

**The use of phenylephrine to obtund oxytocin induced hypotension and  
tachycardia during caesarean section**

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## List of abbreviations

BP	Blood Pressure
c-GMP	Cyclic guanosine monophosphate
CNAP	Continuous non-invasive blood pressure
CO	Cardiac output
COX-1	Cyclooxygenase-1
COX-2	Cyclooxygenase-2
cPLA2	Cytosolic phospholipase A2
CS	Caesarean section
CSF	Cerebrospinal fluid
DAG	Diacylglycerol
DBP	Diastolic blood pressure
eNOS	Nitric oxide synthase
Hb	Haemoglobin
HR	Heart rate
IM	Intra-muscular
IP3	Inositol tri-phosphate
IU	International units
IV	Intravenous
MAP	Mean arterial pressure
MLCK	Myosin light chain kinase
NIBP	Non-invasive blood pressure
NO	Nitric oxide
PGE2	Prostaglandin
PIP2	Phosphatidyl-inositol bisphosphate
PLC	Phospholipase C
PPH	Post-partum haemorrhage
SA	Spinal anaesthesia
SBP	Systolic blood pressure
SVR	Systemic vascular resistance

## **Part A: Study protocol**

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

## 1. Introduction

Obstetric haemorrhage remains a major peripartum complication, and has been shown to be on the increase around the world, particularly in South Africa<sup>1</sup> as well as in the United States.<sup>2,3</sup>

Oxytocin is accepted as the first line uterotonic in the prevention and treatment of post-partum haemorrhage (PPH). However, oxytocin causes transient relaxation of vascular smooth muscle cells, probably via calcium-dependent stimulation of the nitric oxide pathway, which results in peripheral vasodilatation, hypotension and increased cardiac output (mediated by an increase in heart rate and stroke volume). Oxytocin also causes atrial and brain natriuretic peptide release, and may have a mild negative inotropic effect on atrial myocytes.<sup>4</sup> There may be associated dizziness and nausea and vomiting, tachycardia, myocardial ischaemia and arrhythmias, particularly when given in bolus doses of >5 IU. In addition, if a parturient is haemodynamically unstable due to haemorrhage, inappropriate use of oxytocin may cause cardiovascular collapse. A maternal death was reported by the Confidential Enquiry into Maternal Deaths of the UK when 10 IU oxytocin was given to a hypovolaemic patient during resuscitation. Hence recent recommendations are to administer an initial dose of 3 IU after delivery during elective caesarean section.<sup>5</sup> Ultra-low oxytocin doses (dose range=0.05-0.5 IU) repeated as needed, have been recommended in pregnant patients with cardiac disease.<sup>6</sup> Extreme care is also recommended in pre-eclampsia, where impaired left ventricular function may reduce compensatory mechanisms.

It would be of clinical value to know whether an alpha agonist is effective in reducing oxytocin - induced hypotension. This could have implications for the reduction of hypotension and maternal symptoms during the administration of oxytocin infusions for prophylaxis of PPH, or as therapy during active bleeding. Co-administration of phenylephrine has been shown

to obtund, but not eliminate hypotension, followed by some overshoot of alpha agonist effects and an increase in blood pressure.<sup>7</sup> These authors suggested that a bolus of phenylephrine given immediately before oxytocin, may be more effective to maintain haemodynamic stability. Therefore it was decided to examine the effects of prior administration of 50 µg phenylephrine on the hypotensive effect of a slow bolus of 3 IU oxytocin.

## **2. Objectives**

To determine whether hypotension and tachycardia caused by oxytocin administered post-delivery during elective caesarean section, can be obtunded by the prior administration of phenylephrine. The Null Hypothesis was that administration of phenylephrine prior to oxytocin inadequately obtunds the hypotensive effect of oxytocin.

## **3. Study Design**

Prospective, randomized, controlled, double blind study.

## **4. Study Location**

Single-Centre Study at Mowbray Maternity Hospital, Mowbray, Cape Town, South Africa.

## **5. Study Outcomes**

Primary Outcome: Between-group comparison of mean peak percentage SBP changes due to oxytocin, preceded by phenylephrine or placebo.

Secondary Outcome: Between-group comparison of mean peak percentage changes in values of all other haemodynamic indices (DBP, MAP and HR), and a comparison of mean percentage changes in these indices.

## **6. Patients and Methods**

Approval will be sought for the study from the University of Cape Town Human Research Ethics Committee. Forty patients will be recruited into the study. They will be American Society of Anesthesiologists (ASA) class 1 or 2 patients, aged >18 and <40 years, who are scheduled for elective caesarean delivery under spinal anaesthesia at Mowbray Maternity Hospital.

Exclusion criteria will be emergency C/S, pre-eclampsia or any cardiac, respiratory, renal or neurological disease, allergy to any study drug, Hb < 7 g/dL, body mass index (BMI) > 40 kg/m<sup>2</sup>. Patients will be randomized, using a table of random numbers, into 2 groups of 20. One group will receive a 50 µg bolus of phenylephrine (1 mL) as vasopressor and the other group placebo (1 mL saline), followed by intravenous oxytocin (3 IU in 5 mL saline over 15 seconds). Recruitment and randomisation will be done at least 12 hours before caesarean section. The anaesthesiologist and patient will be blinded as to the group allocation. The procedure will be explained to the patient either by the recruiting investigator or by a skilled translator, and the patient will receive a detailed consent form the day before caesarean delivery. Written informed consent will be obtained. Block randomisation will be used, using nQuery Advisor Version 6, Statistical Solutions, Cork, Ireland), and sealed envelopes will be prepared by the statistician.

## **7. Study Procedure**

Every participant will be weighed, height measured and body mass index calculated. Immediately pre-operatively 30 mL of sodium citrate will be given orally to every participant. In theatre, intravenous access will be established via a 18-gauge cannula. 1 g Cefazolin will then be administered intravenously slowly. During this time standard non-invasive monitoring will be applied to the patient. This includes electrocardiography and pulse oximetry as well as the CNAP (Continuous Non-Invasive Arterial Pressure) device. Recorded data will consist of heart rate (HR), systolic (SBP),

diastolic (DBP), and mean arterial pressure (MAP). The CNAP 500 Monitor System (CN Systems Medizintechnik AG, Graz, Austria) consists of a sensor placed on the second and third digits of one hand; a NIBP cuff on the same arm will be used for calibration and the CNAP monitor. The measurement is done continuously on one finger at a time and then changes to the other finger after a defined period. This allows long-term measurement of up to 24 hours on one hand. The sensor, placed around the finger, detects infrared light which is transmitted through the finger. Part of the transmitted light is absorbed by the blood pulsating through the finger. The light that is detected by the sensor is then calculated to be a measure of the pulsatile blood volume. The finger cuff is inflated so that the blood volume is kept constant and therefore also the transmission of light. The inflation pressure of the finger cuff achieves this constant blood volume, and is the primary signal used for blood pressure measurement. The NIBP on the same arm is used to calibrate this signal.

The CNAP device will be calibrated prior to baseline measurements and again on commencement of surgery. Immediately before administration of the spinal anaesthesia (SA), a baseline blood pressure (BP) will be taken by the CNAP device. Baseline systolic blood pressure (SBP) will be defined as the average of 3 measurements in a 5 minute period, not differing by more than 10%, with the patient in the left lateral position. Spinal anaesthesia (SA) will be conducted in the following manner. A bolus crystalloid co-load of Modified Ringer's Lactate solution (20 mL/kg) will be rapidly administered using a pressure bag, after cerebrospinal fluid appears in the hub of the spinal needle. Further crystalloid solution will not be given unless blood loss is > 1L. This will be determined by suction bottle measurement and swab inspection. Spinal anaesthesia will consist of 2.0 mL of 0.5% hyperbaric bupivacaine (10 mg) plus 10 µg of fentanyl administered over 20 seconds at the L3/4 interspace. After 20 s in the sitting position, patients will be positioned supine, with at least 15 degrees of left lateral tilt, to minimise aorto-caval compression. The effectiveness of the block will be assessed by the patient's sensitivity to cold via ethyl chloride spray. A block level will then

be determined. Supplemental oxygen will only be administered if arterial oxygen saturations decrease to below 92%. As soon as a sensory level is achieved to T4, surgery will commence. Bolus phenylephrine (50-100 µg) will be administered to maintain SBP within 20% of baseline.

Thirty seconds after delivery, a 3 mL bolus of either saline or 50 µg phenylephrine will be administered immediately prior to 3 IU of oxytocin in 10 mL of water given intravenously over a period of 15 seconds. The anaesthesiologist will be blinded to whether phenylephrine or placebo is given. No vasopressor will be given for 3 min after the oxytocin. The HR and the SBP will be recorded from the start of SA by the CNAP device. The CNAP device allows recording of all the information onto a portable storage device, which can later be analysed using Microsoft Excel. An event marker will be recorded on the machine, at the time of administration of oxytocin, for later identification of the study intervention.

## **8. Statistical Methods**

The response to oxytocin will be analysed as follows: Haemodynamic data, i.e. HR, SBP, DBP, MAP, will be averaged for 20 seconds before the administration of oxytocin (baseline pre-oxytocin value). In the 40 patients randomised to receive either oxytocin and placebo or oxytocin and phenylephrine, the change in haemodynamic variables (blood pressure and heart rate) will be compared during the 150 seconds after administration. A sample size of five patients in each group would have 90% power to detect a difference in mean peak SBP change of 25%, assuming that the common SD is 10%, using a two group t-test with a two-sided alpha value of 0.05 as the significance level. Twenty patients will be included in each group, in order to account for inter-patient variability. The primary outcome will be a between-group comparison of mean peak percentage SBP changes. Secondary outcomes will be changes in mean peak percentage values of all other haemodynamic indices, and a comparison of mean percentage changes in these indices during the 150 seconds after oxytocin administration. To depict

the summary profile of the response to oxytocin administration in the two groups, a Lowess median smooth will be used. This approach will give an estimate that is robust to extreme values and sensitive to acute changes in haemodynamic variables. These will be presented as graphic ensembles. Statistical significance is defined as  $P < 0.05$ .

## **9. Confidentiality**

The name of the patient will be on the consent form. This form will be kept safe in a locked location. Further identification of the patients is in the form of a unique number when used in graphs.

## **10. Conflicts of interest**

There are no conflicts of interest to declare.

## References

- 1 Pattinson RC, editor. Saving mothers 2008-2010: Fifth report on the confidential enquiries into maternal deaths in South Africa. Pretoria: National Department of Health, Republic of South Africa; 2012.
- 2 Al-Zirqi I, Vangen S, Forsen L, Stray-Pedersen B. Prevalence and risk factors of severe obstetric haemorrhage. *BJOG* 2008;**115**(10):1265–72.
- 3 Callaghan WM, Kuklina E V, Berg CJ. Trends in postpartum hemorrhage: United States, 1994-2006. *Am J Obstet Gynecol* 2010;**202**(4):353.e1–6.
- 4 Dyer RA, van Dyk D, Dresner A. The use of uterotonic drugs during caesarean section. *Int J Obstet Anesth* 2010;**19**(3):313–9.
- 5 Dyer RA, Butwick AJ, Carvalho B. Oxytocin for labour and caesarean delivery: implications for the anaesthesiologist. *Curr Opin Anaesthesiol* 2011;**24**(3):255–61.
- 6 Langesaeter E, Dragsund M, Rosseland LA. Regional anaesthesia for a Caesarean section in women with cardiac disease: a prospective study. *Acta Anaesthesiol Scand* 2010;**54**(1):46–54.
- 7 Dyer RA, Reed AR, Dyk D Van, James MF, Ph D. Hemodynamic Effects of Ephedrine, Phenylephrine and the Coadministration of Phenylephrine with Oxytocin during Spinal Anesthesia for Elective Cesarean Delivery. *Anesthesiology* 2009;(4):753–65.

## **Part B: Literature Review**

## **1. Objectives**

This review aims to discuss the importance of the need for the use of oxytocin despite its clear potentially dangerous haemodynamic side - effect profile in the context of a caesarean section (CS) operation. To make this clear, a thorough discussion of the pharmacodynamics of oxytocin is presented, emphasis on the cardiovascular effects. Current methods to prevent these effects are discussed. A brief review of the literature on the equipment used in the current study is presented, with respect to validation and applicability.

## **2. Literature Search Strategy**

The full text of relevant publications was obtained online, from the University of Cape Town Health Science Library search facility, which accesses 17 medical digital archive databases worldwide. Literature published between the years 1908 and 2014 was included. In total 33 relevant papers were identified. Literature not published in the English language was excluded.

## **3. Quality criteria**

The keywords used for the search, included each of the following, in various combinations: oxytocin, phenylephrine, side-effects, spinal anaesthesia, caesarean section, hypotension, tachycardia, continuous non-invasive arterial blood pressure, and validation. Using reference lists, further appropriate papers were identified.

## **4. Summary of the literature**

### **4.1. Introduction**

Obstetric haemorrhage remains a major complication peripartum, both during and after normal delivery or CS. The latest interim report into maternal

deaths in South Africa indicated an increasing trend of deaths due to bleeding during or after CS. Deaths rose from 27.5% in 2011 to 35.3% in 2012.<sup>1</sup> A recent systematic analysis performed by the World Health Organisation estimates that 287 000 maternal deaths occurred world wide in 2010. Of these deaths, Sub-Saharan Africa and Southern Asia were responsible for 83.8%. They concluded that haemorrhage was the leading cause, followed by hypertensive disorders and sepsis.<sup>2</sup> The main reason for these alarming trends has been identified to be a lack of access to good quality maternity care in health facilities as a result of delayed referral due to a lack of adequately trained staff in dealing with these complications.<sup>3</sup> This included the incorrect use of uterotonic drugs such as oxytocin<sup>4</sup> and the vasopressors phenylephrine and ephedrine.

During the past 60 years, oxytocin has become an essential first-line medical intervention in the prevention and treatment of postpartum haemorrhage (PPH), of which a major cause is uterine atony. A recent Cochrane review reiterated the importance of oxytocin in reducing blood loss when given at any dose prophylactically after delivery.<sup>5</sup> Oxytocin is a powerful uterotonic agent, and thus prevents uterine atony and reduces postpartum haemorrhage if administered immediately after delivery of the fetus, intramuscularly (IM) in the case of a normal vaginal delivery or intravenously (IV) as in the case of CS. Unfortunately oxytocin is not without its own complications, which include hypotension, tachycardia, myocardial ischaemia and arrhythmias. Inappropriate oxytocin administration was implicated in five maternal deaths reported on in the Fifth Report on the Confidential Enquiry into Maternal Deaths of South Africa (2008-2010). In these cases bolus doses of 10 IU and more of oxytocin were administered to hypovolaemic patients during resuscitation.<sup>4</sup> This prompted the necessity for further investigations into the dose and method of administration of oxytocin. Current guidelines recommend a bolus IV dose of 2.5 IU oxytocin given over 30 seconds.<sup>4</sup>

Although the cardiovascular side-effects have been known for some time, there is limited research on their prevention. Obtunding hypotension may also benefit the patient directly by preventing headache and/or nausea and vomiting. The results of this study may also form the basis for further investigations into the effect of oxytocin in the context of patients with comorbidities undergoing CS, for example severe pre-eclampsia. This study aimed to examine the efficacy of IV phenylephrine administered immediately before IV oxytocin, in obtunding the hypotension and tachycardia during CS. For this purpose, new technology employing beat by beat blood pressure (BP) measurement was used.

#### **4.2. History of Oxytocin**

The credit for associating oxytocin with uterine contractions belongs to Sir Henry Dale. In 1906 he discovered that domestic animals undergo uterine contractions after receiving injections of extracts from the posterior pituitary gland of oxen.<sup>6</sup> William Blair Bell recognised three years later, in 1909, that not only does oxytocin cause uterine contractions, but also prevents postpartum haemorrhage.<sup>7</sup>

Over the next 50 years, there was little work regarding the clinical use of oxytocin, due to technical difficulties accessing the hormone, and lack of information concerning the synthesis and transport within the pituitary. It was Vincent du Vigneaud who, in 1954, was able to synthesise the oxytocin polypeptide hormone for the first time, fully realising its clinical potential.<sup>6</sup> Oxytocin could now be used pharmacologically, and this opened the way for further studies of its hormonal and cardiovascular effects.

