Haemodynamics
during Vaginal and Caesarean Delivery
in Healthy Parturients

PhD Thesis
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What lies behind us and what lies ahead of us are tiny matters compared to what lies within us.

Ralph Waldo Emerson

To

My parents. Your unwavering support, wise counsel, and help to place things in the right order of importance have grounded and sustained me in all of my endeavours.

My late brother Jörg. The memory of your spirit, your sense of humour, and your matchless laughter continue to brighten my mind. I will carry you with me wherever I go.

My family and friends. You all are a part of who I am, and I treasure what you have given me on my way.

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Writing this note of thanks closes a circle whose end often seemed out of sight during the rather intense past eight years, and has me look back to its beginning, before I embark on a fresh section of life.

This thesis was primarily motivated by clinical interest and by my wish to contribute to the continuing process of improving the clinical management of parturients. If it had not been for that, I would most likely have never completed the PhD programme, which I signed up for after commencing the research itself, and which has demanded important personal and professional sacrifices on the way. I am pleased that this project has brought forth some interesting and useful findings, yet these are very tiny pieces in the large mosaic of past, current, and future obstetric anaesthesiological research. Studying this field has filled me with interest, inspiration, and deep respect towards the gifted clinicians and researchers out there, but it has also filled me with a great deal of self-consciousness concerning the limits of my own knowledge, reason, and skills. Arriving at the end of this project, I feel immense gratitude for every form of support that I have received along the way.

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Oslo, November 2017

Jana C. Kuhn
PAPERS INCLUDED IN THIS THESIS

Paper I

Kuhn JC, Hauge TH, Rosseland LA, Dahl V, Langesæter E.

Hemodynamics of Phenylephrine Infusion versus Lower Extremity Compression during Spinal Anesthesia for Caesarean Delivery: A Randomized, Double-Blind, Placebo-Controlled Study.


Paper II

Kuhn JC, Falk RS, Langesæter E.

Haemodynamic changes during labour: continuous minimally invasive monitoring in 20 healthy parturients.

## ABBREVIATIONS

### General abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>CD</td>
<td>Caesarean delivery</td>
</tr>
<tr>
<td>CO</td>
<td>Cardiac output</td>
</tr>
<tr>
<td>CVP</td>
<td>Central venous pressure</td>
</tr>
<tr>
<td>HR</td>
<td>Heart rate</td>
</tr>
<tr>
<td>SAP</td>
<td>Systolic arterial pressure</td>
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<tr>
<td>SHT</td>
<td>Spinal hypotension</td>
</tr>
<tr>
<td>SV</td>
<td>Stroke volume</td>
</tr>
<tr>
<td>SVR</td>
<td>Systemic vascular resistance</td>
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<tr>
<td>VD</td>
<td>Vaginal delivery</td>
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</table>

### Treatment group abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phe</td>
<td>Phenylephrine group in Study I</td>
</tr>
<tr>
<td>Leg</td>
<td>Leg wrapping group in Study I</td>
</tr>
<tr>
<td>Control</td>
<td>Sham treatment group in Study I</td>
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1 BACKGROUND

1.1 The Research Field of this Thesis
Childbirth is ‘one of life’s biggest cardiovascular challenges’. Pregnant women, during vaginal and surgical delivery, constitute a large and vulnerable group of patients with a need for optimal treatment, both under normal and complicated conditions. Understanding and optimisation of maternal haemodynamics is a prerequisite for maximal safety and wellness of the mother and the newborn. Both maternal and neonatal safety have been improved considerably during the past decades. Lately, however, the prevalence of risk factors such as obesity and cardiac disease among parturients has increased. So has maternal mortality from indirect death, i.e. from ‘diagnosed or undiagnosed disease which is aggravated by the physiological effects of pregnancy or childbirth’, ‘Substandard care’, in part due to failed recognition or inappropriate management of (sub-) acute cardiac pathology, was identified in half of indirect maternal deaths in the UK between 2006 and 2008. Ameliorating an in-depth understanding of maternal circulation, and optimising cardiovascular management in the obstetric context, still constitute an important research focus in order to further improve maternal and neonatal safety under physiological and pathological conditions. This Ph.D. project aimed to contribute to this continual process with two studies on haemodynamics in healthy parturients.

Parturients may give birth either by vaginal delivery (VD), or by caesarean delivery (CD). Caesarean delivery may be performed in (semi-) acute settings, such as delayed labour progress, compromised maternal condition, or because the foetus becomes critically stressed during ongoing labour. By contrast, elective CD is scheduled a few days or weeks in advance, because of maternal request, breech position of the foetus, or complications anticipated with VD. Caesarean delivery can be performed either under general anaesthesia or with the help of regional techniques, i.e. spinal or epidural anaesthesia. Regional anaesthesia is a generally safe and convenient technique in which a local anaesthetic is used to anaesthetise only the lower part of the body, thus avoiding the disadvantages of general anaesthesia. Spinal anaesthesia is used most frequently, because of its simplicity, rapid onset, low drug dose, and good muscle relaxation during surgery.

Both VD and anaesthesia for CD can have a profound impact on maternal circulation. During labour contractions, pain and physical strain expose the mother to haemodynamic stress, but the evidence base is limited since only a few studies have investigated the haemodynamic effects of labour. Women delivering by elective CD escape contractions, but may suffer from spinal hypotension, i.e. a decrease in blood pressure which is a frequent side effect of spinal anaesthesia. In spite of numerous studies over the past decades, no final consensus on optimal prophylaxis against spinal hypotension during CD had been established by the time we started our research project.
Both of our studies examined the haemodynamic condition of healthy parturients in an obstetric-anaesthesiological context. Study I compared two different methods for stabilising maternal haemodynamics during spinal anaesthesia for CD. Study II investigated the impact of labour and VD on maternal haemodynamics.

