthesia; Preeclampsia; Obstetric anaesthesia; Spinal anaesthesia

## INTRODUCTION

The choice of general or regional anaesthesia for patients with severe preeclampsia continues to attract debate. Epidural anaesthesia has become generally acceptable but the risk of hypotension following spinal anaesthesia remains a focus for concern.<sup>1–3</sup> However, this view has not been supported by clinical studies.<sup>4–7</sup> A previous prospective study in our centre compared epidural versus spinal anaesthesia in severely hypertensive preeclamptic patients.<sup>8</sup> We found that profound hypotension did not occur with either technique and that spinal anaesthesia was not only more time-efficient but also offered more effective and reliable anaesthesia. Pre-

eclampsia appeared to confer a condition of relative haemodynamic stability following spinal and epidural anaesthesia. We therefore designed this study to evaluate this hypothesis further, by measuring ephedrine requirement following spinal anaesthesia in severely hypertensive preeclamptic patients versus a normotensive control group presenting for caesarean section.

## METHODS

Following ethics approval we obtained written informed consent from 40 non-labouring parturients: 20 women were normotensive and 20 had severe preeclampsia requiring antihypertensive therapy. All study patients were scheduled for elective or urgent but not emergency delivery. In the preeclamptic group obstetric medical staff made the diagnosis of preeclampsia following the onset of hypertension and proteinuria after 20 weeks' gestation using standard criteria.<sup>9</sup> Severely preeclamptic patients were recruited on the basis of a sustained pre-treatment diastolic blood pressure >110 mmHg. These preeclamptic women were stabilised with nifedipine, labetalol or methyldopa alone or in combination as indicated according to obstetric preference within our unit protocol. The study was completed before magnesium

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sulphate was added to our unit preeclampsia protocol. The preeclamptic patients were recruited over a 20-month period as they presented to the investigators. The control patients were recruited in parallel until 20 patients had been studied. Randomisation was not appropriate due to the study design. Any patient who had an eclamptic fit, a coagulopathy, declined regional anaesthesia, was <153 or >170 cm tall or >100 kg in weight, was excluded from the study. Written informed consent was obtained.

Preoperatively patients were given ranitidine either in a dose of 150 mg orally or 50 mg i.m. or i.v. according to the urgency of the delivery; 0.3 M sodium citrate 30 mL was administered orally in the anaesthetic room. Baseline systolic pressure was measured as the mean of three readings taken 5 min after arrival in the anaesthetic room and before instituting any invasive procedures. A systolic pressure 20% below the baseline was set as the level for administration of intravenous ephedrine.

The spinal anaesthetic was sited in the left lateral position with a 24-gauge Sprotte needle at the second or third lumbar interspace. Hyperbaric 0.5% bupivacaine 2.5 mL and fentanyl 12.5 µg were injected into the subarachnoid space. The patient was then turned supine with a wedge placed under the right buttock to prevent aortocaval compression. After 5 min the block was tested for analgesia to pinprick with a blunt needle. When analgesia was demonstrated to T5 bilaterally (T5 being the first unblocked segment), surgery proceeded.

Fluid management up to the completion of surgery was standardised for both groups in the study. Before siting the spinal anaesthetic, a large bore i.v. cannula was inserted and an infusion of Hartmann's solution was started. The drip rate was adjusted so that by the end of instituting the spinal anaesthetic 250 mL of the solution had been infused. Intra-operative blood loss was replaced with Hartmann's solution or blood as judged clinically appropriate. The restricted intravenous preload for the preeclamptic group is required by our unit protocol; we also applied it to the control group since a larger intravenous preload has not been found to reduce the incidence of hypotension after spinal anaesthesia in normal obstetric patients.<sup>10</sup> Postoperatively the preeclamptic patients were restricted to 80 mL/h plus losses.

Patient monitoring included electrocardiography, pulse oximetry and automated non-invasive blood pressure recordings (Datex Cardiacap 2 monitor) at 2-min intervals. Oxygen was given at 4 L/min via a Hudson mask until delivery when synthetic oxytocin (Syntocinon), 10 units, was given i.v. (the study was completed before publication of the recent recommendation that this Syntocinon bolus be limited to 5 units<sup>11</sup>). If pain

was felt during surgery, Entonox (50:50 mixture of nitrous oxide and oxygen) and morphine were given as required. If the initial block was inadequate (failed to reach the specified height of T5), the patient was to be withdrawn from the study and an appropriate alternative anaesthetic administered. Ephedrine in 6-mg increments was given at 2-min intervals if the systolic blood pressure fell below 20% of the baseline or if the patient exhibited symptoms associated with hypotension (nausea or vomiting). The presence of nausea, vomiting or bradycardia was recorded. A paediatrician recorded 1- and 5-min Apgar scores. Postoperatively mothers who had preeclampsia were monitored in our high dependency unit for a minimum of 24 h. Postoperatively, all patients received i.v. morphine by patient-controlled analgesia (PCA) for 24 h.

Results are presented as mean  $\pm$  standard deviation, with 95% confidence intervals. Power analysis based on published research indicated that 20 study and 20 control group patients would be required for a 90% power to detect a significant difference of 11 mg in ephedrine dose between the groups assuming a common standard deviation of 11.6 mg at the  $P < 0.05$  significance level. GraphPad Prism 3 statistical software was used; ephedrine requirement was analysed using the Mann-Whitney test.

## RESULTS

Of the 40 women recruited no patient had to be excluded from the study. There were no demographic differences between the two groups apart from the earlier gestational age of preeclamptic patients (Table 1). The preeclamptic patients were all stabilised on antihypertensive drugs and had no clinical evidence of pulmonary oedema; SpO<sub>2</sub> measurements were all within the normal range. The mean ephedrine requirement of the normotensive group ( $27.9 \pm 11.6$  mg, 95% CI 22.5, 33.3) was significantly greater ( $P < 0.01$ ) than that in the preeclamptic group ( $16.35 \pm 15.0$  mg, 95% CI 9.3, 23.4) (Fig. 1).

## DISCUSSION

In 1950 Assali and Prystowsky demonstrated that severely hypertensive preeclamptic patients were resistant to the haemodynamic effect of sympathetic blockade; they used both spinal anaesthesia and ganglionic blockade.<sup>12</sup> Despite this early finding there is a persisting dogma to the effect that these patients may become severely hypotensive following spinal anaesthesia for caesarean section. Wallace et al. challenged this view with a prospective study in which 80 women were

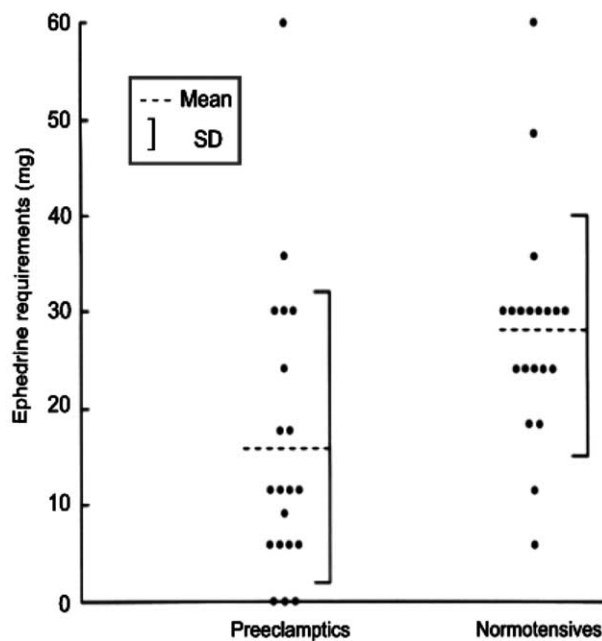
**Table 1. Patient characteristics, ephedrine usage, incidence of nausea and vomiting, blood pressure and bradycardia data, neonatal Apgar scores, antihypertensive therapy and indications for caesarean delivery**

	Preeclampsics (n = 20)	Normotensives (n = 20)
Age (years)	30.9 (6.2)	29.7 (4.7)
Height (cm)	160 (63)	160 (44)
Gestation (weeks)	34.9 (3.9)	39.4 (1.2)
Pre-spinal systolic blood pressure (mmHg)	147 (18.4)**	123 (10.9)**
Ephedrine requirement (mg)	16.4 (15.0)*	27.9 (11.6)*
Ephedrine not required (n)	3	0
Nausea	8	12
Vomiting	1	6
Bradycardia <60 beats/min	1	4
Apgar scores <7		
1 min	5	0
5 min	1	0
Labetalol and Nifedipine	8	0
Labetalol	7	0
Methyldopa	2	0
Nifedipine	2	0
Methyldopa and Nifedipine	1	0
Indications for caesarean delivery		
Preeclampsia	20	0
Previous caesarean delivery	0	7
Breech presentation	0	11
Unstable lie	0	1
Fractured pelvis	0	1

Data are mean (SD) or numbers of patients.