#### **4.3. Pharmacodynamics**

Oxytocin acts on the oxytocin receptor which belongs to the G-Protein coupled receptor family, which are expressed in many organs including the uterus, mammary gland, ovary, kidney, heart, bone, endothelial cells, as well as widely throughout the central nervous system.<sup>6</sup> With respect to the

uterus, the oxytocin peptide binds to the G-Protein of the trans-membrane oxytocin receptor complex, causing activation. This triggers various intra-cellular signal pathways, including the activation of phospholipase C (PLC), which is responsible for hydrolysing phosphatidyl-inositol bisphosphate (PIP<sub>2</sub>) to inositol tri-phosphate (IP<sub>3</sub>) and diacylglycerol (DAG).<sup>8</sup> DAG is responsible for activating protein kinase type C, which further phosphorylates prostaglandins. IP<sub>3</sub> causes calcium ions to be released from the intracellular sarcoplasmic reticulum.<sup>9</sup> Calcium ions bind to calmodulin, forming a complex activating myosin light chain kinase (MLCK). MLCK then assists in the cross-bridging cycle of myosin and actin causing contraction.<sup>10</sup> Calcium also enters the myocyte via voltage-gated L-type Calcium channels after depolarisation therefore increasing intra-cellular calcium.<sup>8</sup> Oxytocin also indirectly stimulates uterine contraction by increasing cytosolic phospholipase A<sub>2</sub> (cPLA<sub>2</sub>) activity.<sup>8</sup> This increase in cPLA<sub>2</sub> activity increases prostaglandin (PGE<sub>2</sub>) production via cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2) activity.<sup>8,11</sup> Prostaglandins also increase intra-myometrial calcium concentrations via G-Proteins and activation of calcium channels.<sup>9</sup>

#### **4.4. Haemodynamic effects of oxytocin at delivery**

A bolus administration of oxytocin causes hypotension and tachycardia, which together with nausea, vomiting, headache and arrhythmias are its most common side-effects.<sup>9</sup> Chest pain, pulmonary oedema and amniotic fluid embolism are less common complications.

Oxytocin causes an increase in cardiac output (CO) due predominantly to arteriolar vasodilatation,<sup>12</sup> resulting in a decrease in systemic vascular resistance (SVR). As mean arterial pressure (MAP) is the product of CO and SVR, a drop in MAP is observed clinically. The mechanism of vascular smooth muscle relaxation is probably due to the activation of the nitric-oxide (NO) pathway.<sup>13</sup> NO is a gas that occurs naturally in the body. It has a very short half-life and is synthesised by, among other synthases, endothelial

derived nitric oxide synthase (eNOS). NO stimulates guanylate cyclase to produce cyclic guanosine monophosphate (c-GMP), which causes a reduction in  $Ca^{2+}$  release from the endoplasmic reticulum, decreasing vessel tone.<sup>14</sup>

Oxytocin causes release of atrial and brain natriuretic peptide from the atria and ventricles respectively. Both produce a decrease in SVR as well as increasing natriuresis, resulting in a decrease in BP. A baroreceptor-mediated increase in heart rate (HR) results. Another contributor to an increase in CO is relief of aorto-caval compression at delivery and auto-transfusion of blood following uterine contraction. However a recent study suggests that these effects may be minor when compared with the effects of oxytocin.<sup>15</sup> In addition, oxytocin may cause ST-segment depression in healthy women when given as a bolus of 10 IU, which could have serious consequences for the cardiovascularly unstable patient.<sup>16</sup>

Healthy patients tolerate this period of cardiovascular instability, brought on by delivery and oxytocin. However in a patient with hypovolaemia secondary to excessive intrapartum bleeding, or a stenotic valvular heart lesion, compensation for hypotension is limited, putting the patient at risk of cardiovascular collapse.<sup>17</sup> Pre-eclamptic patients have left ventricular diastolic dysfunction, and hence may also have reduced compensatory mechanisms.<sup>13</sup>

#### **4.5. Current methods to obtund the cardiovascular effects of oxytocin**

Recent work has shown that the ED90 for oxytocin at elective CS is 0.35 IU, and after labour arrest, 3 IU.<sup>18–20</sup> Therefore, the recommendation is that the oxytocin dose for routine prophylaxis of uterine atony and postpartum haemorrhage at CS, should be considerably reduced.<sup>21</sup> This decrease was supported by numerous studies including Sartain et al, who showed less HR and BP changes after a bolus of 2 than 5 IU,<sup>22</sup> suggesting a dose-dependent response. However, obstetricians worldwide still often request 10 IU oxytocin.<sup>18,20,23</sup> In pregnant women with severe cardiac disease, the

recommendation is that ultra-low oxytocin doses (0.05-0.5 IU) be used. In one such case-series of cardiac patients there was adequate uterine contraction, after being administered titrated doses of oxytocin.<sup>24</sup> This was effective in preventing the haemodynamic effects of oxytocin. Caution is also recommended in pre-eclamptic patients, in whom diastolic dysfunction may reduce compensatory mechanisms.<sup>13</sup>

Another technique shown to be effective is to administer oxytocin slowly, as opposed to as a rapid bolus. Thomas et al showed that when a dose of 5 IU is given as a slow infusion, the HR and BP changes were limited to within 10% of baseline values.<sup>25</sup>

Phenylephrine is a potent direct-acting alpha-1 adrenergic receptor agonist, which causes vasoconstriction and reflex bradycardia. It has a rapid onset and is short acting. Phenylephrine has become the drug of choice for reversing the spinal anaesthesia (SA) - induced hypotension, which is due to arterial vasodilatation, which causes a decrease in SVR.<sup>26</sup>

Recent work from our institution showed an early peak BP effect at 45 seconds and a second peak at 70 seconds following bolus phenylephrine during SA, compared to 90 seconds in the case of ephedrine. Ephedrine was also associated with a significant initial increase in HR. The maximum effects of oxytocin on BP occurred on average 44 seconds after administration.<sup>27</sup> Taking these pharmacodynamic effects of phenylephrine and oxytocin into account, as well as their times of onset, it would therefore appear to be appropriate to use phenylephrine to counter the decrease in SVR and tachycardia caused by oxytocin.

One study examined the effect of coadministration of phenylephrine and oxytocin at elective caesarean delivery in healthy women. This was a secondary outcome of a study on the haemodynamics of vasopressors administered for spinal hypotension.<sup>27</sup> The authors used a LiDCOPlus monitor, which is a minimally invasive device employing pulse waveform analysis, calibrated with lithium dilution. A monitor of transthoracic

bioimpedance changes was also used in each patient. Two groups were randomised to receive either a phenylephrine dose of 80 µg co-administered with 2.5 IU oxytocin, or saline placebo with oxytocin. The haemodynamic effects of oxytocin were obtunded but not eliminated. The data also showed an increase in SVR, due to the phenylephrine, as well as an increase in MAP above baseline, indicating an overshoot of the effects of phenylephrine. Prior administration of a smaller dose could be more effective in obtunding the cardiovascular effects of oxytocin.

#### **4.6. Validation of monitoring equipment**

Assessment of the effects of rapid-acting vasopressors such as phenylephrine, optimally requires a non-invasive monitor with the capacity to measure BP on a beat by beat basis. The first tool to measure continuous BP in a non-invasive manner using a finger cuff, was introduced in 1986 and was marketed as the Finapres™. This was based on the principle of arterial wall unloading developed by Jan Peňáz in 1973.<sup>28</sup> Continuing improvements on the principle resulted in the development of the CNAP™ (Continuous Non-Invasive Arterial Pressure) monitor, which was initially released in 2007 and has undergone numerous software upgrades. The current CNAP™ 500 Monitor System consists of a double finger sensory cuff, a pressure transducer on the forearm, an oscillometric non-invasive blood pressure (NIBP) cuff, preferably placed on the same arm, together with the CNAP monitor. The measurement is performed continuously on one finger at a time, and then changes to the other finger after a defined period. The sensor in the cuff placed around the finger, detects infrared light transmitted through the finger. The pulsatile blood volume absorbs part of the transmitted light. The light that is detected by the sensor is then calculated to be a measure of the pulsatile blood volume. An electronic system controlling the pressure inside the cuff around the finger, then inflates the cuff to a pressure needed to keep the transmission of light, and hence the blood volume, constant during arterial pulsation. This pressure corresponds to the arterial pressure. The results are a non-invasive, beat-to-beat estimate of BP, HR and MAP.



The CNAP<sup>500</sup> Monitor. Reprinted with permission from CN Systems

Since CNAP is a relatively new BP measuring tool, several validation studies have been performed in various anaesthesia environments, including general and SA, as well as in the intensive care unit.<sup>29</sup> One validating study that examined CNAP monitoring during SA for healthy women undergoing elective CS, showed that the device detected more hypotensive events than a standard oscillometric NIBP device.<sup>30</sup> This suggested that hypotensive events would go undetected by the oscillometric NIBP device with its longer measurement interval. A continuous BP measurement would therefore be more effective in the detecting of rapidly occurring hypotension in the period following oxytocin administration.

Ilies et al compared the agreement between CNAP readings and intra-arterial BP readings in patients undergoing general anaesthesia (GA). They found that there was poor agreement between SBP and DBP when comparing the two devices, but good agreement between MAP.<sup>31</sup> This discrepancy could be due to the differing sites of pressure monitored using the two monitors. A NIBP device measuring at the brachial artery calibrates the CNAP monitor, whereas invasive pressure is measured at the radial artery. This could result

in differing systolic and diastolic measurements, but the mean pressures would agree. Calibration times during this study were at 30 minute intervals. Disagreements were found between intra-arterial measurements and CNAP during the induction period. This implies that re-calibration should occur at shorter intervals than 30 minutes, after changes in vascular tone due to the use of induction agents. This would be important during SA, as vascular tone is decreased considerably after induction of anaesthesia. Further validation studies<sup>32,33</sup> showed similar results regarding disagreement between SBP and DBP, but good agreement in MAP.

#### **4.7. Conclusion**

It would be of clinical value to know whether an alpha-1 agonist is effective in reducing oxytocin induced hypotension and tachycardia. This could have implications for the reduction of hypotension and maternal symptoms during the administration of oxytocin infusions for prophylaxis of PPH, or as therapy during active bleeding. Co-administration of phenylephrine has been shown to obtund, but not eliminate hypotension, followed by some overshoot of alpha-1 agonist effects and an increase in BP. These authors suggested that a bolus of phenylephrine given immediately before oxytocin might be more effective to maintain haemodynamic stability.<sup>27</sup> Therefore it was decided to examine the effects of prior administration of 50 µg phenylephrine on the hypotensive effect of a slow bolus of 3 IU oxytocin.

## References:

1. Pattinson RC, Fawcus S, Moodley J. Saving Mothers 2012: tenth interim report on confidential enquiries into maternal deaths in South Africa. Pretoria: National Department of Health, Republic of South Africa (2013). Available at [http://indicators.hst.org.za/indicators/ChildHealth/Saving\\_Mothers\\_2012.pdf](http://indicators.hst.org.za/indicators/ChildHealth/Saving_Mothers_2012.pdf)
2. Say L, Chou D, Gemmill A *et al.* Global causes of maternal death: a WHO systematic analysis. *Lancet Glob. Heal.* 2014;**2**:e323–e333.
3. Fawcus S, Mbombo N, Hofmeyr GJ. Trends in maternal deaths from Obstetric Haemorrhage in South Africa 2008-2010. *Obstetrics and Gynaecology Forum.* **5**, 9–17 (2012).
4. Pattinson RC, editor. Saving Mothers 2008-2010: fifth report on the confidential enquiries into maternal deaths in South Africa. Pretoria: National Department of Health, Republic of South Africa; 2012. Available from [www.health.gov.za/docs/reports/2012/savingmothersshort.pdf](http://www.health.gov.za/docs/reports/2012/savingmothersshort.pdf)
5. Westhoff G, Cotter AM, Tolosa JE. Prophylactic oxytocin for the third stage of labour to prevent postpartum haemorrhage. *Cochrane Database of Systematic Reviews* 2013, Issue 10.
6. Carson DS, Guastella AJ, Taylor ER & McGregor IS. A brief history of oxytocin and its role in modulating psychostimulant effects. *J. Psychopharmacol* 2013;**27**:231–47.
7. Bell, W. B. the Pituitary Body and the Therapeutic Value of the Infundibular Extract in Shock, Uterine Atony, and Intestinal Paresis. *Br. Med. J.* 1909;**2**:1609–1613.

8. Vrachnis N, Malamas F, et al. The oxytocin-oxytocin receptor system and its antagonists as tocolytic agents. *Int. J. Endocrinology* 2011;Article ID 350546.
9. Dyer RA, van Dyk D. & Dresner A. The use of uterotonic drugs during caesarean section. *Int. J. Obstet. Anesth* 2010;**19**:313–9.
10. Wray, S. Insights into the uterus. *Exp. Physiol.* 2007;**92**:621–31.
11. Blanks A. The role of oxytocin in parturition. *BJOG* 2003;**110**:46–51.
12. Archer TL, Knape K, Liles D, Wheeler AS, Carter B. The hemodynamics of oxytocin and other vasoactive agents during neuraxial anesthesia for cesarean delivery: findings in six cases. *Int J Obstet Anesth* 2008;**17**(3):247–54.
13. Dyer R a, Butwick AJ, Carvalho B. Oxytocin for labour and caesarean delivery: implications for the anaesthesiologist. *Curr Opin Anaesthesiol* 2011;**24**(3):255–61.
14. Quinn AC, Petros AJ, Vallance P. Nitric oxide: An endogenous gas. *Br J Anaesth* 1995;**74**:443–51.
15. Rosseland LA, Hauge TH, Grindheim G, Stubhaug A, Langesæter E, Changes in Blood Pressure and Cardiac Output during Cesarean Delivery. *Anesthesiology* 2013;(X):541–51.
16. Jonsson M, Hanson U, Lidell C, Nordén-Lindeberg S. ST depression at caesarean section and the relation to oxytocin dose. A randomised controlled trial. *BJOG* 2010;**117**(1):76–83.
17. Langesæter E, Rosseland LA, Stubhaug A. Haemodynamic effects of oxytocin in women with severe pre-eclampsia. *Int J Obstet Anesth* 2011;**20**(1):26–9.

18. Carvalho JC, Balki M, Kingdom J, Windrim R. Oxytocin requirements at elective cesarean delivery: a dose-finding study. *Obstet Gynecol* 2004;**104**:1005–10.
19. Balki M, Ronayne M, Davies S, et al. Minimum oxytocin dose requirement after cesarean delivery for labor arrest. *Obstet Gynecol* 2006;**107**(1):45–50.
20. Butwick A, Coleman L. Minimum effective bolus dose of oxytocin during elective Caesarean delivery. *Br J Anaesth* 2010;**104**(3):338–43.
21. Tsen LC, Balki M. Editorial: Oxytocin protocols during cesarean delivery: Time to acknowledge the risk/benefit ratio? *Int J Obstet Anesth* 2010;**19**(3):243–5.
22. Sartain JB, Barry JJ, Howat PW, McCormack DI, Bryant M. Intravenous oxytocin bolus of 2 units is superior to 5 units during elective Caesarean section. *Br J Anaesth* 2008;**101**(6):822–6.
23. Stephens LC, Bruesself T. Systematic review of oxytocin dosing at caesarean section. *Anaesth Intensive Care* 2012;**40**:247–52.
24. Langesaeter E, Dragsund M, Rosseland LA. Regional anaesthesia for a Caesarean section in women with cardiac disease: a prospective study. *Acta Anaesthesiol Scand* 2010;**54**(1):46–54.
25. Thomas JS, Koh SH, Cooper GM. Haemodynamic effects of oxytocin given as i.v. bolus or infusion on women undergoing Caesarean section. *Br J Anaesth* 2007;**98**(1):116–9.
26. Langesæter E, Dyer R a. Maternal haemodynamic changes during spinal anaesthesia for caesarean section. *Curr Opin Anaesthesiol* 2011;**24**(3):242–8.
27. Dyer RA, Reed AR, Dyk D Van, James MF. Hemodynamic Effects of Ephedrine, Phenylephrine and the Coadministration of Phenylephrine

with Oxytocin during Spinal Anesthesia for Elective Cesarean Delivery. *Anesthesiology* 2009;(4):753–65.

28. Biais, M. *et al.* Continuous non-invasive arterial pressure measurement: evaluation of CNAP device during vascular surgery. *Ann. Fr. Anesth. Reanim.* 2010;**29**:530–5.
29. Fortin J, Wellisch A, Maier K. CNAP - Evolution of continuous non-invasive arterial blood pressure monitoring. *Biomed Tech* 2013;**58**(Suppl 1):10–1.
30. Ilies C, Kiskalt H, Siedenhans D, *et al.* Detection of hypotension during Caesarean section with continuous non-invasive arterial pressure device or intermittent oscillometric arterial pressure measurement. *Br J Anaesth* 2012;**109**(3):413–9.
31. Ilies C, Bauer M, Berg P, *et al.* Investigation of the agreement of a continuous non-invasive arterial pressure device in comparison with invasive radial artery measurement. *Br J Anaesth* 2012;**108**(2):202–10.
32. Hahn R, Rinösl H, Neuner M & Kettner SC. Clinical validation of a continuous non-invasive haemodynamic monitor (CNAP™ 500) during general anaesthesia. *Br. J. Anaesth* 2012;**108**:581–5.
33. Jeleazcov C, Krajinovic J, Munster T *et al.* Precision and accuracy of a new device (CNAP™) for continuous non-invasive arterial pressure monitoring: assessment during general anaesthesia. *Br. J. Anaesth* 2010;**105**:264–72.