\*  $P < 0.01$ .

\*\*  $P < 0.001$ .



**Fig. 1** Dot plots showing individual ephedrine requirements for the preeclamptic and normotensive control groups. The mean ephedrine requirement for the preeclamptic group was 16.4 mg and for the normotensive group it was 27.9 mg.

randomised to general, epidural or combined spinal/epidural anaesthesia.<sup>7</sup> Hood and Curry followed with a retrospective review of 103 spinal and 35 epidural anaesthetics administered to severely preeclamptic patients.<sup>6</sup> They found similar blood pressure changes and ephedrine requirements in both groups, suggesting that

severe hypotension was not a problem. Further studies have confirmed these findings.<sup>4,5</sup> Despite these studies, theoretical reasons for maintaining a cautious approach to the safety of spinal anaesthesia have been advanced in two editorials and a standard textbook.<sup>1-3</sup> We originally published a prospective study in which we used ephedrine requirement as an index of haemodynamic stability during epidural versus spinal anaesthesia.<sup>8</sup> We found that blood pressure could be safely controlled with both techniques but the epidural group so consistently demonstrated inadequate analgesia that the study size was limited by ethical concerns. Our methodology contrasted in important ways with that used by the other investigators. In both the study reported here and also our previous one, patients were haemodynamically stabilised before anaesthesia. Additionally, preoperative i.v. fluid administration was standardised. Also, rather than observing any resultant hypotensive episodes we took a pro-active approach in line with our unit protocol. The intention was to control systolic blood pressure within our predetermined safe limits. We used systolic rather than diastolic or mean arterial pressure in line with normal clinical practice during obstetric spinal anaesthesia. The rationale for this is as follows. Estimation of mean arterial pressure depends on intermittent manual or automated systolic and diastolic blood pressure measurements; diastolic blood pressure measured in this way is subject to uncertainty since both Korotkov 4 and 5 recordings may be unreliable in pregnancy.<sup>13</sup> Invasive monitoring is not ethically justified in



stabilised and otherwise uncomplicated patients; non-invasive continuous blood pressure measurement presents technical difficulties in obstetric patients.

Symptoms of nausea and vomiting are arguably a more sensitive indicator of rapid-onset hypotension than non-invasive blood pressure measurements. In this study only one preeclamptic patient experienced vomiting in contrast to six in the normotensive group (Table 1).

It is useful to review the cardiovascular changes that might account for the significantly reduced ephedrine requirements we found in the preeclamptic group. It could be argued that the lower gestational age of preeclamptic patients at delivery would result in a reduced degree of caval compression. Two studies oppose this theory. There was no decrease in cardiac output in 128 preeclamptic subjects studied in the supine position,<sup>14</sup> conversely decreased cardiac output has been observed at only 20-24 weeks' gestation in normal pregnancies.<sup>15</sup> A more convincing explanation is to be found in the oestrogen-dependant vascular changes of normal pregnancy. From the tenth week of gestation there is a decrease in endogenous pressor responsiveness (especially to angiotensin II) due to an endothelium-dependant alteration of vascular smooth muscle, an increased synthesis of vasodilator prostaglandins and an increased rate of nitric oxide synthesis leading to a decrease in vasodilator tone.<sup>16-18</sup> The net effect is a decrease in peripheral vascular resistance beginning in early pregnancy. Consequently, in normal pregnancy there appears to be an increased dependence on sympathetic vasoconstriction for the control of vascular tone; together with the problem of supine caval compression this probably explains the profound falls in blood pressure sometimes seen following spinal anaesthesia in otherwise uncomplicated obstetric patients. By contrast a consistent feature of preeclampsia is damage to the maternal endothelial vascular mechanism;<sup>19</sup> consequently there may be a paradoxical resistance to hypotension following sympathetic blockade.

Although the preeclamptic group demonstrated a relatively reduced hypotensive response, six individuals more closely resembled the normotensive control group (Fig. 1), with the requirement for more than 18 mg ephedrine being an apparent separator. It was not possible to define any other clinical characteristics, such as hypotensive therapy or pre-existing hypertension, specific to this group and the number was too small for analysis. This finding may simply represent the heterogeneous pathology of preeclampsia.

In summary, we have studied a group of severely hypertensive preeclamptic women who had been stabilised with antihypertensive drugs before receiving spinal anaesthesia for caesarean section. This group required significantly less ephedrine to maintain systolic blood pressure within predetermined limits than an uncompli-

cated obstetric control group. In terms of ephedrine requirement the preeclamptic group was more haemodynamically stable than the normal control group. This study adds to recent evidence suggesting that hypertensive but stabilised patients with severe preeclampsia who have no other contraindication to spinal anaesthesia should not be denied this effective form of anaesthesia for operative delivery.

## ACKNOWLEDGEMENT

Dr. Bernhard Heidemann gave valuable advice on data analysis.

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**Bruce J, Sharwood-Smith G, Drummond G. Pulse transit time: a new approach to haemodynamic monitoring in obstetric spinal anaesthesia. *Int J Obstet Anaesth* 2002; 11, Supplement 1, 1-38**

### **Pulse transit time: a new approach to haemodynamic monitoring in obstetric spinal anaesthesia**

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**Introduction:** Hypotension is a frequent complication of obstetric spinal anaesthesia. Slow response of non-invasive blood pressure measurements or using symptoms such as nausea and vomiting can delay treatment, but early use of vasopressors may be unnecessary. Pulse Transit Time (PTT) is obtained from routine non-invasive monitors, and shows beat-to-beat vascular changes during regional anaesthesia.<sup>1</sup>

**Method:** After ethical committee approval we studied 62 patients scheduled for elective or urgent Caesarean Section. Patients with major medical complications or pre-eclampsia were excluded. Spinal anaesthesia was with hyperbaric bupivacaine 0.5% and diamorphine. A Datex Cardiocap provided non-invasive blood pressure, ECG, and plethysmograph signals for analysis. We recorded the time between the ECG R wave and the maximum rate of change of the optical plethysmograph at the second toe by analogue computer. Values given are median (quartiles).

**Results:** Data from 58 patients were analysed. Maximal changes in PTT occurred 2.39 (1.4,3.4) minutes after spinal anaesthetic. Changes in PTT and mean arterial pressure (MAP) were significantly related ( $r^2 = 0.55$ ,  $P < 0.0001$ ). Measurements of the second value of PTT were taken 0.2 (-0.2,1.0) min before the measurements of MAP.

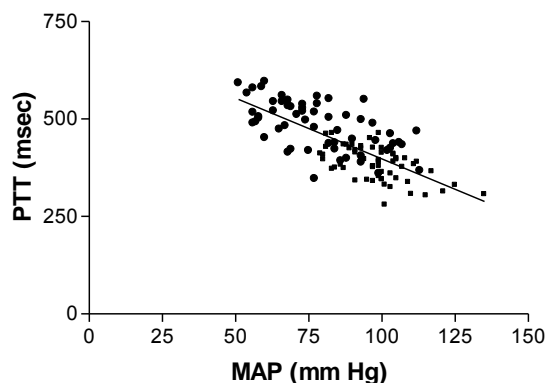


Figure 1: Individual values of PTT and MAP before (small squares), and following (large circles) spinal anaesthesia.

**Conclusions:** PTT can be derived from standard non-invasive monitors and gives early information on the vascular effects of spinal anaesthesia. PTT is worthy of further investigation in this context.

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**Sharwood-Smith G, Drummond G, Bruce J. Pulse transit time confirms altered haemodynamic response to spinal anaesthesia in pregnancy induced hypertension. *Hypertension in Pregnancy* 2002; 21 suppl 1: 31**

**Pulse Transit Time Confirms Altered Haemodynamic Response to Spinal Anaesthesia in Pregnancy Induced Hypertension.**

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**Background:** Despite evidence to the contrary, spinal anaesthesia in patients with Pregnancy Induced Hypertension (PIH) is considered likely to cause severe hypotension. Pulse transit time (PTT) gives a non invasive beat to beat measurement of vascular changes.

**Methods:** After ethical approval, we studied 15 patients with PIH and 58 control patients having elective or urgent Caesarean section. Spinal anaesthesia was with hyperbaric bupivacaine 0.5% and diamorphine. A Datex Cardiocap provided non-invasive blood pressure, ECG, and plethysmograph signals for analysis. We recorded the time between the ECG R wave and the maximum rate of change of the optical plethysmograph at the second toe by analogue computer. Values given are median (quartiles).

**Results:** Mean arterial pressure (MAP) before spinal anaesthesia was 99 (91,104) mm Hg in control and 115(104,119) mm Hg in the PIH patients. After spinal anaesthesia, MAP decreased by 18 (5, 33) mm Hg and 22 (11,29) mm Hg in control and PIH patients respectively. Before anaesthesia, PTT was similar in the two groups (Control, 390 (346,417) mSec and PIH, 353 (325,383) mSec). PTT increased significantly more quickly in the control patients (32 (14,56) mSec/min) than in the patients with PIH (7 (6,18) mSec/min). ( $P < 0.01$ , Mann Whitney U test)

**Conclusions:** PTT changes can be used to study PIH. The slow change of PTT after spinal anaesthesia suggests that arteries relax more slowly in PIH.

**Funding:** This study was supported by a grant from the Obstetric Anaesthetists' Association (UK)

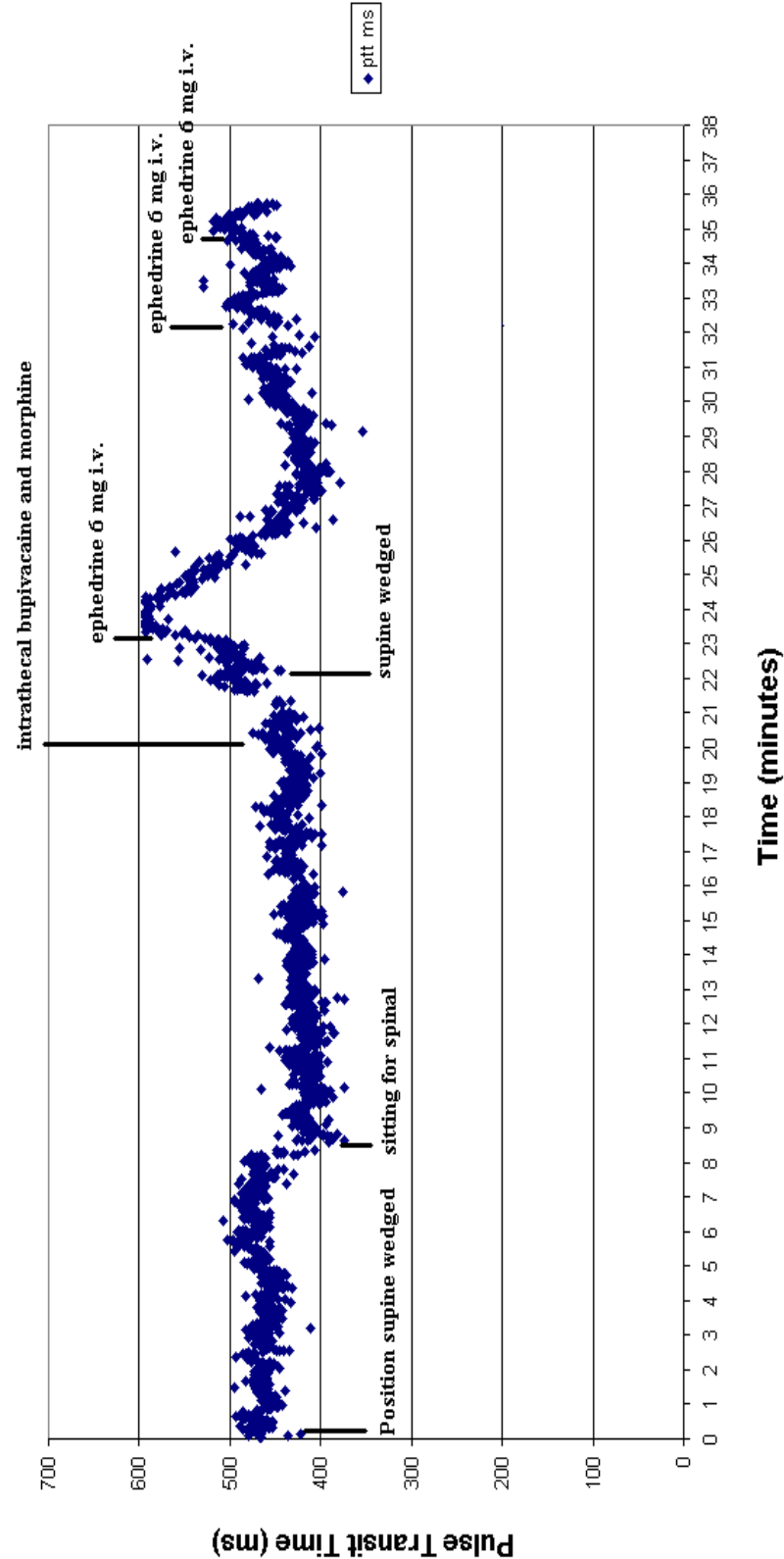


Background

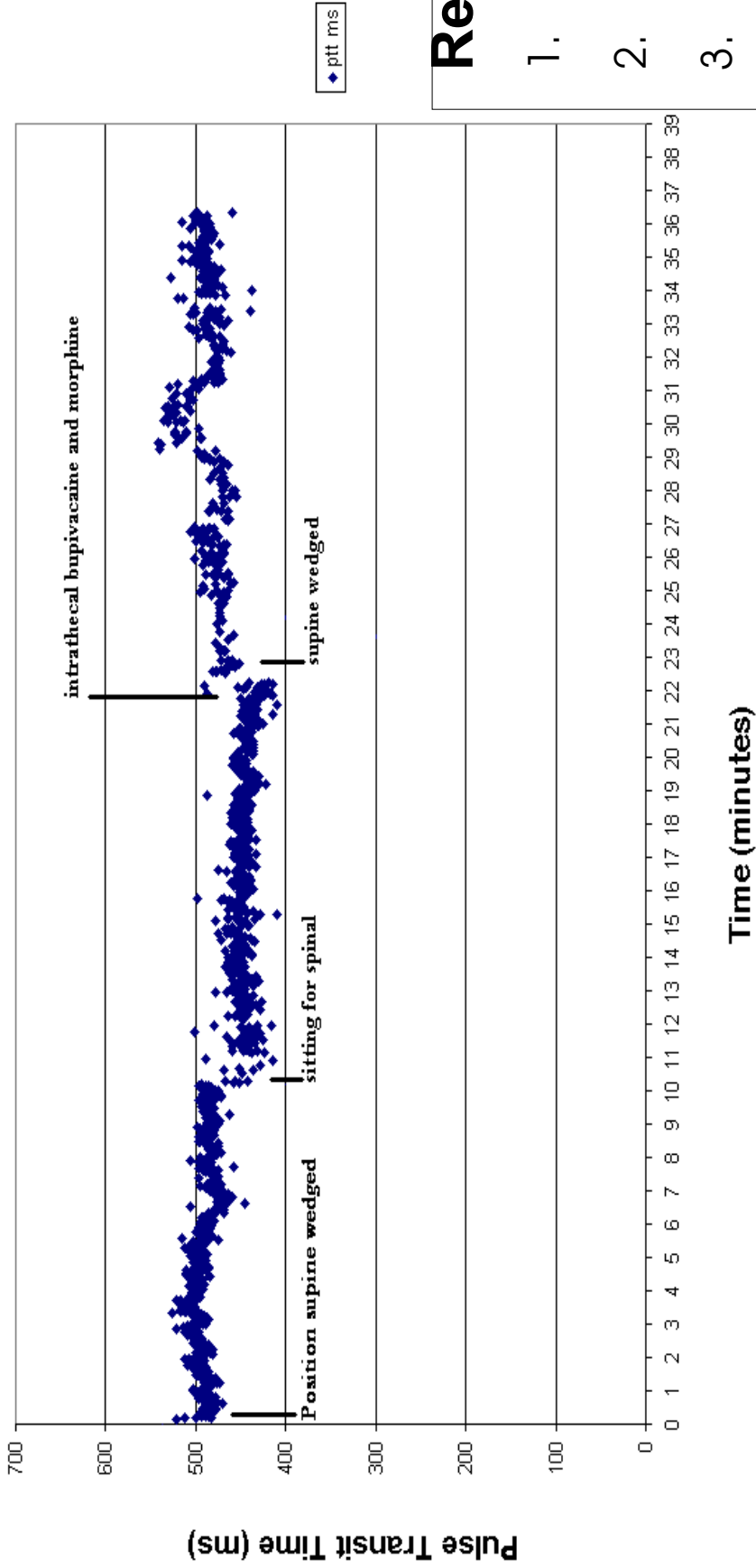
Despite contrary evidence, <sup>1</sup> spinal anaesthesia in patients with pregnancy induced hypertension (PIH) is still considered a potential cause of severe hypotension. <sup>2</sup> The vessel changes in PIH give a physiological basis for recent clinical findings of resistance to hypotension following spinal anaesthesia: endothelial damage impairs the nitric oxide and prostaglandin mediated vasodilatation of normal pregnancy - so blood pressure in PIH may be less dependant on sympathetic tone. We set out to investigate pulse transit time (PTT) as a means of studying these changes.