## Part C: Manuscript

## **Title Page**

### **The use of phenylephrine to obtund oxytocin-induced hypotension and tachycardia during caesarean section**

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There are no conflicts of interest to declare

## **Abstract**

**Background:** Oxytocin causes clinically significant hypotension and tachycardia. This study examined whether the prior administration of phenylephrine obtunds these unwanted haemodynamic effects.

**Methods:** Forty pregnant women undergoing elective caesarean section under spinal anaesthesia were randomised to receive either a 50 µg bolus of phenylephrine (Group P) or saline (Group S) immediately prior to oxytocin (3 IU over 15 seconds). Systolic blood pressure [SBP], diastolic blood pressure [DBP], mean arterial pressure [MAP] and heart rate [HR]) were recorded using a continuous non-invasive arterial pressure device. Baseline values were averaged for 20 seconds post-delivery. Between-group comparisons were made of the mean peak changes in BP and HR, and the mean percentage changes from baseline, during the 150 seconds after oxytocin administration.

**Results:** The mean peak percentage change (SD) in SBP was -16.9% (2%) in Group P, and -19.0% (1.9%) in Group S and the estimated mean difference was 2.1% (95% CI: -3.5 to 7.8 %) and  $P=0.44$ ; corresponding changes in HR were 13.5% (2.3%) and 14.0% (1.5%) and the mean estimated difference was 0.5% (95% CI -6.0 to 5%) and  $P=0.87$ . The mean percentage change from the baseline measurements during the 150 s period of measurement was greater for Group S than Group P: SBP -5.9% vs -3.4%;  $P=0.149$ ; DBP -7.2% vs -1.5%,  $P=0.014$ ; MAP -6.8% vs -1.5%,  $P=0.007$ ; HR 2.1% vs -2.4%,  $P=0.033$ .

**Conclusion:** Intravenous phenylephrine 50 µg immediately before 3 U oxytocin during elective caesarean section does not prevent maternal hypotension and tachycardia.

**Keywords:** Oxytocin, phenylephrine, caesarean section, CNAP

**Main text**

## **Introduction**

Obstetric haemorrhage remains a major peripartum complication, and has been shown to be on the increase around the world, particularly in South Africa<sup>1</sup> as well as in the United States.<sup>2</sup> Oxytocin is accepted as the first line uterotonic in the prevention and treatment of post-partum haemorrhage (PPH). However, oxytocin causes hypotension and tachycardia, and may be associated with nausea and vomiting, tachycardia, myocardial ischaemia and arrhythmias, particularly when given in bolus doses of >5 IU. In addition, if a parturient is haemodynamically unstable due to haemorrhage, inappropriate use of oxytocin may cause cardiovascular collapse. Hence recent recommendations are to administer an initial dose of 3 IU for adequate uterine contraction and prophylaxis for postpartum haemorrhage, after delivery during elective caesarean section (CS).<sup>3</sup> It would be of clinical value to know whether an alpha agonist is effective in reducing oxytocin - induced hypotension. This could have implications for the reduction of hypotension and maternal symptoms during the administration of oxytocin infusions for prophylaxis of PPH, or as therapy during active bleeding. Co-administration of phenylephrine has been shown to obtund, but not eliminate hypotension, followed by some overshoot of alpha agonist effects and an increase in blood pressure (BP).<sup>4</sup> These authors suggested that a bolus of phenylephrine given immediately before oxytocin, may be more effective to maintain haemodynamic stability. Therefore it was decided to examine whether the prior administration of 50 µg phenylephrine IV obtunds hypotension and tachycardia caused by a slow bolus of 3 IU oxytocin.

## **Methods**

This was a single-centre, prospective, randomised, double blind, placebo-controlled study that was done during August and September 2013 at Mowbray Maternity Hospital, Cape Town, South Africa. The study was registered with the South African National Clinical Trials Register,

www.sanctr.gov.za: DOH27-0114-4619, and the protocol was approved by the Human Ethics Research Committee of the University of Cape Town. Participants gave informed written consent. All patients recruited were aged between 18 and 40 years, American Society of Anesthesiologists class 1 or 2, and scheduled for elective caesarean delivery under spinal anaesthesia (SA). Exclusions were emergency CS, pre-eclampsia or any cardiac, respiratory, renal or neurological disease, allergy to any study drug, Hb < 7 g/dL, or body mass index > 40 kg/m<sup>2</sup>.

Patients were randomised, using a table of random numbers, into 2 treatment groups of 20. One group received a 50 µg bolus of phenylephrine (3 mL) and the other group placebo (3 mL saline), followed by intravenous oxytocin (3 IU in 5 mL saline over 15 seconds). The anaesthesiologist and patient were blinded as to the group allocation. The procedure was explained to the patient either by the recruiting investigator or by a skilled translator, and detailed informed written consent was obtained in the ward prior to transfer to the operating theatre. Block randomisation was used, using nQuery Advisor Version 6, Statistical Solutions (Cork, Ireland), and the statistician prepared sealed envelopes.

Immediately pre-operatively, 30 mL of sodium citrate was given orally to every participant. In theatre, intravenous access was established via an 18-gauge cannula. Cefazolin 1 g was then administered intravenously slowly. During this time standard non-invasive monitoring was applied to the patient. This included electrocardiography and pulse oximetry as well as the CNAP (Continuous Non-Invasive Arterial Pressure) device. The data recorded consisted of the heart rate (HR), systolic (SBP), diastolic (DBP), and mean arterial pressure (MAP). The CNAP 500 Monitor System (CN Systems Medizintechnik AG, Graz, Austria) consists of a sensor placed on the second and third digits of one hand. A non-invasive blood pressure cuff (a component of the CNAP system) on the same arm was used for calibration with the CNAP monitor. The measurement was done continuously on one finger at a time, and then changed to the other finger after a defined period.

The sensor, placed around the finger, detects infrared light transmitted through the finger. The blood pulsating through the finger absorbs a part of the transmitted light. The light that is detected by the sensor is then calculated to be a measure of the pulsatile blood volume. The finger cuff is inflated so that the blood volume is kept constant and therefore also the transmission of light. The inflation pressure of the finger cuff achieves this constant blood volume, and is the primary signal used for BP measurement.

The CNAP device was calibrated prior to baseline measurements and again on commencement of surgery. A baseline BP was taken by the CNAP device immediately before administration of SA. Baseline SBP were defined as the average of 3 measurements in a 5 minute period, not differing by more than 10%, with the patient in the left lateral position. The SA was then conducted in the following manner. A bolus crystalloid co-load of Modified Ringer's Lactate solution (20 mL/kg) was rapidly administered using a pressure bag, after the appearance of cerebrospinal fluid in the hub of the spinal needle. Further crystalloid solution was not given unless blood loss was > 1L, as determined by suction bottle measurement and swab inspection. SA consisted of 2.0 mL of 0.5% hyperbaric bupivacaine (10 mg) plus 10 µg of fentanyl, administered over 20 seconds at the L3/4 interspace. After a further 20 seconds in the sitting position, patients were positioned supine, with at least 15 degrees of left lateral tilt, to minimise aorto-caval compression. The effectiveness of the block was assessed by the patient's sensitivity to cold via ethyl chloride spray. A block level was then determined. Supplemental oxygen was only administered if arterial oxygen saturation decreased below 92%. Surgery was allowed to commence when the sensory level achieved T4. Bolus phenylephrine (50-100 µg) was administered to maintain SBP within 20% of baseline.

Thirty seconds after delivery, a 3 mL bolus of either saline or 50 µg phenylephrine, prepared by a specialist anaesthesiologist not involved in the study, was given intravenously immediately prior to the administration of 3 IU of oxytocin in 5 mL of water over a period of 15 seconds. The

anaesthesiologist administering the study drug was blinded as to the contents of the syringe. No vasopressor was given for 3 min after the oxytocin. The HR and the SBP were recorded from the start of SA by the CNAP device. All this information was recorded electronically onto a portable storage device, to be later analysed using Microsoft Excel. An event marker was recorded on the machine, at the time of administration of oxytocin, for later identification of the study intervention.

In no case was the uterus exteriorised. Placental separation was spontaneous, and uterine massage was employed if uterine contraction was inadequate, in conjunction with further uterotonics. Further bolus oxytocin was only required in two cases in this study.

### **Statistical analysis**

The response to oxytocin was analysed as follows: Haemodynamic data, i.e. HR, SBP, DBP, MAP, were averaged for 20 seconds before the administration of oxytocin (baseline pre-oxytocin value). A sample size of five patients in each group would have 90% power to detect a difference in mean peak SBP change of 25%, assuming that the common SD is 10%, using a two group t-test with a two-sided alpha value of 0.05 as the significance level. Twenty patients were included in each group, in order to allow for more than the predicted variability. The primary outcome was a between-group comparison of mean peak percentage SBP changes. Secondary outcomes were changes in mean peak percentage values of all other haemodynamic indices, and a comparison of mean percentage changes in these indices during the 150 seconds after oxytocin administration. A two sample t-test was used to assess primary and secondary outcomes. To depict the summary profile of the response to oxytocin administration in the two groups, a Lowess median smooth was used. This approach gives an estimate that is robust to extreme values and sensitive to acute changes in haemodynamic variables. These were presented as graphic ensembles. Statistical significance was defined as  $P < 0.05$ .

## Results

Forty patients were enrolled and randomised to receive phenylephrine and oxytocin or placebo and oxytocin. No patients were excluded from analysis. Patients were enrolled from August to September 2013. Demographic data and baseline haemodynamic values were similar in the groups (Table 1).

The mean peak percentage change (SD) in SBP was -16.9% (2%) in Group P, and -19.0% (1.9%) in Group S and the estimated mean difference was 2.1% (95% CI: -3.5 to 7.8 %) and  $P = 0.44$ ; corresponding changes in HR were 13.5% (2.3%) and 14.0% (1.5%) and the mean estimated difference was 0.5% (95% CI -6.0 to 5%) and  $P = 0.87$ . The mean percentage change from the baseline measurements during the 150 s period of measurement was greater for Group S than Group P: SBP -5.9% vs -3.4%;  $P = 0.149$ ; DBP -7.2% vs -1.5%,  $P = 0.014$ ; MAP -6.8% vs -1.5%,  $P = 0.007$ ; HR 2.1% vs -2.4%,  $P = 0.033$ . The data is also depicted as median smooth plots for the 150 seconds following oxytocin administration (Figures 1-5, 6). No patient experienced any side-effects attributable to the interventions.

## Discussion

This randomised, controlled study demonstrated that 50 µg phenylephrine does not obtund hypotension and tachycardia induced by a slow bolus of 3 IU oxytocin in healthy women undergoing elective CS. The main findings indicated no significant difference between the two groups regarding the peak percentage change in SBP, DBP, MAP and HR from baseline values. The initial brief rise in blood pressure and decrease in HR in Group P, was rapidly reversed by the vasodilatation induced by oxytocin (Figures 1-5). In view of the poor response to the dose of phenylephrine used, our subsequent clinical practice has included the administration of a dose of 75 µg phenylephrine prior to 3 IU oxytocin. Figure 6 shows data from 9 such patients. The increased dose appeared to be ineffective, although no statistical analysis was performed in these cases.

Delivery of the fetus causes an increase in venous return due to relief of aorto-caval compression and uterine auto-transfusion. This translates into an increase in cardiac output (CO). However a recent study suggests that these effects may be minor when compared with the effects of oxytocin.<sup>5</sup> Bolus administration of oxytocin causes hypotension and tachycardia, which together with nausea, vomiting, headache and arrhythmias are its most common side-effects.<sup>6</sup> Chest pain and pulmonary oedema are less common complications. Thus the prevention of these side-effects is clinically important. Oxytocin causes an increase in CO, predominantly due to arteriolar vasodilatation, resulting in a decrease in systemic vascular resistance (SVR).<sup>7</sup> As MAP is the product of CO and SVR, a decrease in MAP is observed clinically, with an accompanying baroreceptor-mediated increase in HR.

The mechanisms of hypotension due to oxytocin are complex. Vascular smooth muscle relaxation is probably the consequence of activation of the nitric-oxide (NO) pathway.<sup>8</sup> NO has a very short half-life and is synthesised by endothelial derived nitric oxide synthase (eNOS). NO stimulates guanylate cyclase to produce cyclic guanosine monophosphate (c-GMP), which causes a reduction in  $Ca^{2+}$  release from the endoplasmic reticulum, decreasing vessel tone. Oxytocin also causes release of atrial and brain natriuretic peptide from the atria and ventricles respectively. Both produce a decrease in SVR as well as increasing natriuresis, resulting in a decrease in blood pressure (BP). In addition, oxytocin may cause ST-segment depression in healthy women when given as a bolus of 10 IU.<sup>9</sup> Healthy patients tolerate this period of cardiovascular instability induced by delivery and oxytocin. However in a patient with hypovolaemia secondary to excessive intrapartum bleeding, or a stenotic valvular heart lesion and/or severe pulmonary hypertension, compensation for hypotension is limited, putting the patient at risk of cardiovascular collapse. Pre-eclamptic patients have left ventricular diastolic dysfunction, and hence may also have reduced compensatory mechanisms.<sup>10</sup>

Recent work has shown that the ED90 for oxytocin at elective CS is 0.35 IU, and after labour arrest 3 IU.<sup>11-13</sup> Therefore, the recommendation is that the oxytocin dose for routine prophylaxis of uterine atony and postpartum haemorrhage at CS, should be considerably reduced.<sup>3,14</sup> This decrease was supported by numerous studies including Sartain et al, who showed less HR and BP changes after a bolus of 2 than 5 IU, suggesting a dose-dependent response.<sup>15</sup> A recent randomised trial showed that 3 IU oxytocin administered over 15 seconds, repeated twice if necessary in response to inadequate uterine contraction, was associated with a lower total oxytocin dose compared with continuous infusion of oxytocin during elective caesarean delivery.<sup>14</sup> However, obstetricians worldwide still often request 10 IU oxytocin.<sup>11,13,16</sup> In pregnant women with severe cardiac disease, the recommendation is that ultra-low oxytocin doses (0.05-0.5 IU) be used. In one such case-series of cardiac patients there was adequate uterine contraction, after being administered titrated doses of oxytocin.<sup>17</sup> This was effective in preventing the haemodynamic effects of oxytocin. Another technique shown to be effective is to administer oxytocin slowly, as opposed to as a rapid bolus. Thomas et al showed that when a dose of 5 IU is given as a slow infusion, the HR and BP changes were limited to within 10% of baseline values.<sup>18</sup>

Phenylephrine is a potent direct-acting alpha-1 adrenergic receptor agonist, which causes vasoconstriction and reflex bradycardia. Its actions on the human circulation, and more specifically on maternal haemodynamics, have been well reviewed recently.<sup>19,20</sup> Phenylephrine is a rapid onset and short-acting agent, and has become the drug of choice for reversing the SA - induced hypotension, which is due to arterial vasodilatation resulting in a decrease in systemic vascular resistance.<sup>21</sup> Recent work from our institution showed an early peak blood pressure effect at 45 seconds and a second peak at 70 seconds following bolus phenylephrine during SA, compared to 90 seconds in the case of ephedrine. Ephedrine was also associated with a significant initial increase in HR. The maximum effects of oxytocin on blood

pressure occurred on average 44 seconds after administration.<sup>4</sup> Taking these pharmacodynamic effects of phenylephrine and oxytocin into account, as well as their times of onset, it would therefore appear to be appropriate to use phenylephrine to counter the decrease in SVR and tachycardia caused by oxytocin. One study employed minimally invasive CO monitoring to study the effects of coadministration of phenylephrine and oxytocin at elective caesarean delivery in healthy women.<sup>4</sup> Two groups of patients were randomised to receive either a phenylephrine dose of 80 µg co-administered with 2.5 IU oxytocin, or saline placebo with oxytocin. The haemodynamic effects of oxytocin were obtunded but not eliminated. The data also showed an increase in SVR, due to the phenylephrine, as well as an increase in MAP above baseline, indicating an overshoot of the effects of phenylephrine when administered in this manner. Therefore the current study examined whether prior administration of a smaller dose could be more effective in obtunding the cardiovascular effects of oxytocin.

Assessment of the effects of rapid-acting vasopressors such as phenylephrine, optimally requires a non-invasive monitor with the capacity to measure blood pressure on a beat by beat basis. The CNAP™ 500 Monitor System consists of a double finger sensory cuff, which provides non-invasive beat to beat estimates of BP. Several validation studies have been performed in anaesthesia environments, including general and SA, as well as in the intensive care unit.<sup>22</sup> One validating study that examined CNAP monitoring during SA for healthy women undergoing elective CS, showed that the device detected more hypotensive events than a standard oscillometric NIBP device.<sup>23</sup> This suggested that hypotensive events would go undetected by the oscillometric NIBP device with its longer measurement interval. A continuous BP measurement would therefore be more effective in the detecting of rapidly occurring hypotension in the period following oxytocin administration. One recent study found that there was poor agreement between SBP and DBP when comparing CNAP and intra-arterial monitoring, but good agreement between MAP values.<sup>24</sup> The current study involved short term percentage changes in SBP and the monitor was thus regarded

as adequate for this purpose. A disadvantage of the monitor is that frequent re-calibration is required. However, this was not required in the present study, since calibration was performed immediately before the intervention, and the data was collected over only 150 seconds.