**Pulse Transit Time.....** *Is the time taken for the arterial pressure wave to travel between the aortic valve and the periphery - it can be measured non-invasively - it has been used to investigate changes in arterial stiffness due to sympathetic blockade in epidural anaesthesia. <sup>3</sup>*

EXAMPLE PULSE TRANSIT TIME DATA DURING SPINAL ANAESTHESIA - CONTROL PATIENT



EXAMPLE PULSE TRANSIT TIME DATA DURING SPINAL ANAESTHESIA - PIH PATIENT



Methods

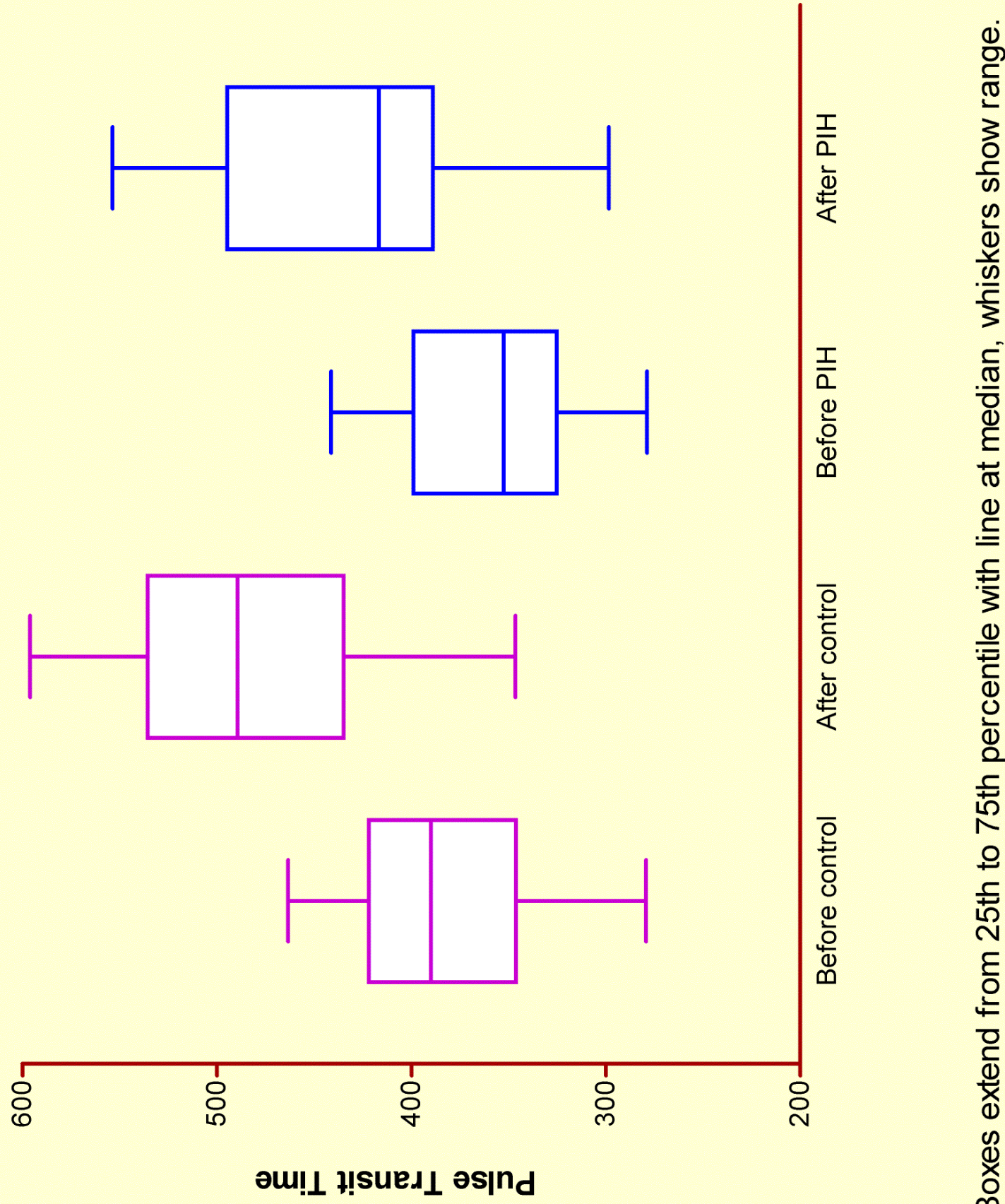
Ethical approval was obtained - cardiac disease, diabetes and other causes of hypertension were excluded - non-invasive blood pressure, ECG and plethysmograph signals were obtained from a Datex Cardiocap monitor - the time between the ECG R wave and the maximum rate of change of the optical plethysmograph at the second toe was measured by analogue computer - spinal anaesthesia was with 2.5-2.7 ml hyperbaric bupivacaine 0.5% + 300-400 mcg diamorphine - a block was established to above the T6 dermatome bilaterally in all subjects - PIH patients were treated with nifedipine and/or labetalol according to our unit protocol

Results

We recruited 82 patients for an observational study, 78 provided adequate data. Major medical conditions were present in 5. We present data from 58 control patients and 15 patients with PIH

	Control	PIH
Age	32 (30,34)	31 (30, 34)
Gestation (weeks)	39 (39)	36 (33, 38)
Height (cm)	62 (158, 167	162 (162, 168)
Weight (kg)	69.5 (61,76	72 (66, 79)

PTT before and after spinal anaesthesia



**PTT increased significantly more quickly in the control patients (32 (14,56) mSec/min) than in the PIH patients (7(6,18) mSec/min). (P<0.01 Mann Whitney U test)**

Conclusions

- PTT changes can be used to study PIH
- The slow change of PTT suggests that arteries relax more slowly after spinal anaesthesia in PIH
- The relative safety of spinal anaesthesia in PIH is confirmed.

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# Assessment of pulse transit time to indicate cardiovascular changes during obstetric spinal anaesthesia<sup>†</sup>

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**Background.** Pulse transit time (PTT) measurement may provide rapidly available beat-to-beat cardiovascular information when conditions change quickly and routine invasive arterial pressure measurement is not justified, for example during obstetric spinal anaesthesia.

**Method.** We obtained ethics approval for an observational study of PTT during the onset of spinal anaesthesia in patients having elective or urgent Caesarean section. PTT was measured as the difference in time between the peak of the ECG R wave and the upstroke of the toe plethysmograph. Arterial pressure was measured by non-invasive sphygmomanometry.

**Results.** We analysed data from 58 normotensive patients and 15 patients with pregnancy-induced hypertension (PIH). PTT increased with the onset of spinal anaesthesia as arterial pressure decreased. An increase of 20% in PTT was 74% sensitive and 70% specific in indicating a decrease in mean arterial pressure of more than 10%. Changes in PTT were related to changes in mean arterial pressure ( $r^2=0.55$ ,  $P<0.0001$ ). Arterial pressure changes were greater and PTT increased significantly more quickly in the normotensive patients than in the patients with hypertension [median, quartiles: 32 (14, 56) ms min<sup>-1</sup> compared with 7 (6, 18) ms min<sup>-1</sup>;  $P<0.01$ , Mann–Whitney *U*-test]. However, the relationship between PTT and arterial pressure was similar for the normotensive patients and the patients with PIH.

**Conclusion.** PTT measurement gave a beat-to-beat indication of arterial pressure during spinal anaesthesia, and could be developed to allow prediction of the onset of hypotension.

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**Keywords:** anaesthesia, obstetric; anaesthetic techniques, regional, spinal; cardiovascular system; monitoring, pulse transit time; pregnancy

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In clinical conditions, arterial pressure may change so quickly that intermittent non-invasive measurements may be too slow and inaccurate to allow early detection and prompt treatment, especially in obese subjects. However, routine invasive measurement may be inappropriate, for example in obstetric spinal anaesthesia, where hypotension is the most frequent complication and poses risks to both mother and foetus. In conscious subjects, arm movement can delay the display of an arterial pressure reading through two or three measurement cycles, often at a time when changes may be considerable. An additional non-invasive measurement that could give early warning of arterial pressure change would be useful clinically.

Pulse transit time (PTT) measurement offers beat-to-beat cardiovascular information.<sup>1</sup> Such measurements have been used previously to infer changes in autonomic activity<sup>2</sup> and arterial pressure.<sup>3</sup> PTT, measured as the interval from the

ECG R wave to the pulse plethysmograph upstroke, was used recently to assess cardiovascular responses to anaesthesia and intubation.<sup>4</sup> Both the ECG and the plethysmograph wave can be obtained from standard monitoring equipment. We used a custom-built analogue device to acquire automatically the interval between the ECG R wave and the pulse plethysmograph upstroke.

PTT is of clinical interest as an index of arterial stiffness and hence of arterial pressure,<sup>3,5</sup> since arterial stiffness increases as arterial pressure increases.<sup>6–8</sup> However, other factors may affect arterial stiffness. For example, recent studies suggest that hypotension following spinal

<sup>†</sup>Data from this study were presented in part at the Obstetric Anaesthetists Association Meeting at Nottingham, UK, on May 10, 2002 and at the 13th World Congress of the International Society for the Study of Hypertension in Pregnancy at Toronto, Canada, on June 2, 2002.

anaesthesia is less likely in patients with pregnancy-induced hypertension (PIH) than in normotensive patients.<sup>9</sup> Changes in PTT following spinal anaesthesia may indicate differences in arterial stiffness in these patients.

The prime aim of this study was to observe PTT in a clinical scenario where sudden onset of hypotension is relatively frequent, and assess its value for predicting such changes. A secondary aim was to compare the responses of patients with and without PIH.

## Methods

The local ethics committee approved collection and recording of data from routine cardiovascular monitoring devices, but not the modification of routine management in any other way. We obtained informed verbal consent for the data collection. We recorded PTT during the onset of spinal anaesthesia in non-labouring women having Caesarean section for routine elective or urgent indications. Patients were recruited as they presented over a 6-month period; of these, 74 were normotensive. Eighteen patients had severe PIH, defined using standard criteria<sup>10</sup> as hypertension which developed after 20 weeks of gestation and required anti-hypertensive medication with nifedipine, labetalol or methyldopa, singly or in combination. We included patients with or without proteinuria. We undertook this study before our unit introduced i.v. magnesium sulphate treatment for severe PIH.

The values were obtained from before the spinal anaesthetic to the time the patient was ready for surgery. Vasopressor or vagolytic drugs were given by the clinician managing the anaesthesia, according to normal practice, in response to changes in arterial pressure, heart rate, or the onset of symptoms suggestive of hypotension, such as dizziness, nausea or vomiting. Some of these clinicians did not routinely give vasopressor agents prophylactically, others did, and some gave them occasionally.

Patients were placed in a supine wedged position and an infusion of Hartmann's solution was started. ECG monitoring and an automated arterial pressure (NIBP) recording cuff were applied (Cardiacap 2; Datex). The baseline arterial pressure was recorded as the mean of three measurements taken at 2-min intervals. An oximeter probe was placed on the second toe of the left foot. Spinal anaesthesia was then administered with the patient in either the sitting or left lateral position. A 24 gauge Sprotte needle was used to give between 2.5 and 2.7 ml of hyperbaric bupivacaine 0.5% with diamorphine 0.3 or 0.4 mg according to the anaesthetists' preference. The patient was then returned to the wedged supine position. The time was recorded, and the events that were marked electronically included the following: the connection of monitoring equipment; the initial change of position for the spinal; the return to a wedged supine position; the administration of vasopressor or other i.v. drugs; and the transfer of the patient to the operating theatre. IV fluids given before spinal anaesthesia and the

total given over the study period were recorded. Heart rate and NIBP were recorded at 2-min intervals. The ECG and photoplethysmograph signals from the analogue output of the Cardiacap monitor were transferred to a purpose-built analogue computer constructed by Leiden University. This computed the time between the peak of the ECG R wave and the maximum rate of the plethysmograph wave upswing. The time intervals and digital signals from the Datex monitor were recorded in digital form on a Satellite Pro 4300 (Toshiba) laptop computer.

Before data analysis, spurious ECG and photoplethysmograph signals generated by patient movement were removed. These artefacts were defined using an Excel function (Excel version 9.0, 1999; Microsoft, Redmond, WA, USA) as values that were 20% less or greater than the rolling mean PTT, and were filtered from the data before analysis.

Statistical analysis was with GraphPad Prism version 3.02 and Analyse-It software for Excel, version 1.71 (Analyse-it Software, Leeds, UK). Data are presented as medians (quartile values) unless stated otherwise.

## Results

Ninety-two patients were studied; we obtained data suitable for analysis from 58 normotensive patients and 15 with PIH. There were no obvious systematic differences in the reasons for exclusion between the two groups of patients (Table 1). The two groups were similar in respect of height and weight, but, as might be expected, heart rate was less, arterial pressure was greater and gestational age was less in the patients with PIH (Table 2). Before the spinal anaesthetic, normotensive patients were given 400 (300, 500) ml of Hartmann's solution and the patients with PIH received 150 (100, 225) ml. The dose of bupivacaine was 13 (12.5, 13.5) mg in both the normotensive and the hypertensive patients. Most patients received diamorphine 300 µg, but nine were given 400 µg. Ephedrine had to be given to 46 of the normotensive patients and three of the patients with PIH ( $P < 0.001$ ); other vasopressor and vagolytic agents (phenylephrine, atropine and glycopyrrolate) were also used more frequently in the normotensive patients.

Data from five patients were not analysed because vasopressor drugs were given prophylactically by personal preference of the anaesthetist immediately after spinal

**Table 1** Reasons for exclusion from analysis

	Normotensive	PIH
Total number before exclusions	74	18
Reasons for exclusion		
Inadequate data	9	1
Vasopressor given prophylactically	5	0
Computer failure	1	0
Conversion to general anaesthetic	1	0
Insulin-dependent diabetes	0	1
Essential hypertension	0	1
Number of patients analysed	58	15

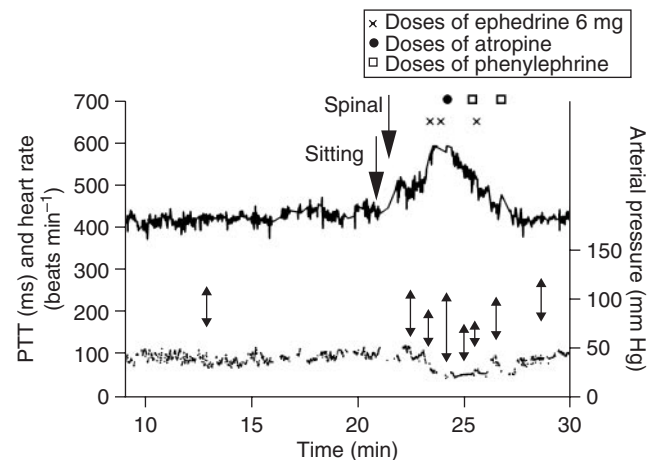
**Table 2** Patient details and cardiovascular measurements before and after spinal anaesthesia. Values are median (interquartile values). ns, not significant. Student's *t*-test, \**P*<0.05, \*\**P*<0.0001; Mann–Whitney *U*-test, #*P*<0.01

	Normotensive subjects	Pregnancy-induced hypertension	Significance
Patient details			
Number	58	15	
Age	32 (30, 35)	32 (30, 37)	
Height (cm)	162 (158, 168)	162 (160, 170)	
Weight (kg)	70 (61, 78)	72 (62, 83)	
Gestation (weeks)	39 (39, 39)	36 (33, 38)	
Cardiovascular values			
Before spinal anaesthesia			
Heart rate (beats min <sup>-1</sup> )	89 (78, 102)	80 (74, 94)	*
Arterial pressure (mm Hg)			
Mean	99 (91, 104)	115 (104, 119)	**
Systolic	126 (118, 138)	144 (138, 160)	**
Pulse transit time (ms)	390 (345, 422)	353 (325, 399)	*
After spinal anaesthesia			
Heart rate (beats min <sup>-1</sup> )	87 (78, 109)	80 (71, 101)	ns
Arterial pressure (mm Hg)			
Mean	92 (86, 99)	106 (98, 111)	**
Systolic	124 (116, 136)	140 (136, 154)	ns
Pulse transit time (ms)	413 (373, 454)	370 (342, 417)	*
Measurements at greatest pulse transit time or first intervention			
Heart rate (beats min <sup>-1</sup> )	96 (78, 109)	79 (75, 98)	ns
Mean arterial pressure (mm Hg)	77 (66, 90)	89 (98, 111)	**
Change in mean arterial pressure	18 (5, 33)	22 (11, 29)	ns
Systolic arterial pressure (mm Hg)	106 (92, 120)	119 (111, 134)	ns
Pulse transit time (ms)	488 (429, 532)	417 (389, 495)	*
Greatest change in PTT (ms)	94 (62, 123)	75 (54, 118)	ns
Greatest change in PTT (%)	24%	21%	ns
Rate of change in PTT (ms min <sup>-1</sup> )	32 (14, 56)	7 (6, 18)	#
Time to greatest PTT change (min)	2.4 (1.4, 3.4)	5.0 (3.2, 7.7)	#
Minimum arterial pressure after spinal anaesthesia			
Mean	69 (60, 78)	83 (78, 95)	**
Systolic	97 (87, 108)	116 (108, 126)	**

anaesthesia and before PTT and arterial pressure recordings could be obtained. A standardized format of clinical practice was not imposed in this observational study. In 10 patients, technical problems with recording either PTT or arterial pressure yielded insufficient data for analysis.