A recent animal study showed that the haemodynamic effects of phenylephrine are dependent upon the position on the Frank-Starling curve. In fluid replete animals phenylephrine depressed CO due to an increase in SVR, while in acutely fluid-depleted animals, the effects of phenylephrine appeared to include splanchnic vasoconstriction and improved venous return.<sup>25</sup> This may have relevance when phenylephrine is used in conjunction with oxytocin in a patient with ongoing postpartum haemorrhage. Further studies are needed to examine this interaction. The clinical implications of our results are that bolus phenylephrine in the usual clinical dose range, may not be effective in preventing arteriolar dilatation and hypotension following a slow bolus of oxytocin in healthy normovolaemic parturients during SA for CS.

## References

- 1 Pattinson RC, editor. Saving mothers 2008-2010 : fifth report on the confidential enquiries into maternal deaths in South Africa. Pretoria: National Department of Health, Republic of South Africa; 2012. [www.health.gov.za/docs/reports/2012/savingsmothersshort.pdf](http://www.health.gov.za/docs/reports/2012/savingsmothersshort.pdf). Last accessed on: 14 November 2014.
- 2 Callaghan WM, Kuklina EV, Berg CJ. Trends in postpartum hemorrhage: United States, 1994-2006. *Am J Obstet Gynecol* 2010;**202**:353.e1–6.
- 3 Tsen LC, Balki M. Editorial: Oxytocin protocols during cesarean delivery: Time to acknowledge the risk/benefit ratio? *Int J Obstet Anesth* 2010;**19**:243-5.
- 4 Dyer RA, Reed AR, van Dyk D, James MF. Hemodynamic effects of ephedrine, phenylephrine and the coadministration of phenylephrine with oxytocin during spinal anesthesia for elective cesarean delivery. *Anesthesiology* 2009;**4**:753–65.

- 5 Rosseland LA, Hauge TH, Grindheim G, Stubhaug A, Langesæter E. Changes in blood pressure and cardiac output during cesarean delivery. *Anesthesiology* 2013;**119**:541–51.
- 6 Dyer RA, van Dyk D, Dresner A. The use of uterotonic drugs during caesarean section. *Int J Obstet Anesth* 2010;**19**:313–9.
- 7 Archer TL, Knape K, Liles D, Wheeler AS, Carter B. The hemodynamics of oxytocin and other vasoactive agents during neuraxial anesthesia for cesarean delivery: findings in six cases. *Int J Obstet Anesth* 2008;**17**:247–54.
- 8 Quinn AC, Petros AJ, Vallance P. Nitric oxide: An endogenous gas. *Br J Anaesth* 1995;**74**:443–51.
- 9 Jonsson M, Hanson U, Lidell C, Nordén-Lindeberg S. ST depression at caesarean section and the relation to oxytocin dose. A randomised controlled trial. *BJOG* 2010;**117**:76–83.
- 10 Langesæter E, Rosseland LA, Stubhaug A. Haemodynamic effects of oxytocin in women with severe pre-eclampsia. *Int J Obstet Anesth* 2011;**20**:26–9.
- 11 Carvalho JC, Balki M, Kingdom J, Windrim R. Oxytocin requirements at elective cesarean delivery: a dose-finding study. *Obstet Gynecol* 2004;**104**:1005–10.
- 12 Balki M, Ronayne M, Davies S, et al. Minimum oxytocin dose requirement after cesarean delivery for labor arrest. *Obstet Gynecol* 2006;**107**:45–50.
- 13 Butwick A, Coleman L. Minimum effective bolus dose of oxytocin during elective Caesarean delivery. *Br J Anaesth* 2010;**104**:338–43.
- 14 Kovacheva VP, Soens MA, Tsen LC. A randomized, double-blinded trial of a "Rule of Threes" algorithm versus continuous infusion of oxytocin during elective cesarean delivery. *Anesthesiology* 2015;**123**:92–100.
- 15 Sartain JB, Barry JJ, Howat PW, McCormack DI, Bryant M. Intravenous oxytocin bolus of 2 units is superior to 5 units during elective caesarean section. *Br J Anaesth* 2008;**101**:822–6.
- 16 Stephens LC, Bruesself T. Systematic review of oxytocin dosing at caesarean section. *Anaesth Intensive Care* 2012;**40**:247–52.
- 17 Langesaeter E, Dragsund M, Rosseland LA. Regional anaesthesia for a caesarean section in women with cardiac disease: a prospective study. *Acta Anaesthesiol Scand* 2010;**54**:46–54.

- 18 Thomas JS, Koh SH, Cooper GM. Haemodynamic effects of oxytocin given as i.v. bolus or infusion on women undergoing caesarean section. *Br J Anaesth* 2007;**98**:116–9.
- 19 Thiele RH, Nemergut EC, Lynch C. The clinical implications of isolated alpha1 adrenergic stimulation. *Anesth Analg* 2011;**113**:297–304.
- 20 Habib AS. A review of the impact of phenylephrine administration on maternal hemodynamics and maternal and neonatal outcomes in women undergoing cesarean delivery under spinal anesthesia. *Anesth Analg* 2012;**114**:377–90.
- 21 Langesæter E, Dyer RA. Maternal haemodynamic changes during spinal anaesthesia for caesarean section. *Curr Opin Anaesthesiol* 2011;**24**:242–8.
- 22 Fortin J, Wellisch A, Maier K. CNAP – Evolution of continuous non-invasive arterial blood pressure monitoring. *Biomed Tech* 2013;**58**:10–1.
- 23 Ilies C, Kiskalt H, Siedenhans D, et al. Detection of hypotension during caesarean section with continuous non-invasive arterial pressure device or intermittent oscillometric arterial pressure measurement. *Br J Anaesth* 2012;**109**:413–9.
- 24 Ilies C, Bauer M, Berg P, et al. Investigation of the agreement of a continuous non-invasive arterial pressure device in comparison with invasive radial artery measurement. *Br J Anaesth* 2012;**108**:202–10.
- 25 Cannesson M, Jian Z, Chen G, Vu TQ, Hatib F. Effects of phenylephrine on cardiac output and venous return depend on the position of the heart on the Frank-Starling relationship. *J Appl Physiol* 2012;**113**:281–9.

Table 1: Patient characteristics. Data are mean (range) or number. No statistically significant difference between the two groups.

	Group P (n=20)	Group S (n=20)
Age (years)	29.7 (22-40)	28.95 (24-36)
Weight (kg)	72.6 (47-93)	75.2 (51-102)
Height (cm)	159.8 (143-177)	160.25 (150-173)
Baseline systolic BP (mmHg)	126.5 (109-157)	125.25 (105-145)
Baseline diastolic BP (mmHg)	80.1 (70-93)	77.5 (63-100)
Baseline mean arterial pressure (mmHg)	95.4 (85-114)	93.3 (79-115)
Baseline heart rate	86.6 (61-131)	84.5 (61-102)

Figure 1a: Median smooth plot of percentage change of SBP in the two groups receiving either 50  $\mu$ g phenylephrine (P) or saline (S) prior to oxytocin.

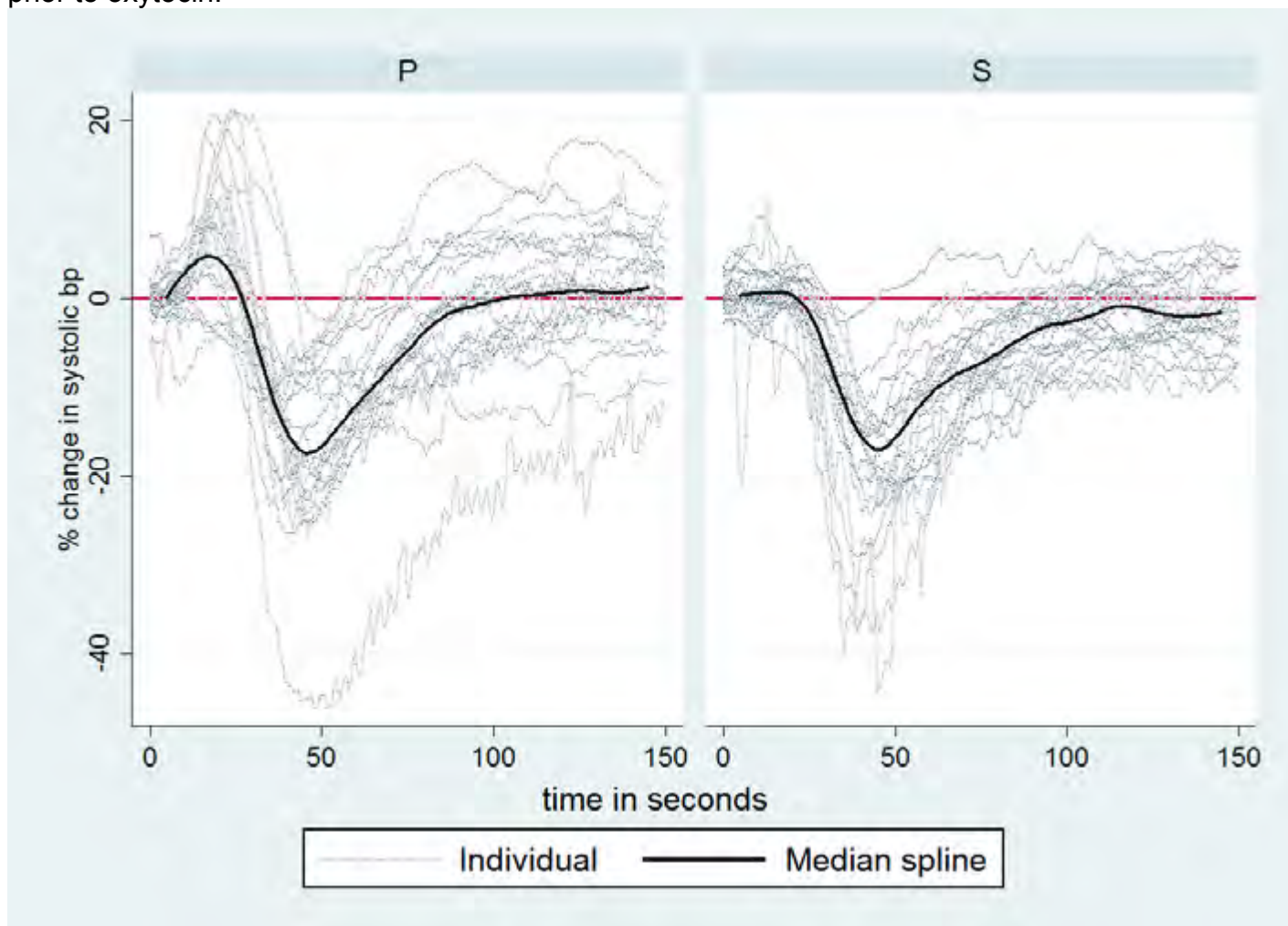


Figure 1b: Median smooth plot of percentage change of DBP in the two groups receiving either 50  $\mu$ g phenylephrine (P) or saline (S) prior to oxytocin.

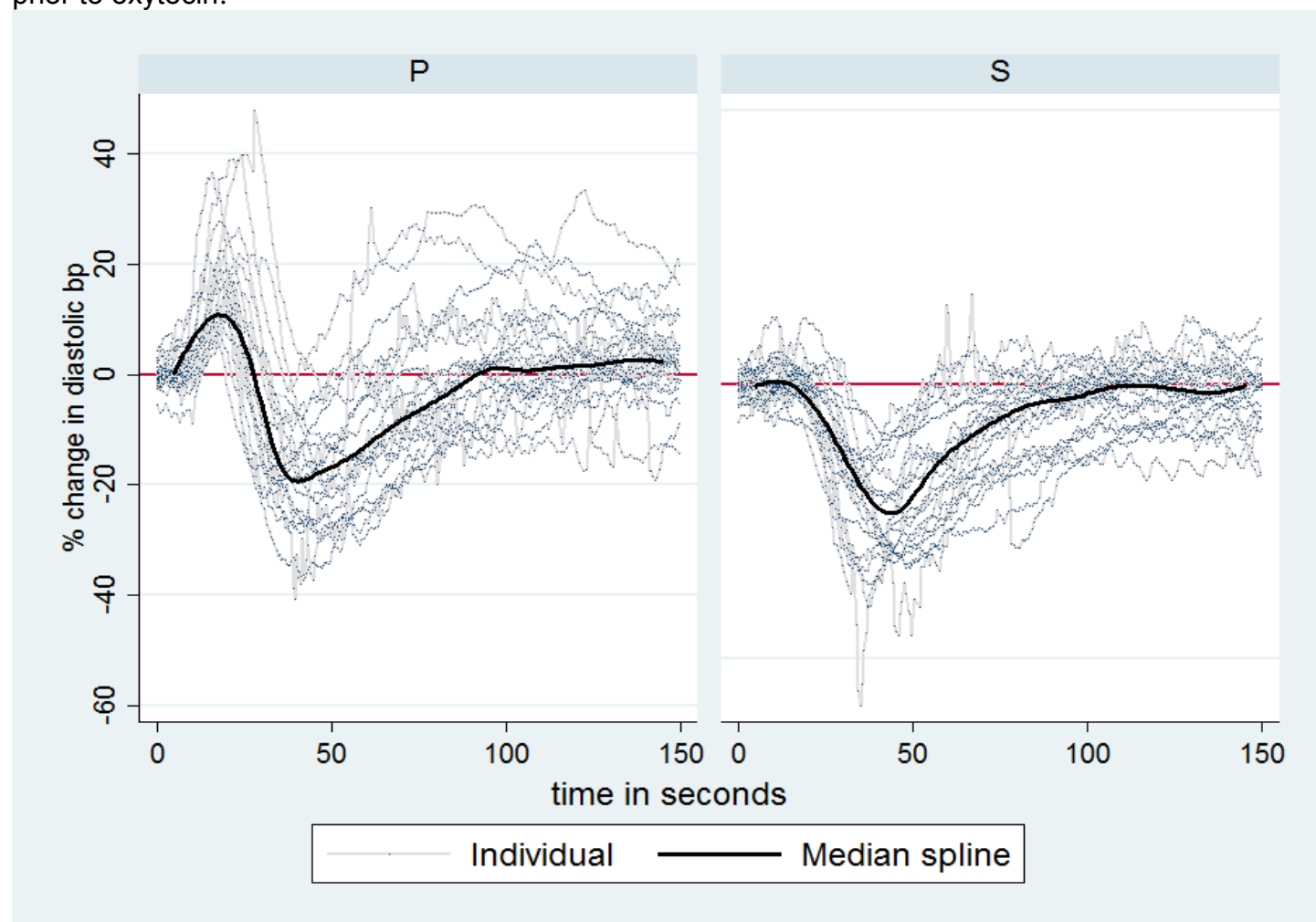


Figure 1c: Median smooth plot of percentage change of MAP in the two groups receiving either 50  $\mu$ g phenylephrine (P) or saline (S) prior to oxytocin.

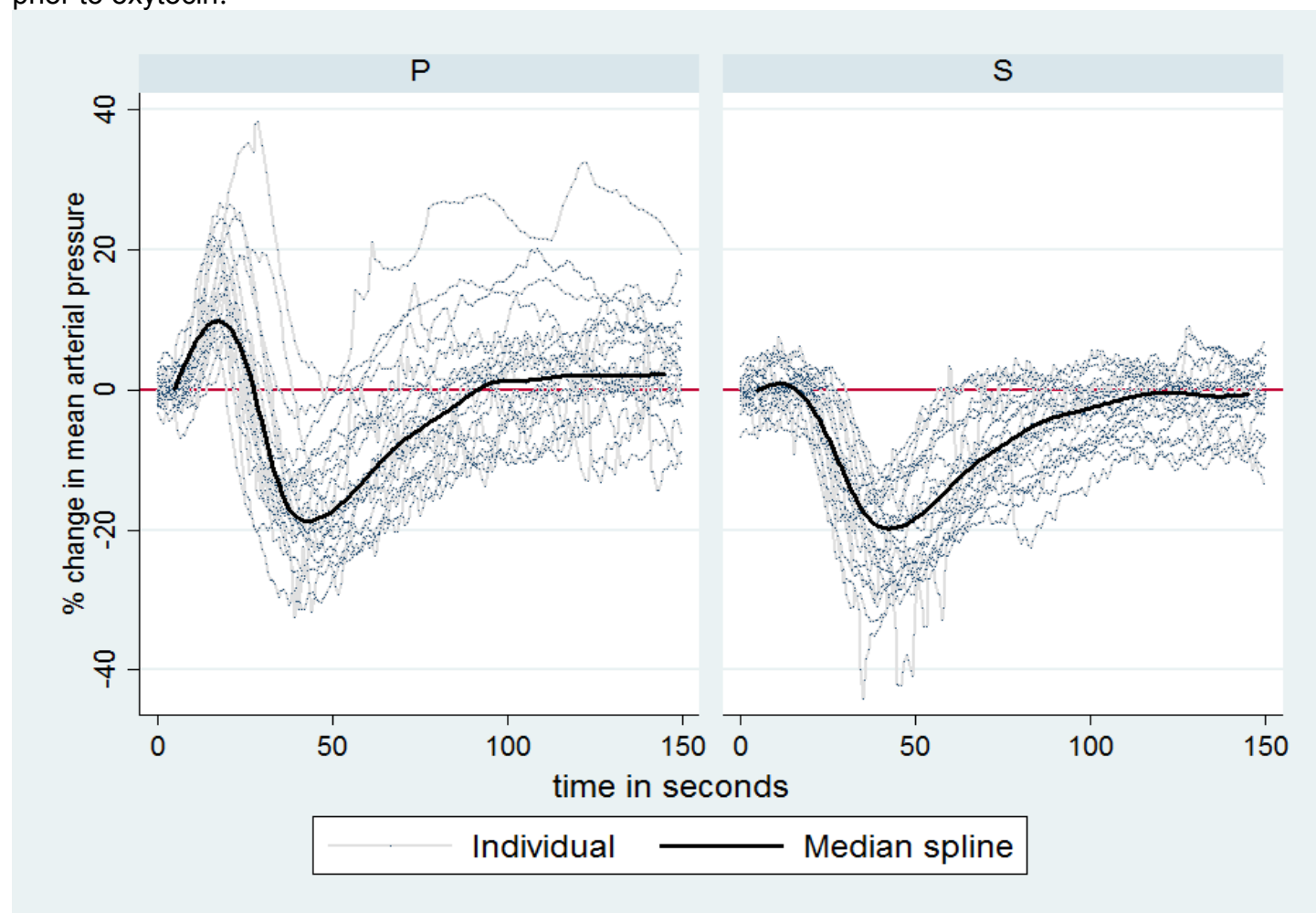


Figure 1d: Median smooth plot of percentage change of HR in the two groups receiving either 50 µg phenylephrine (P) or saline (S) prior to oxytocin.



Figure 1e: Median spline plot of percentage changes in MAP and HR in the two groups receiving either 50  $\mu$ g phenylephrine (P) or saline (S) prior to oxytocin.

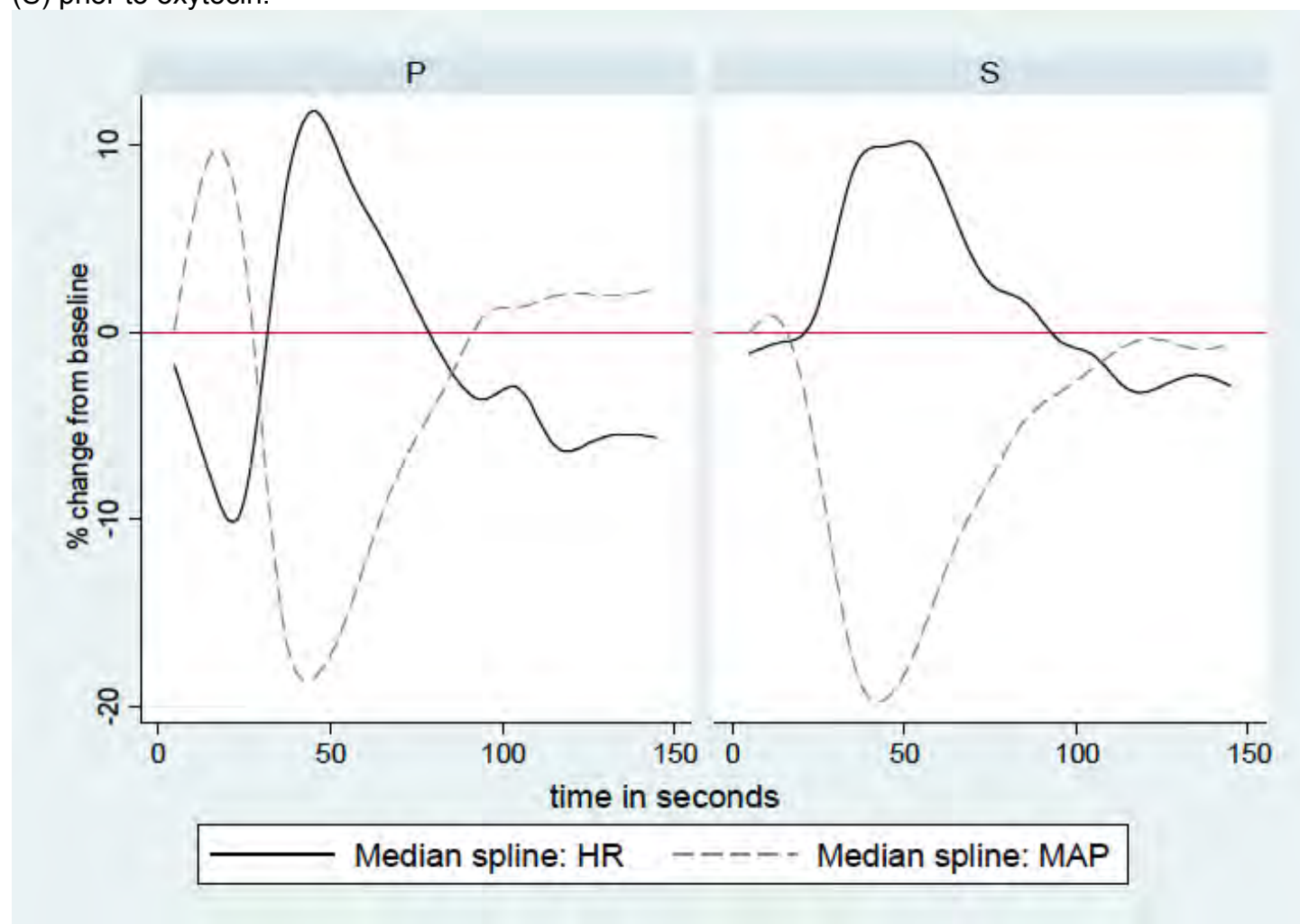


Figure 2a: Percentage SBP changes of individual cases randomised to either P=Phenylephrine or S=Saline.

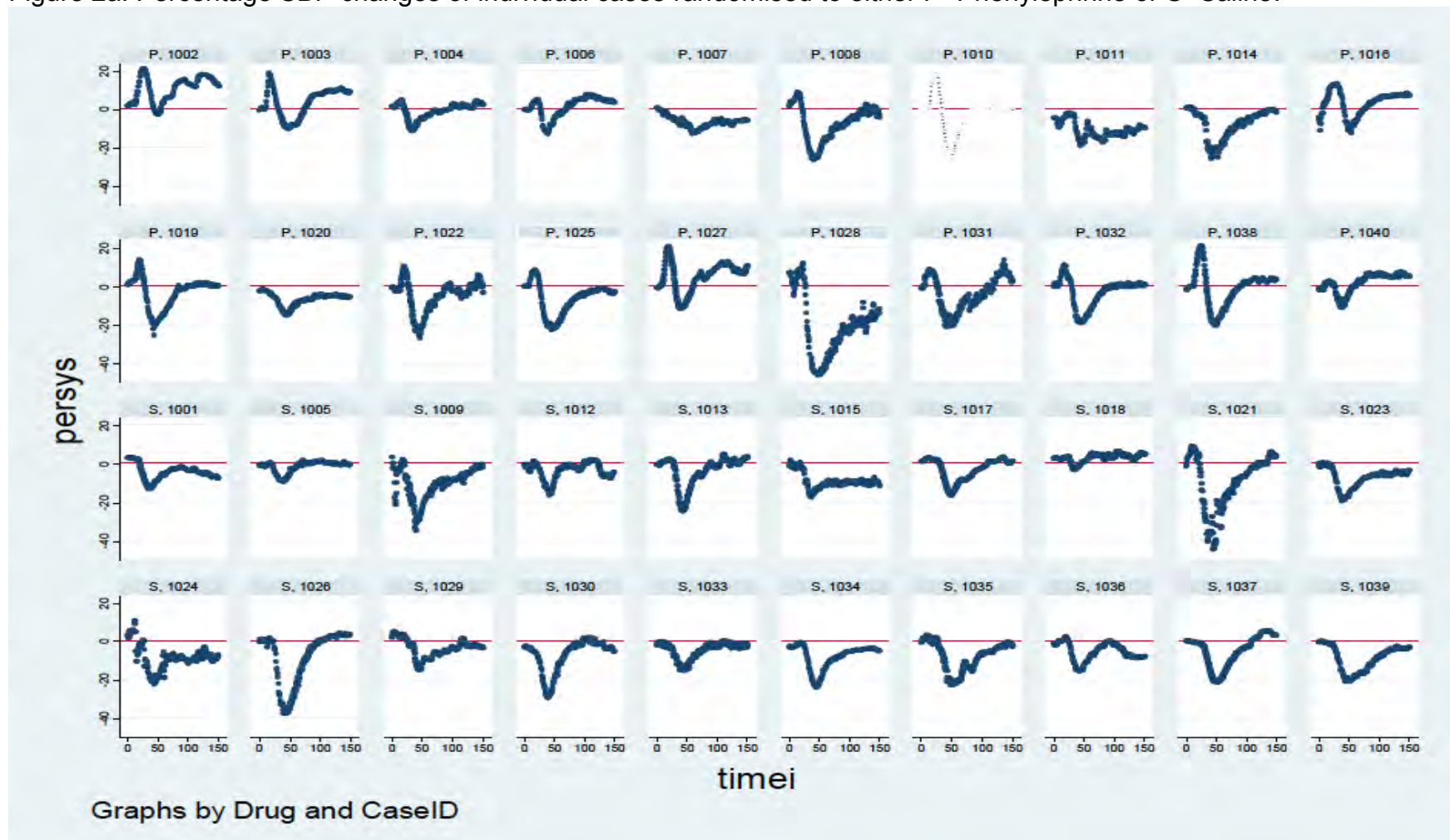


Figure 2b: Percentage DBP changes of individual cases randomised to either P=Phenylephrine or S=Saline.

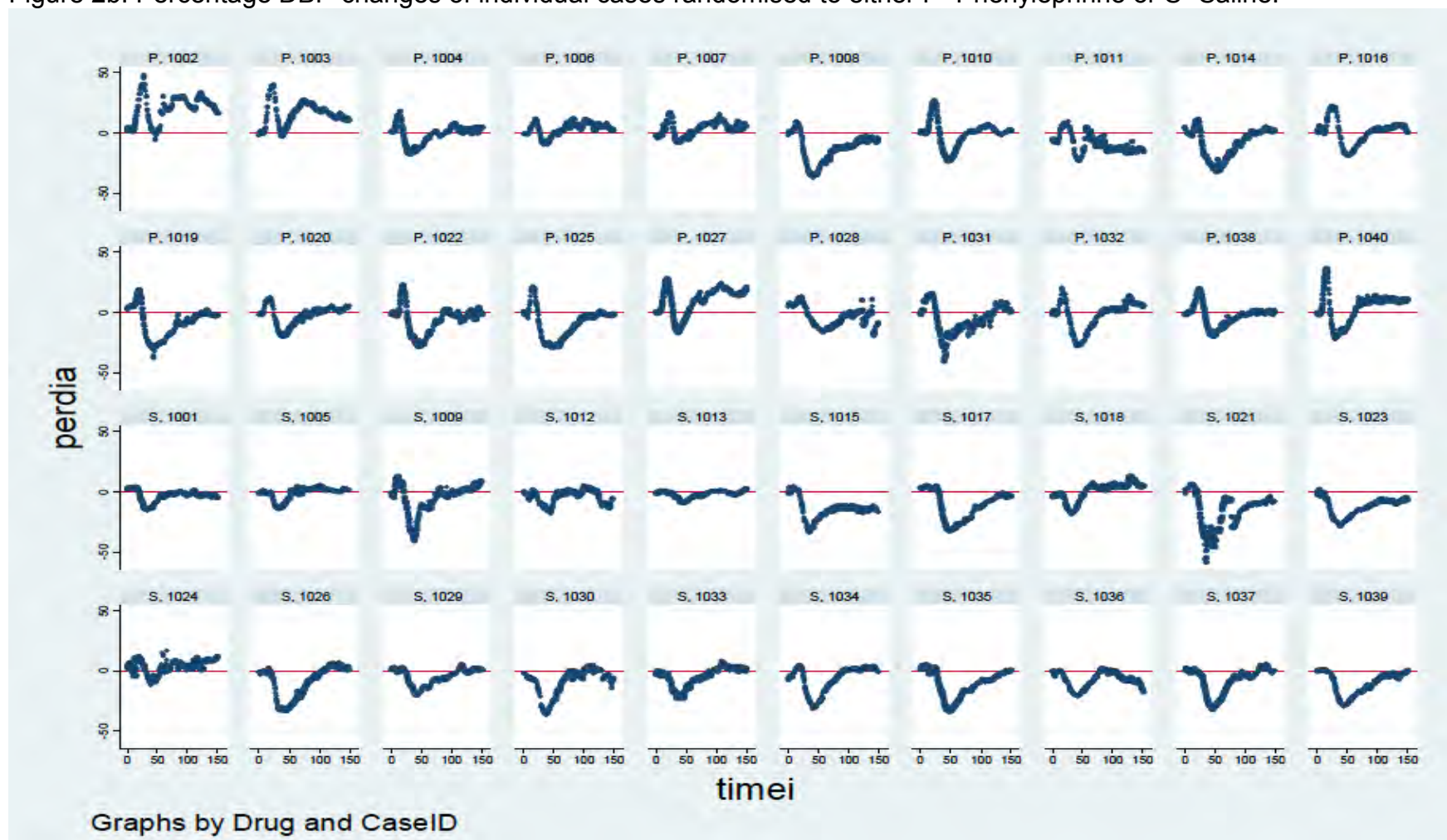


Figure 2c: Percentage MAP changes of individual cases randomised to either P=Phenylephrine or S=Saline.

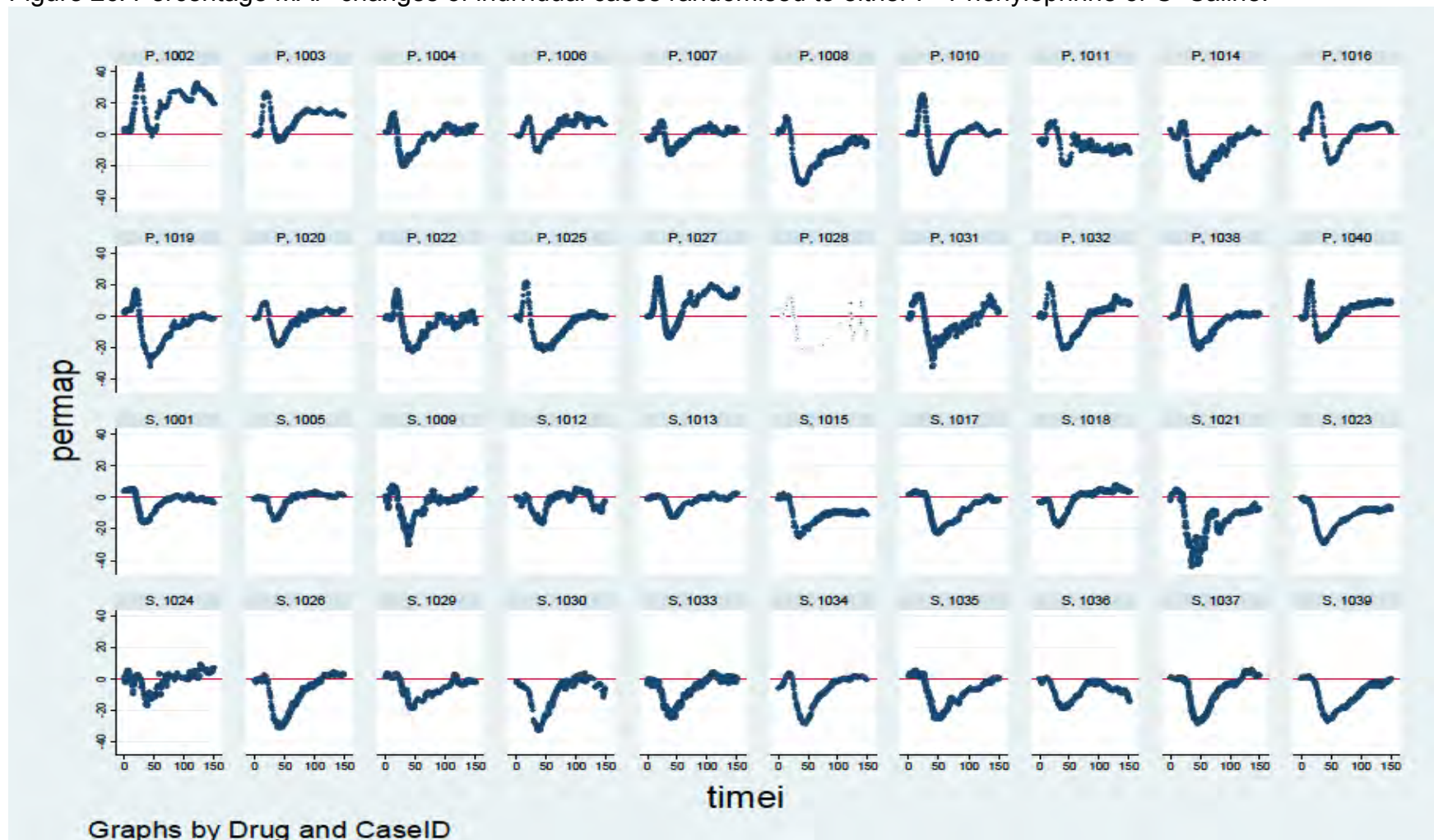


Figure 2d: Percentage HR changes of individual cases randomised to either P=Phenylephrine or S=Saline.