Mean arterial pressure (MAP) before spinal anaesthesia was 99 (91, 104) mm Hg in the normotensive patients and 115 (104, 119) mm Hg in patients with PIH. With the onset of spinal anaesthesia, MAP decreased by 18 (5, 33) and 22 (11, 29) mm Hg in normotensive and PIH patients respectively.

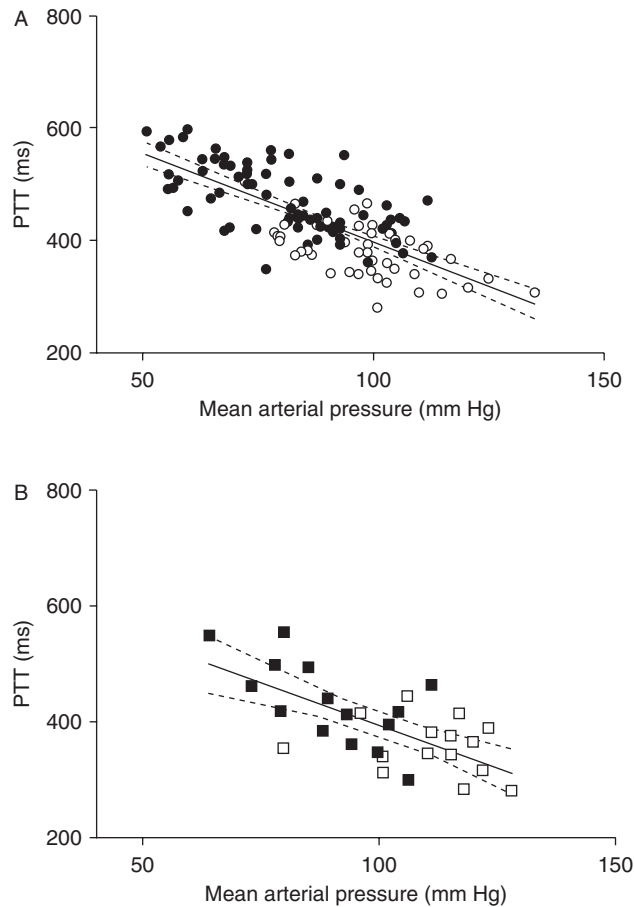
Patient movement and repositioning after carrying out the block disturbed the ECG and plethysmograph signals, and could cause spurious PTT values. These were less than 3% of the total values obtained. Before anaesthesia, PTT was significantly less in the patients with PIH: 353 (325, 383) ms (*P*<0.05) compared with 390 (346, 417) ms in the normotensive group (*P*<0.05). PTT changed during the onset of spinal anaesthesia (Fig. 1) by 24% in the normotensive group and 21% in the PIH group. The greatest change in PTT occurred 2.4 (1.4, 3.4) min after spinal anaesthetic in the normotensive group and 5.0 (3.2, 7.7) min after spinal anaesthetic in the hypertensive group. Thus, PTT increased more rapidly in the normotensive patients [32 (14, 56) ms min<sup>-1</sup>]



**Fig 1** An example of patient responses. Upper, continuous trace: pulse transit time (ms). Lower, discontinuous trace: heart rate calculated from successive R-R intervals. Systolic and diastolic arterial pressures are shown as vertical bars and arrowheads.

than in the patients with PIH [7 (6, 18) ms min<sup>-1</sup>] (*P*<0.01, Mann–Whitney *U*-test).

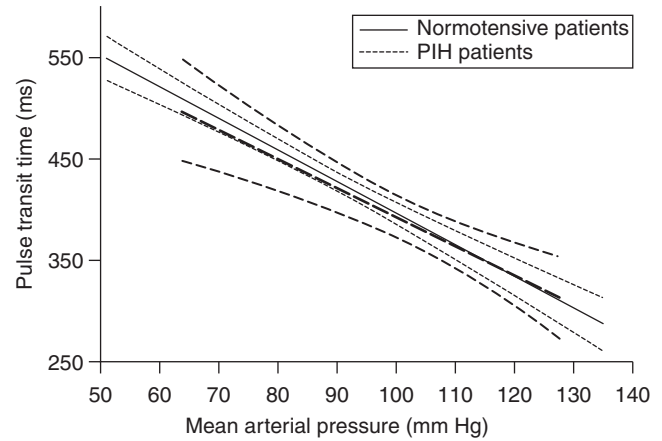
The relationship between PTT and MAP was examined before and after spinal anaesthesia (Fig. 2). There was a



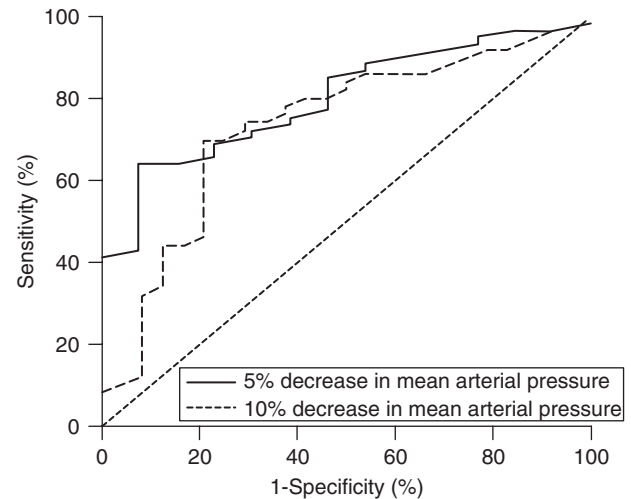
**Fig 2** Relationship of pulse transit time to mean arterial pressure in (A) normotensive subjects and (B) patients with pregnancy-induced hypertension. The open symbols are before and the closed symbols after spinal anaesthesia. The linear regression relationships are shown with the 95% confidence interval for the line. Both relationships are significant ( $P < 0.0001$ ).

significant correlation in both the normotensive ( $r^2 = 0.55$ ,  $P < 0.0001$ ) and the PIH group ( $r^2 = 0.45$ ,  $P < 0.0001$ ) (Fig. 3). The slopes of the relationships between PTT and MAP were not different when normotensive and hypertensive subjects were compared [slopes (95% confidence interval, CI) were  $-3.12$  ( $-3.64$ ,  $-2.59$ ) and  $-2.88$  ( $-4.12$ ,  $-1.64$ ) ms (mm Hg) $^{-1}$  respectively].

We examined the sensitivity and specificity of changes in PTT to indicate the onset of hypotension. The resulting receiver operating characteristic (ROC) curves for decreases in MAP of 5 and 10% are given in Figure 4. For a decrease in MAP of 5%, an increase of 10% in PTT was 95% sensitive but only 15% specific. If a cut-off value of a 20% increase in PTT was taken, the sensitivity and specificity were 69 and 77% respectively. The area under the ROC curve was 0.79 (95% CI, 0.68–0.9;  $P < 0.001$  compared with an area of 0.5). Considering decreases in MAP of more than 10%, an increase of 20% in PTT was 74% sensitive and 70% specific. The area under the ROC curve was 0.72 (95% CI, 0.60–0.85;  $P < 0.001$  compared with an area of 0.5).



**Fig 3** Comparison of the linear regression relationships of pulse transit time and mean arterial pressure in normotensive subjects and patients with pregnancy-induced hypertension. The outer lines represent the 95% confidence interval for the regression.



**Fig 4** Receiver operating characteristic curves for changes in pulse transit time in relation to a decrease in mean arterial pressure by 5 and 10%. For the 5% decrease, the area under the curve is 0.79 (0.68–0.90) and for the 10% decrease the area is 0.73 (0.60–0.85) (95% confidence intervals) Both areas are significantly greater than 0.5 ( $P < 0.001$ ).

## Discussion

To our knowledge, the relationship between PTT and arterial pressure has not previously been studied systematically during obstetric spinal anaesthesia. We chose to study this scenario because rapid and substantial changes in arterial pressure are relatively frequent. We found that changes in PTT were related to arterial pressure changes and that the relationship between PTT and arterial pressure was the same in normotensive patients and those with PIH.