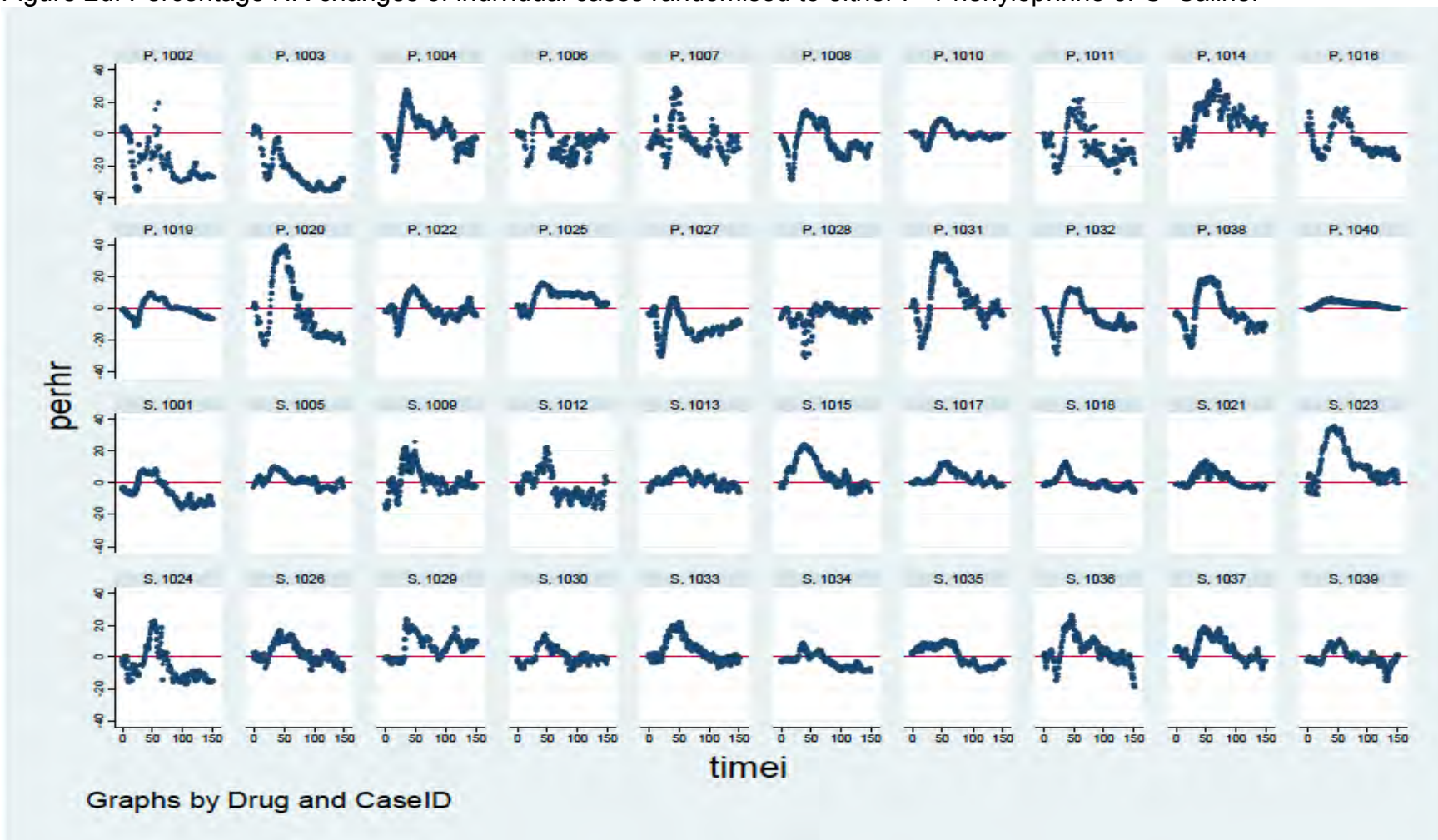


Figure 3a: Percentage change in SBP of individual patients who received 75 µg phenylephrine.

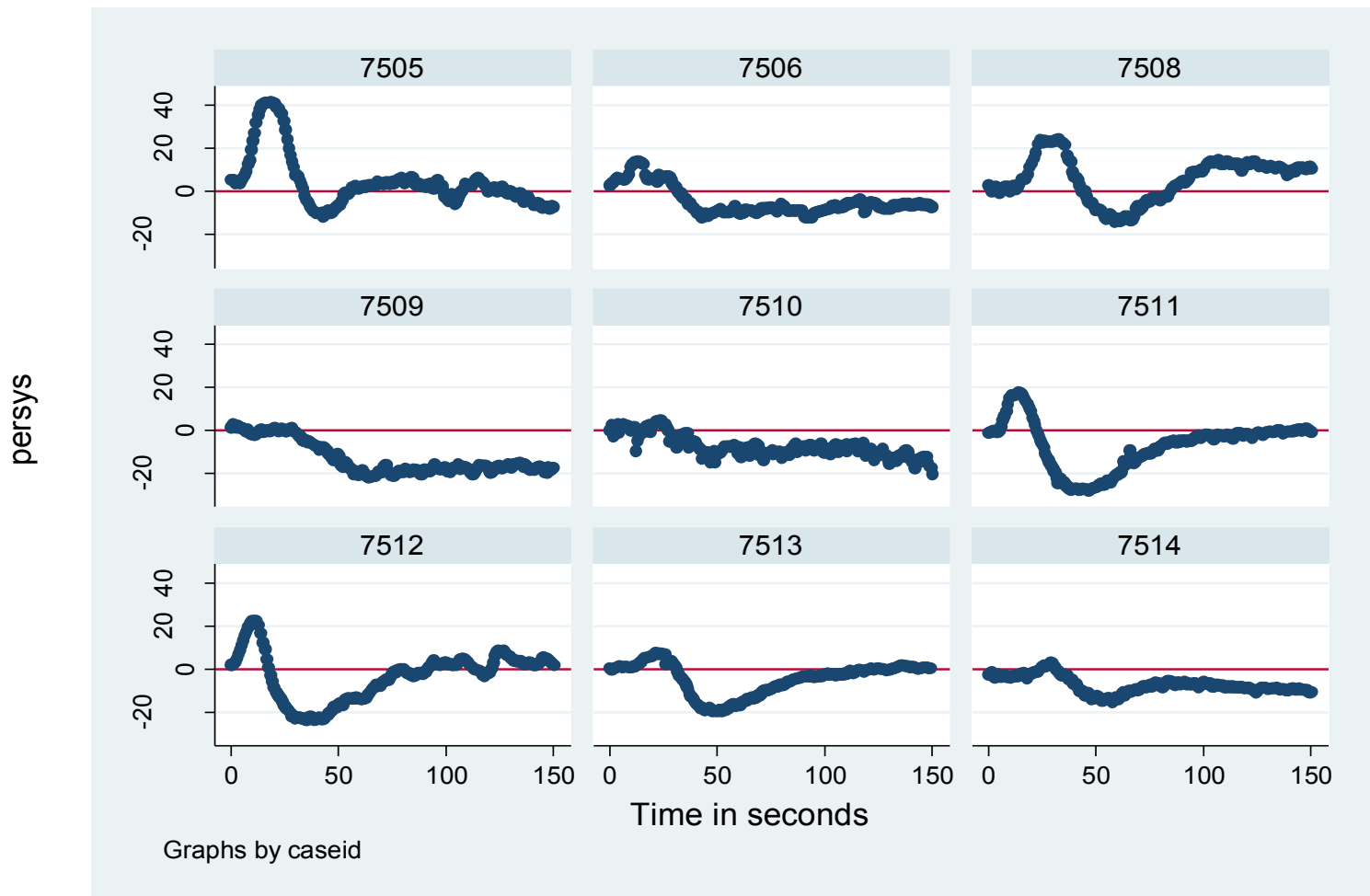


Figure 3b: Percentage change in DBP of individual patients who received 75 µg phenylephrine.

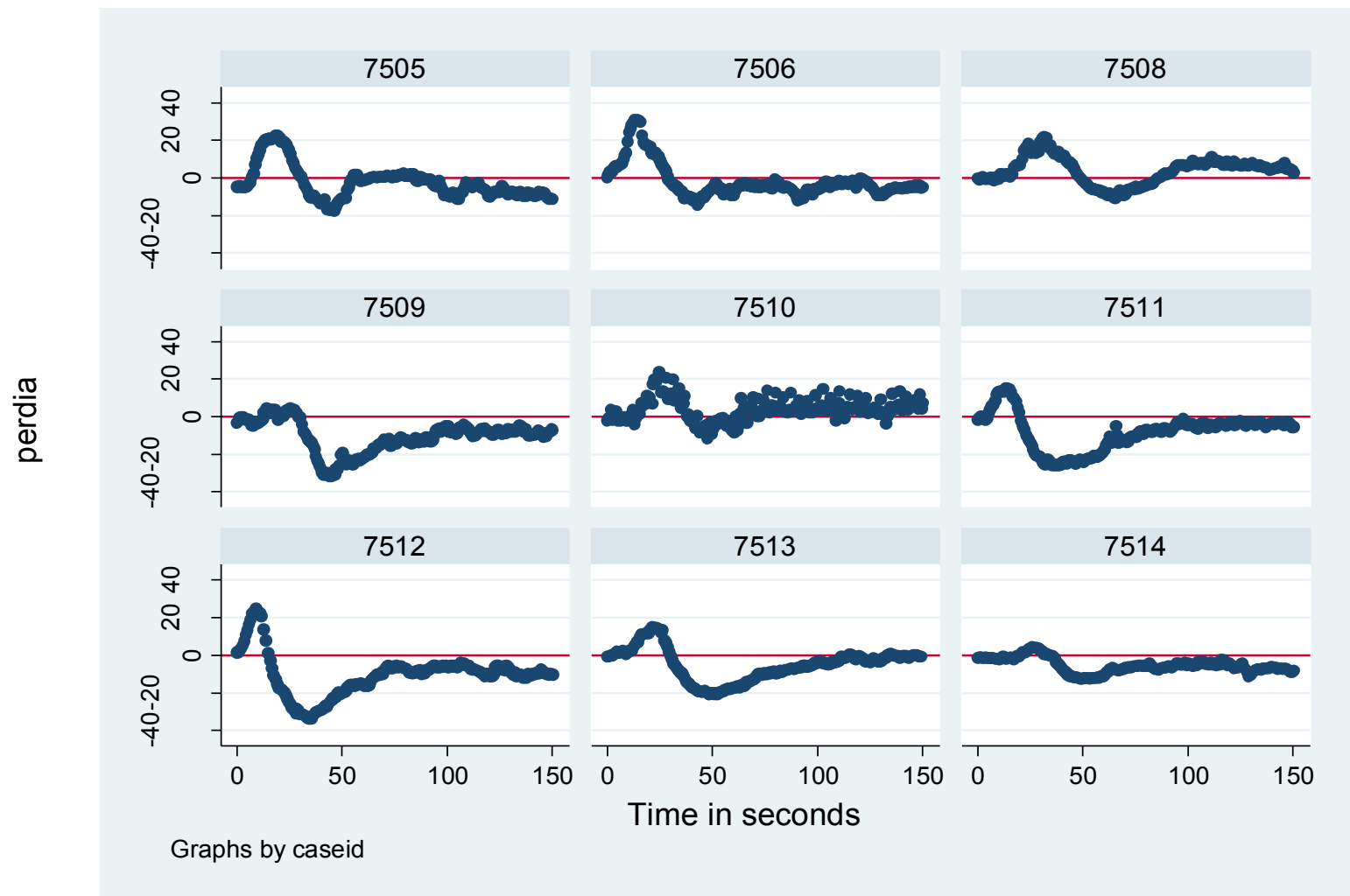


Figure 3c: Percentage change in MAP of individual patients who received 75 µg phenylephrine.

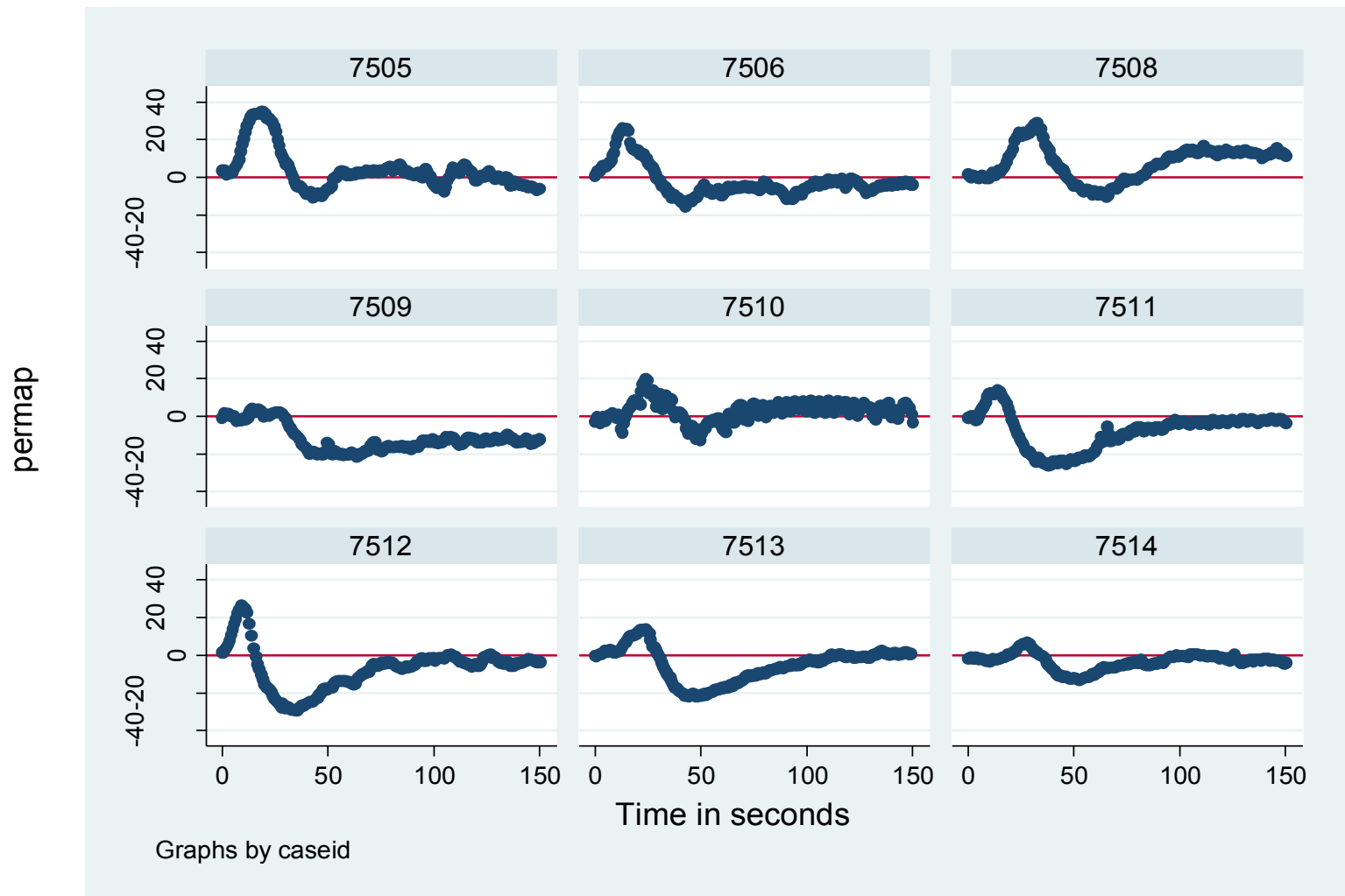


Figure 3d: Percentage change in HR of individual patients who received 75 µg phenylephrine.

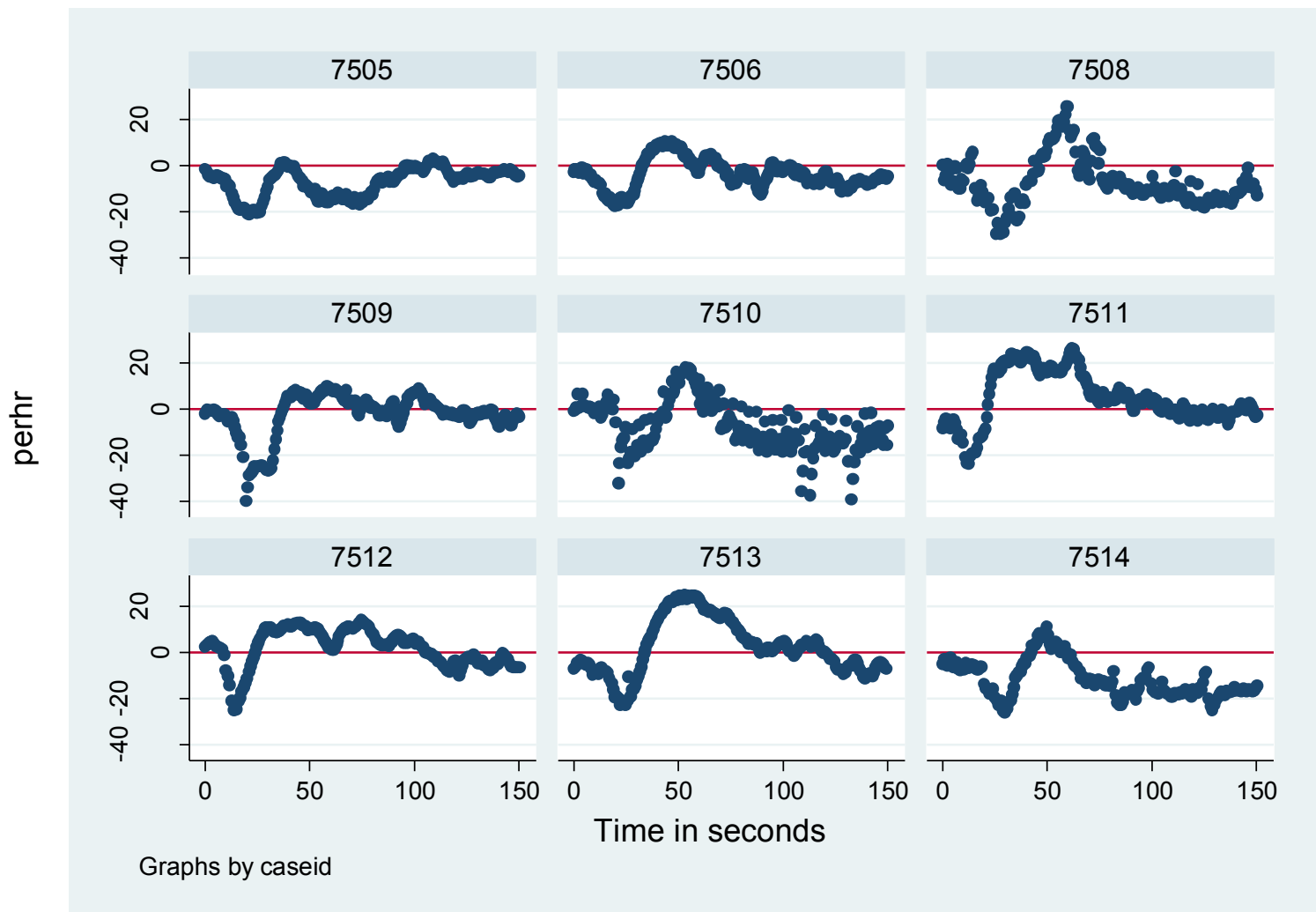


Figure 3e: Ensemble: Percentage change of SBP after 75  $\mu\text{g}$  phenylephrine.

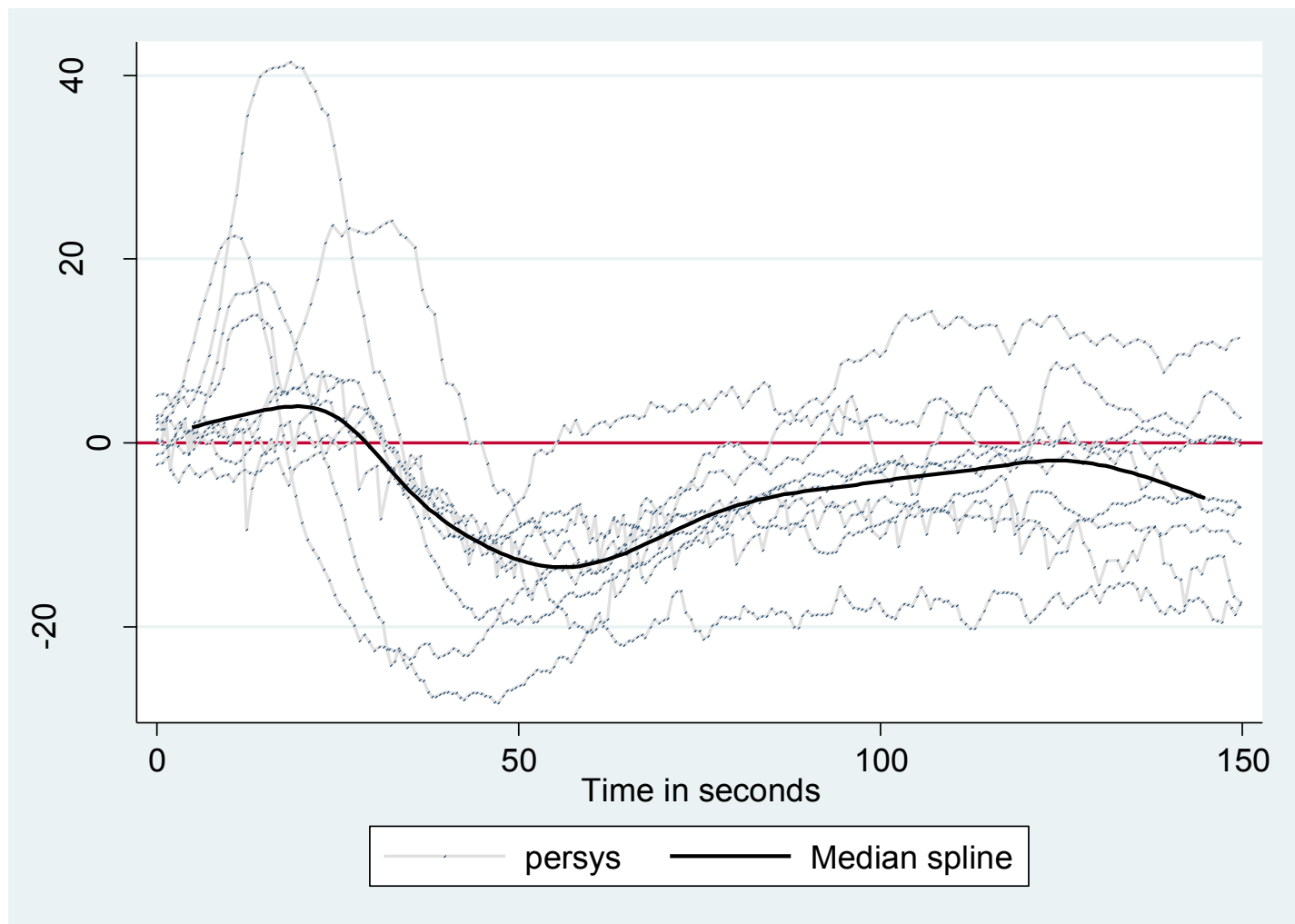


Figure 3f: Ensemble: Percentage change of DBP after 75  $\mu$ g phenylephrine.

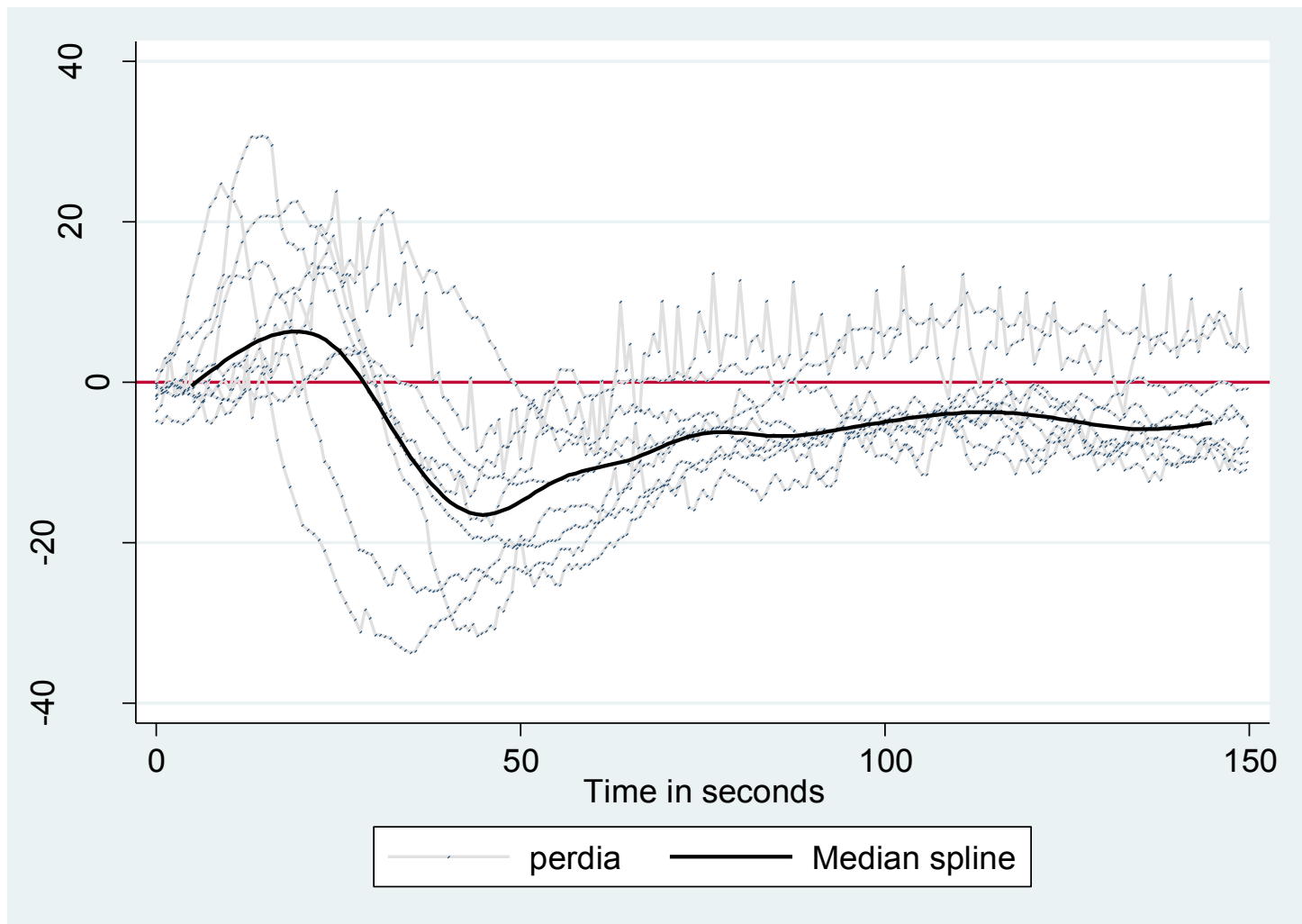


Figure 3g: Ensemble: Percentage change of MAP after 75  $\mu$ g phenylephrine.

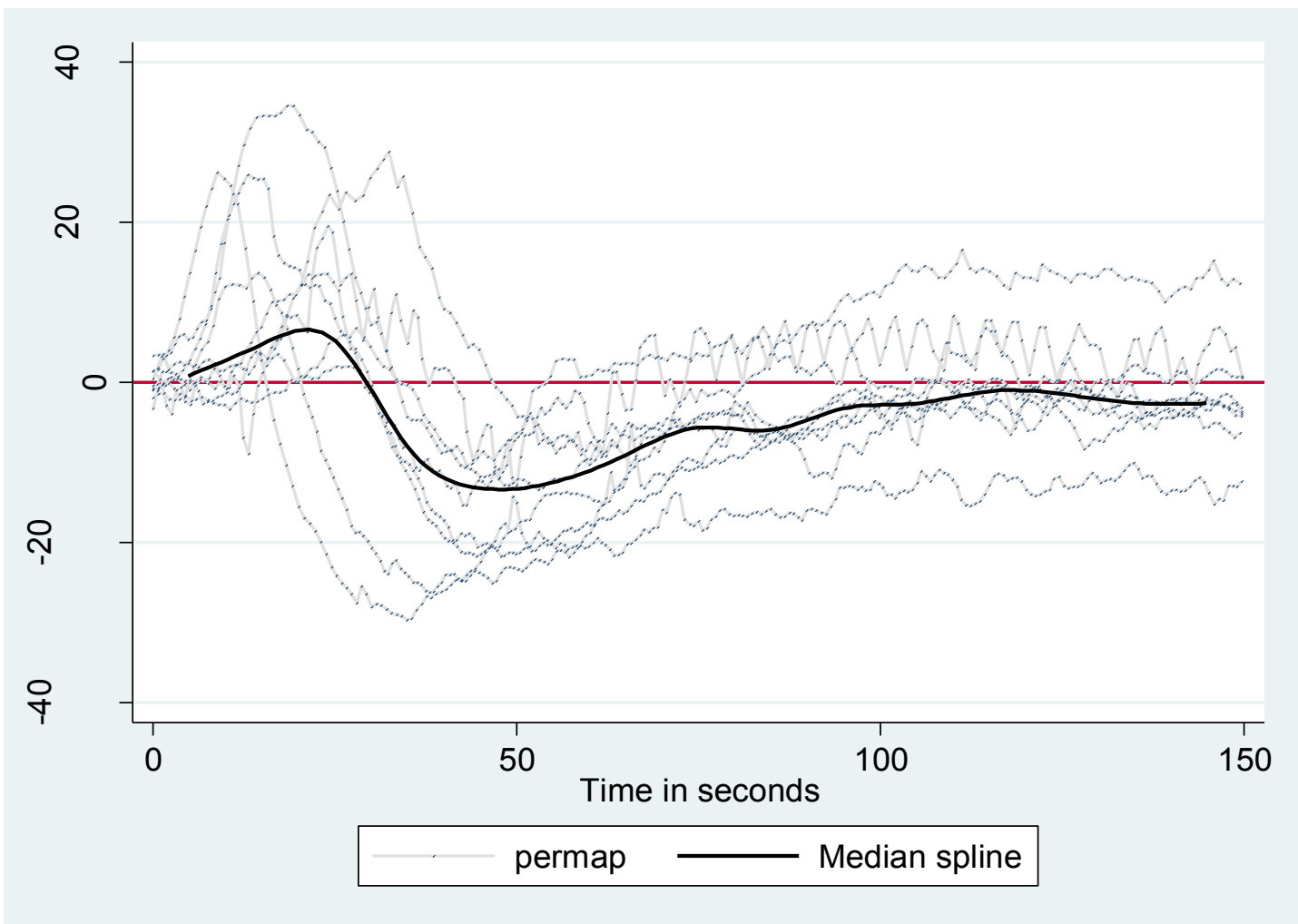


Figure 3h: Ensemble: Percentage change of HR after 75  $\mu$ g phenylephrine.