We measured the time interval between the ECG R wave and the upstroke of the plethysmograph.<sup>11 12</sup> This time includes two principal components, the time between electrical activation of the ventricle and cardiac ejection, and the



time taken for the resultant pressure wave to be transmitted along the artery to generate the plethysmograph upstroke.<sup>11</sup> The time from ventricular activation to cardiac ejection depends upon a number of factors related to preload, heart rate and contractility.<sup>13 14</sup> This time is small compared with the time taken for pulse wave transmission along the vessel, particularly in young normotensive patients. Consequently, the greater part of the PTT we measured indicates vascular elastance according to the Bramwell–Hill relationship<sup>15</sup> described for the velocity of pressure waves:

$$\text{Velocity} = \sqrt{(\Delta P/[V/\Delta V] \times \rho)}$$

where  $\rho$  is the density of blood and  $\Delta P/[V/\Delta V]$  is the specific elastance of the vessel. The pressure–volume relationship of arteries is non-linear: as pressure decreases, elastance decreases, pulse wave velocity decreases and PTT is increased, as we have confirmed. Other factors that affect vascular elastance, such as hypertension and change in sympathetic activation, could also affect PTT, but these influences are disputed. For example, although ultrasound estimates of radial artery elastance suggest that arterial infusion of phenylephrine can increase elastance,<sup>16</sup> others have concluded that greater arterial elastance in hypertensive patients can be explained entirely by differences in arterial pressure.<sup>7 17</sup> These findings are supported by the present study, in which we found no discernible difference between normotensive patients and those with PIH in the relationship for arterial pressure and PTT. We conclude that the mechanical properties of the large conducting vessels in patients with this condition are not affected, whereas the resistance vessels are clearly affected. This finding is not altogether unexpected: the site of modulation of arterial resistance depends upon the type of stimulus.<sup>18</sup>

The shape of the pressure waveform in peripheral arteries varies considerably with age and disease.<sup>19</sup> The rate of increase of the pressure varies considerably with age, but in the limited range of ages that we studied this could not cause much variation.

The analogue device that we used detected the maximum rate of change of the plethysmograph waveform. In preliminary unpublished studies of healthy volunteers, we used a method of intersecting tangents to determine the nadir of the plethysmograph waveform. Measurements of PTT using this nadir were less affected by changes in heart rate than measurements made using the time to the maximum rate of change of the plethysmograph signal. These findings confirm those of others.<sup>20</sup> However, this method was not compatible with analogue preprocessing, in that we not could detect the maximum rate of change of the plethysmograph wave. It was therefore not practical for this study. Thus, one source of variation in the relationship between PTT and arterial pressure could result from heart rate changes and the method used by our analogue detector.

There is a difference in time between the occurrence of plethysmograph waveforms in the finger and toe because of differences in distance along the arteries. Epidural anaesthesia increases this time difference and was attributed by the investigators to sympathetic blockade in the leg arteries.<sup>21</sup> However, the time difference only increased between 10 and 20% and this increase was accompanied by a decrease in arterial pressure. Consequently, an equally plausible alternative explanation is that hypotension, causing a proportional increase in pulse wave transmission time, would have a greater absolute effect in the longer vessel. This effect can account for the changes reported by these workers.

Recently, marked changes in PTT were described during general anaesthesia in association with tracheal intubation, and these changes were attributed to autonomic activation.<sup>4</sup> However, no measurements of arterial pressure were reported. Once again, the changes could have been caused by changes in arterial pressure, because the hypertensive response to insertion of the tracheal tube will increase arterial elastance and reduce PTT, as the authors reported.

Monitoring by means of PTT has been compared with invasive arterial pressure measurements. If the directly measured pressure changed by more than 10 mm Hg, then PTT accurately tracked the change on 67% of occasions. However, the authors of this study concluded that PTT did not have sufficient accuracy to replace direct arterial measurements.<sup>22</sup>

Clinically, PTT changes are of interest as a non-invasive beat-to-beat index of arterial pressure changes. Increased arterial pressure itself causes increased arterial stiffness but the relationship is non-linear at high and low pressures.<sup>23</sup> In the present study, by using a large control group, in which there were considerable changes in PTT, we found a correlation between MAP and PTT changes. More than 50% of the variance in PTT is explained by the value of the MAP. The remainder of the variance must result from other factors, such as patient size, variation in accuracy of estimates of both arterial pressure and PTT, and individual variations in vessel wall characteristics. Arterial behaviour can be altered by obesity,<sup>24</sup> longitudinal tension<sup>25</sup> and vasoactive mediators.<sup>16</sup> Although these additional factors increase the variation between subjects, it is likely that they will not influence the variation within an individual, so PTT can be a useful measure of moment-to-moment changes within a particular patient.

Our results were obtained in pregnant subjects, and the mechanical properties of large vessels such as the aorta can be affected by hormonal changes such as may occur in pregnancy.<sup>26</sup> However, the vascular changes of PIH are probably confined to small resistance vessels,<sup>27 28</sup> explaining the similar relationship between PTT and arterial pressure in normotensive and PIH patients.

Non-invasive methods for arterial pressure measurement, such as automated sphygmomanometers, frequently fail to display values when patient movement causes interference.



This is a particular problem in obstetric anaesthesia, where the subjects are awake and may be agitated and the procedures are often urgent, with little opportunity for careful cuff application and even less for arterial cannulation. We found that PTT could potentially be used, in these circumstances, to predict the onset of hypotension. The sensitivity and specificity are sufficient to indicate instantaneously changes in arterial pressure and provide a rapid, non-invasive, within-subject indication of hypotension. This may be of considerable value if invasive monitoring is not justified. We found no evidence that the properties of large arteries are affected by PIH.

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*"I would have everie man write what he knowes and no more."—Montaigne***BRITISH JOURNAL OF ANAESTHESIA****Volume 102, Number 3, March 2009***British Journal of Anaesthesia* **102** (3): 291–4 (2009)

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**Editorial I****Hypotension in obstetric spinal anaesthesia: a lesson from pre-eclampsia**

Vasopressor use to prevent hypotension occurs after 80% of spinal anaesthetics for Caesarean section.<sup>1</sup> The problem was first recognized 50 yr ago<sup>2</sup> when it was attributed to caval compression. This theory became accepted as the basis for clinical management, and it remains current today.<sup>3–4</sup> However, using this theory as a basis for the management of hypotension has proved disappointingly ineffective.<sup>5–6</sup> Important information from the 'natural experiment' of pre-eclampsia was overlooked, and fresh information from vascular biology now calls for a reconsideration of our management of hypotension in these circumstances.

Previously, the concept of compression of the vena cava and the aorta was linked to three features, which can coexist and are often considered together. However, each probably has a different mechanism. First, spinal anaesthesia almost always causes hypotension in normal pregnancy, and we will consider the reasons for this phenomenon later. Secondly, cardiac output can be reduced by aortocaval compression when some mothers lie in the supine position, although this is not necessarily clinically evident. Thirdly, a marked bradycardia with a reduction in cardiac output and severe hypotension can occur suddenly in a few subjects at some time after the mother moves to the supine position. This reflex effect is the relatively uncommon supine hypotensive syndrome of pregnancy (SHSP).<sup>7</sup>

Holmes<sup>8</sup> proposed that compression of the inferior vena cava by the gravid uterus caused hypotension after spinal anaesthesia because venous return was reduced and thus cardiac output decreased. Marx<sup>9</sup> developed the concept that blood was trapped in the legs, and introduced the treatment strategy of 'acute hydration' supported by a widely cited illustrative case history. Subsequently, fluid administration before spinal anaesthesia became the putative 'prophylaxis' and an almost universal therapy.<sup>10</sup>

The theory of caval compression and supine hypotension was based largely on studies by Scott and colleagues,<sup>11</sup> who measured cardiac output by dye dilution in eight

patients. Overall, cardiac output was 12% less in the supine compared with the lateral position. In three subjects, the mean reduction was only 6% and the investigators suggested that vena caval compression was relieved because the fetal head was engaged.<sup>11</sup> However, in two patients, there was sudden bradycardia, hypotension, and a decrease in cardiac output by more than 50%, suggesting a reflex response. Clearly, this study reported a heterogeneous group of patients, and the patients with bradycardia developed the supine hypotensive syndrome, which is a different phenomenon from the hypotension seen in the other patients in that study. An extensive review of SHSP found a wide range of case selection, clinical features, definitions, and degrees of hypotension.<sup>12</sup> Severe hypotension was reported in 2.5–20% of these patients. In some patients, hypotension only occurred after 20 min in the supine position. The possible reasons given for hypotension in these patients were either vena caval obstruction or a vagal reflex bradycardia, which is a well-known phenomenon associated with poorly filled heart.<sup>13</sup> Later studies found much less difference between supine and lateral positions. Using transcutaneous Doppler, a maximum change of cardiac output of 6% occurred with moving from supine to a left 15° tilt, and fetal head engagement made no difference.<sup>14</sup>