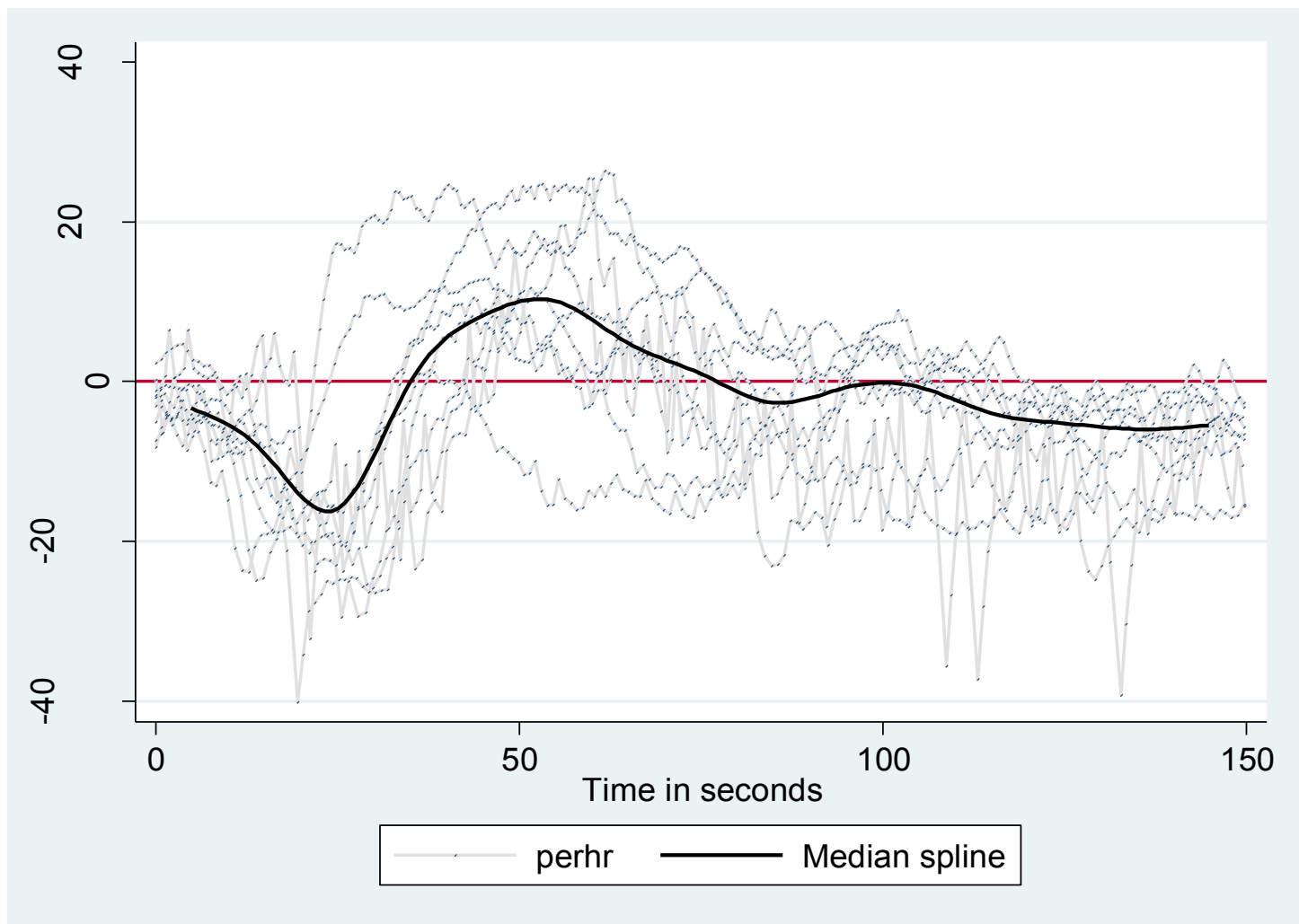


Figure 3i: Median spline plot of HR and MAP responses after 75  $\mu$ g phenylephrine.

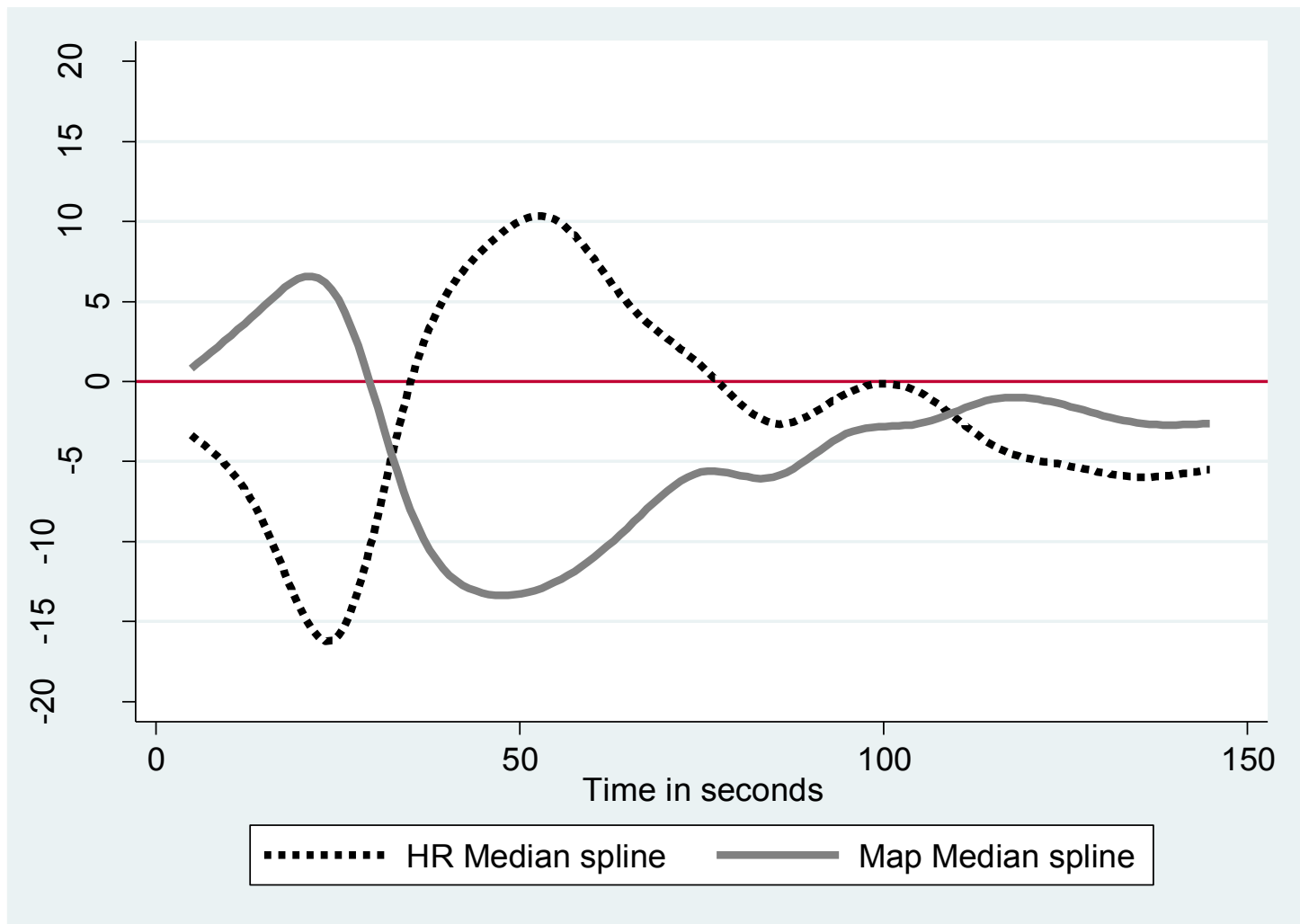
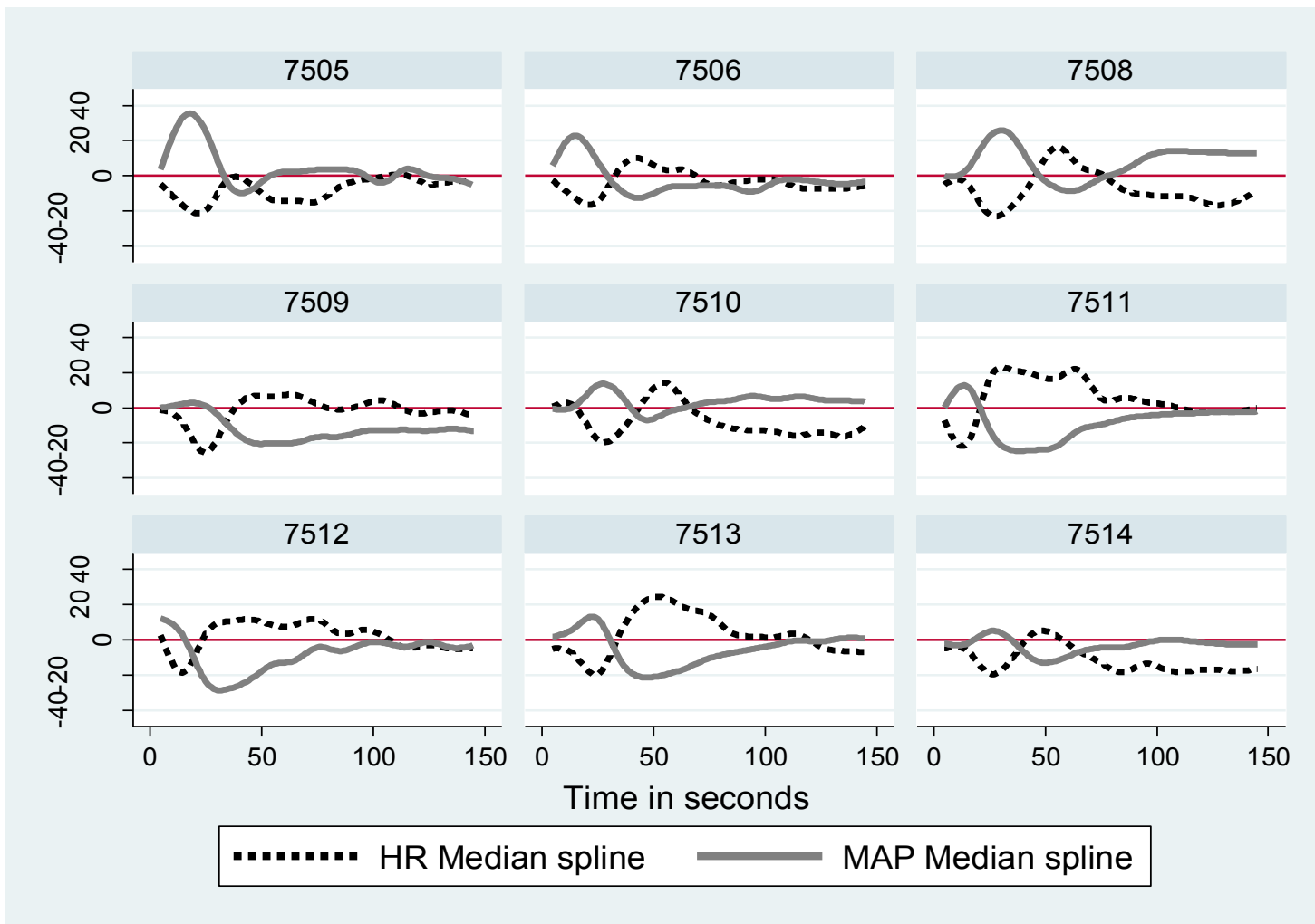


Figure 3j: Spline: Individual joint plots of 75 µg phenylephrine.



## **Part D: Supporting Documents**

## **Information and consent form**

### **THE USE OF PHENYLEPHRINE TO OBTUND OXYTOCIN INDUCED HYPOTENSION AND TACHYCARDIA DURING CAESAREAN SECTION**

#### **Invitation**

You are being invited to take part in a research study. Before you decide whether or not to take part, it is important for you to understand why the research is being done and what it will involve. This information sheet should provide you with this information and it is important that you read it carefully.

If there is something that you do not understand, please ask me to explain further.

#### **What is the purpose of this study?**

A caesarean section operation, is an operation where your baby is removed from the womb, there is always blood loss with this procedure. This is because the baby has a rich blood supply while it is growing inside you. The doctors will give you Oxytocin after delivery of the baby, this is to shrink the womb and stop the bleeding. As medical doctors we know that this medication causes a drop in blood pressure - which is the pressure inside your blood system to move the blood around the body. The reason for this study is to record how low the blood pressure drops while the medication is given, and to test whether giving a second medication, phenylephrine, will reverse the blood pressure drop. Therefore all of the delivering mummies will be given oxytocin, to stop the bleeding; as is always done with all deliveries. The moms will then be divided up into two groups; the one group will be watched after the oxytocin is given to see how the blood pressure drops and how long it stays low for. If at any point any mom in the group has a blood pressure that is low enough to put her in danger, treatment will be given. The second group will get phenylephrine (a medicine to bring the blood pressure up) in order to see how quickly it raised the blood pressure and how long the effects last for.

The reason that we are looking into this is to try make the birthing process as safe as possible for mommy and baby.

#### **How will the study happen?**

Tomorrow you will be taken to theatre when it is your turn for your operation. You will be given a small bottle with very salty tasting fluid to drink. You will then be asked to sit on the theatre bed in a particular position, which we will explain to you there. The anaesthesia doctor will then give you an injection into the back which will numb everything from the belly-button downwards. This is so you do not feel any pain during the operation. After the injection we will make you lie on the theatre bed and get you ready for the operation by putting on stickers and blood pressure monitoring equipment which we do to all patients.

After we made sure you cannot feel anything the surgeon will proceed with the operation. When baby is born the anaesthesia doctor will inject either the phenylephrine medicine or water into your vein, depending on which group you have been assigned to, followed by the oxytocin medicine to make your uterus shrink. While the operation is going on we will be measuring your heart rate and your blood pressure. If your blood pressure were to drop too far we will treat it as we would for any patient.

**Will my identity or personal information be known to others?**

All the information we collect from this research project will be kept **confidential**. Only the researchers will be able to see it. The information about you will have a number on it instead of your name. Only the researchers will know what your number is and we will lock that information up.

The results of the research may also be made public in a medical journal, but no confidential information that may identify you will be published.

**Will you get paid?**

No. No person participating in this study will receive compensation.

**Do you HAVE to take part?**

No. It is your choice whether to take part or not. Your decision will not influence at all the way we treat you in the hospital. If you agree to participate but change your mind, you may do so.

**What if Something Goes Wrong?**

The University of Cape Town (UCT) undertakes that in the event of you suffering any significant deterioration in health or well-being, or from any unexpected sensitivity or toxicity, that is caused by your participation in the study, it will provide immediate medical care. UCT has appropriate insurance cover to provide prompt payment of compensation for any trial-related injury according to the guidelines outlined by the Association of the British Pharmaceutical Industry, ABPI 1991. Broadly-speaking, the ABPI guidelines recommend that the insured company (UCT), without legal commitment, should compensate you without you having to prove that UCT is at fault. An injury is considered trial-related if, and to the extent that, it is caused by study activities. You must notify the study doctor immediately of any side effects and/or injuries during the trial, whether they are research-related or other related complications.

UCT reserves the right not to provide compensation if, and to the extent that, your injury came about because you chose not to follow the instructions that you were given while you were taking part in the study. Your right in law to claim compensation for injury where you prove negligence is not affected. Copies of these guidelines are available on request.

I, ....., hereby consent to randomised treatment with one of two medicines, as explained to me by doctor.....

Signed: .....

Witnessed: (1).....

At: .....Date.....

Should you wish to contact the HREC in connection with questions regarding your rights and welfare as a research subject, the contact details are: Professor Marc Blockman, 0214066492

## Ethics approval letter

UNIVERSITY OF CAPE TOWN



Faculty of Health Sciences  
Human Research Ethics Committee  
Room E52-24 Groote Schuur Hospital Old Main Building  
Observatory 7925  
Telephone [021] 406 6338 • Facsimile [021] 406 6411  
e-mail: [shuretta.thomas@uct.ac.za](mailto:shuretta.thomas@uct.ac.za)  
Website: [www.health.uct.ac.za/research/humanethics/forms](http://www.health.uct.ac.za/research/humanethics/forms)

08 August 2013

**HREC REF: 479/2013**

**Dr C Rumboll**  
c/o Prof R Dyer  
Anaesthesia  
D23  
NGSH

Dear Dr Rumboll

**PROJECT TITLE: THE USE OF PHENYLEPHRINE TO OBTUND OXYTOCIN INDUCED  
HYPOTENSION AND TACHYCARDIA DURING CAESAREAN SECTION**

Thank you for responding to the issues raised by the Faculty of Health Sciences Human Research Ethics Committee.

It is a pleasure to inform you that the HREC has **formally approved** the above-mentioned study.

**Approval is granted for one year till the 15<sup>th</sup> August 2014**

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

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

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

**Please quote the HREC. REF in all your correspondence.**

Yours sincerely

**PROFESSOR M BLOCKMAN**  
**CHAIRPERSON, FHS HUMAN ETHICS**

Federal Wide Assurance Number: FWA00001637.

Institutional Review Board (IRB) number: IRB00001938

This serves to confirm that the University of Cape Town Human Research Ethics Committee complies to the Ethics Standards for Clinical Research with a new drug in patients, based on the Medical Research Council (MRC-SA), Food and Drug Administration (FDA-USA), International Convention on Harmonisation Good Clinical Practice (ICH GCP) and Declaration of Helsinki guidelines.

The Human Research Ethics Committee granting this approval is in compliance with the ICH Harmonised Tripartite Guidelines E6: Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) and FDA Code Federal Regulation Part 50, 56 and 312.

## Guide to Authors – International Journal of Obstetric Anaesthesia

### Introduction

**Types of article** Original research (both clinical and laboratory), case series, reports and correspondence will be considered. To be accepted for publication, individual case reports need to have important and novel learning points; a simple narrative of a complex or challenging patient(s) is insufficient. Case series dealing with important areas of practice with a thorough review of relevant literature will be considered. The journal also publishes invited review articles and debates on topical and controversial subjects in the area of obstetric anaesthesia. Reviews are usually commissioned, although authors may contact the Editor-in-Chief if they wish to discuss potential topics.

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