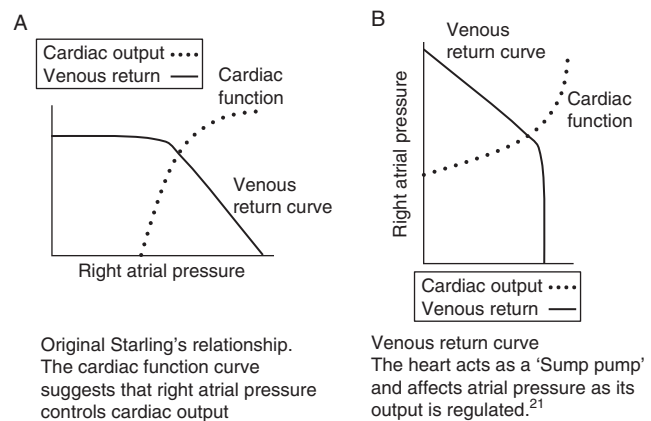
Undoubtedly, the vena cava is affected by the gravid uterus. Femoral venous and distal inferior caval pressures were greater in the supine position. In the lateral position, venous pressure was less, but still not as low as non-pregnant levels.<sup>15</sup> Angiography showed occlusion of the inferior vena cava and distension of the collateral azygos circulation in 12 supine patients having Caesarean section under general anaesthesia. The abdominal vena cava remained partly occluded in the lateral position.<sup>16</sup> However, in these studies, the link between changes in venous behaviour and hypotension was inferred rather than directly proved. No early studies involved spinal anaesthesia because general anaesthesia and increasingly epidural anaesthesia had, by that time, largely replaced spinals for Caesarean section in the UK.

The proponents of the caval compression theory suggested three ways to prevent hypotension after spinal block, but none has withstood careful examination. First, infusion of crystalloid or colloid was proposed to compensate for the venous blood said to be trapped in the legs, but initial reports of success in preventing hypotension<sup>17</sup> were not replicated in subsequent studies.<sup>1 5 6</sup> Colloid administration could increase cardiac output transiently, perhaps by haemodilution and reduced viscosity, but this effect was not sustained after sympathetic block with a spinal. Secondly, leg compression was attempted but was relatively ineffective, despite the success of the anti-G suit in preventing lower limb pooling and hypotension in aerospace medicine.<sup>18</sup> Finally, the tilt manoeuvre was advocated to reduce caval occlusion. Although widely used, this procedure is variably applied,<sup>19</sup> and does not prevent hypotension after spinal anaesthesia.<sup>6</sup> There is no escape from the fact that therapies based on the concept of caval compression do not reliably prevent hypotension after spinal anaesthesia in Caesarean section. Despite this, current books suggest routine use of strategies based on these putative explanations,<sup>4</sup> and current teaching uses these concepts.

The original hypothesis underlying the mechanism of hypotension was that a reduction in central venous pressure would reduce cardiac output, and thus reduce arterial pressure. This concept should be reconsidered. The hypothesis was based on the view that central venous pressure controls cardiac output, as suggested by the experimental studies of Paterson and Starling<sup>20</sup> and Guyton.<sup>21</sup> A clear understanding of the limits of Starling's studies is vital. They were of an isolated heart, supplied with blood from a venous chamber which could be raised or lowered to adjust the atrial pressure. In this 'open' system, output was not related to supply. The supply to the venous reservoir was externally adjusted by the investigator to keep the atrial pressure constant. By raising the reservoir to increase inflow pressure, the stretch of the ventricular muscle was increased, and thus ejection volume increased. To maintain the atrial pressure, the atrial reservoir had to be replenished more rapidly. In these circumstances, atrial pressure regulated cardiac output. This did not mean that the increased flow from the venous reservoir had increased the cardiac output, only that the flow had to be increased to sustain the reservoir pressure. The entirely separate studies of Guyton in which he related atrial pressure and venous return were equally artificial. Venous return was controlled using an adjustable pump. When the pump rate and thus the experimentally controlled 'venous return' was increased, a limit was reached where a decrease in venous pressure occurred and venous return did not change, implying upstream flow limitation.<sup>21</sup> In the whole body, the two factors of venous return and cardiac output are of course linked, in the long term, and neither is the 'cause' or 'effect' of changes in output or venous pressure, merely two sides of the same coin. The

inextricable link between venous return and cardiac output, and the unrealistic question concerning which is the cause and which is the effect, was recognized by Guyton, despite his considering venous pressure to be an independent variable. Even at the time, this highly artificial experiment was recognized as unlikely to be applicable to the intact animal.<sup>22</sup> In recent years, the relationship between venous pressure and cardiac output has been re-evaluated<sup>23 24</sup> and this has led to robust controversy.<sup>25 26</sup> Reddi and Carpenter<sup>27</sup> repeated previous suggestions<sup>23 25</sup> that it makes more sense to re-draw the Guyton plot with cardiac output on the abscissa (Fig. 1), to escape the common misconception that a decrease in right atrial pressure would act to increase blood flow through the veins. The important feature of the venous system is its compliance, not its resistance, and we can relate the central venous pressure to the volume held in the veins.<sup>28</sup> A recent helpful view is that the volume in the venous system is more relevant than the pressure, and that 'Venous Excess' is the important regulating factor on the venous side of the circulation.<sup>27</sup> Venous capacitance and its regulation in pregnancy may be an important element in understanding the haemodynamic response to spinal anaesthesia. For example, the splanchnic component of this capacitance drains directly into the vena cava via the hepatic vein which is not directly compressed by the uterus. However, we lack basic information on these aspects of venous dynamics.

The sensors that normally control arterial pressure, in the carotid sinus and the aorta, lie on the arterial side of the circulation, and are the sensors of the baroreflex. Why does this reflex fail to maintain arterial pressure after



**Fig 1** Comparison of cardiac function and venous return curves. (A) Cardiac function curve, after Guyton.<sup>19</sup> This relationship is based on the function of the isolated heart. An increase in central venous pressure causes an increase in cardiac output. The dependent variable (cardiac output) is plotted on the y-axis. (B) Venous return curve (also termed systemic or vascular function) which is the relationship found when the venous return is modified as the independent variable: under these circumstances, an increase in venous return reduces right atrial pressure.<sup>21</sup> Combining the two curves on one diagram condemns one of the relationships to have an independent variable expressed on the y-axis.

spinal anaesthesia in pregnancy? Part of the answer to this question can be found in the pathophysiology of pre-eclampsia. Remarkably, studies done in the 1950s showed that pregnant women with toxemia (severe pre-eclampsia) were far less likely to develop hypotension after spinal anaesthesia than normal pregnant or non-pregnant women. Similar differences were seen in response to autonomic ganglionic block, supporting the conclusion that withdrawal of sympathetic activity had less effect in the patient with pre-eclampsia.<sup>29 30</sup> For some reason, these studies were downplayed, although the proponents of the caval compression theory knew of them.<sup>2</sup> More recent studies corroborate the ability of pre-eclamptic patients to sustain arterial pressure after the spinal block.<sup>31</sup>

In pre-eclampsia, vascular epithelium is damaged by a process involving placental-derived proteins, leading to an imbalance between pro- and anti-angiogenic growth factors,<sup>32 33</sup> which results in persistent vasoconstriction. In contrast, the normal pregnant patient is very sensitive to spinal anaesthesia, because of an altered balance of vascular tone. Responses to endogenous pressors, particularly angiotensin II, are reduced. This is caused by an endothelium-dependent alteration of vascular smooth muscle function. Additionally, there is increased synthesis of vasodilator prostaglandins and nitric oxide. These effects increase dependence on sympathetic vascular tone in normal pregnancy.<sup>34 35</sup> The use of sympathomimetic vasopressors to sustain arteriolar tone and thus arterial pressure has become the most important strategy for safe spinal anaesthesia in contemporary practice, despite the prevailing theory of caval occlusion being responsible for hypotension after a spinal in normal pregnancy. Indeed, those who suggested that caval compression caused circulatory disturbances had advised against pressor agents to treat hypotension, suggesting that they would cause vasoconstriction but would not improve venous return.<sup>16</sup>

Nevertheless, aortocaval compression can reduce cardiac output and impair placental blood flow, so it remains rational to use tilt during anaesthesia, although the exact contribution of tilt to reducing hypotension in spinal anaesthesia is unclear.

After 40 yr, the relationship between spinal anaesthesia, pre-eclampsia, and hypotension can be properly acknowledged and put into clinical practice. These observations shed light on the circulatory effects of spinal anaesthesia in normal pregnancy. Research in obstetric anaesthesia can now move on from the legacy of an uncertain hypothesis by learning the lessons of pre-eclampsia and understanding how the features of this disorder illuminate our current concepts. Modern non-invasive methods such as ultrasound, MRI, and measures of skin blood flow<sup>36</sup> should be used in pregnancy to explain the effects of spinal anaesthesia more exactly. Better management and training based on logical theories should follow.

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