The following chapters will sum up previous research on haemodynamics during caesarean and vaginal delivery, address the methodological aspects of this Ph.D. project, present the results of both studies, and discuss our findings in the context of current evidence.

1.2 Spinal Hypotension during Caesarean Delivery

Most caesarean deliveries are performed under spinal anaesthesia. Injection of a local anaesthetic into the spinal fluid leads to the blocking of both sensory and motoric, but also autonomic nerve fibres. Inhibition of thoracolumbal sympathetic nerve impulses happens rapidly after injection, and results in the vasodilation of peripheral blood vessels, which in turn leads to a reduction of systemic vascular resistance (SVR) and a subsequent decrease in arterial blood pressure. This so-called spinal hypotension (SHT) can have negative consequences for mother and foetus. Maternal tachycardia or bradycardia, nausea and vomiting are frequent, and, in worst cases, cardiovascular collapse may occur. Furthermore, placental blood supply may be reduced, which can give rise to acidosis and reduced vitality in the newborn. A drop in arterial blood pressure can generally be treated quite rapidly by a choice of medicaments and fluids. However, a period of several minutes may pass from the event to the revealing measurement, and to the effect of the then given treatment. In some parturients, persistent refractory hypotension may lead to prolonged and severe symptoms despite aggressive therapeutic intervention.

Prevention of SHT has been called ‘the Holy Grail’ within obstetric anaesthesia, and a range of methods – such as prophylactic medications, intravenous fluid regimens, positioning techniques during spinal anaesthesia and CD, and other mechanical manoeuvres – have been studied and discussed internationally for many years. None of the methods had optimal effect, and international guidelines for prophylaxis against haemodynamic instability during CD did not exist when we started Study I. Prophylactic routines differed significantly between, and even within, hospitals and countries, and in many places no specific prophylaxis was used at all.

One prophylactic strategy is the use of vasoactive medicaments, and various types and regimens have been studied. Administration of one of these vasopressors, phenylephrine, in combination with crystalloid cohydration, has been established as the ‘gold standard’ prevention technique during the past decade. Phenylephrine is a pure α₁-adrenergic agonist that causes vasoconstriction via stimulation of post synaptic α₁-fibres, and thereby increases SVR and arterial blood pressure. Different dosage regimens have been investigated, but
not led to a definite consensus yet.²⁷,³⁰ Prophylactic high-dose phenylephrine infusion may entirely prevent SHT, but on the other hand may cause reactive hypertension, and reduce maternal heart rate (HR) and cardiac output (CO), which, if profound, may reduce placental blood supply.¹⁹,³¹-³⁴ Continuous low-dose phenylephrine infusion has been shown to stabilise systolic arterial blood pressure (SAP) without reactive hypertension or a significant reduction in CO, but an initial drop in SAP has not been prevented.¹⁹ Finding the optimal pattern for prophylactic administration of phenylephrine has been considered to be of high clinical interest.²⁴,³⁵,³⁶

Several mechanical prophylactic strategies have also been examined. One of the more frequently studied alternatives among them is lower limb compression, which may for example be effectuated by wrapping the legs with tight bandages. This is meant to prevent hypotension by mechanically counteracting venous blood pooling and loss of fluid into connective tissue of the lower extremities, thus increasing venous return. Only a few studies have been conducted,²,³⁷-⁴⁰ showing a moderate stabilising effect on SAP. Small sample sizes and methodological weaknesses have contributed to the absence of definitive recommendations for clinical practice, and no data on international commonness of use have been published. However, a number of institutions in different countries have based their prophylaxis protocols on leg wrapping.⁴¹-⁴⁴ Since the method has been applied in clinical practice despite the lack of high-quality scientific evidence, we considered detailed examination of the effect of leg wrapping in a larger, well-designed study to be of interest.

Phenylephrine and leg wrapping have never been compared in the setting of spinal anaesthesia for CD. As recent evidence shows, a sudden and marked arterial vasodilation is the main haemodynamic effect of spinal anaesthesia.¹⁹,³² The arteriolar vasoconstrictor phenylephrine directly counteracts this side effect.³⁵ By contrast, the leg wrapping approach is based on the historic, but lately disestablished, concept of impaired venous return being the most relevant factor in spinal hypotension.³⁵,⁴¹,⁴⁵ The fundamental change in pathophysiological understanding of spinal hypotension, moving the focus from venous to arterial circulation, had just emerged in the year preceding Study I.¹⁹ Comparison of the detailed haemodynamic effects of the two physiologically different prophylactic approaches seemed particularly interesting in light of this recent paradigm shift.

In summary, SHT during CD was considered a central and incompletely solved problem within obstetric anaesthesia.²⁴,³⁵,³⁶ Since a previously studied continuous low-dose phenylephrine infusion stabilised SAP well, but did not prevent an initial drop in SAP,¹⁹ we thought to investigate whether adding an initial bolus to this regimen would improve its effect. Further, we thought that comparison of this regimen with leg wrapping, using advanced haemodynamic monitoring, might be an interesting contribution to the evidence base on the pathophysiology and the prevention of SHT.
1.3 Haemodynamic Impact of Labour and Vaginal Delivery

During pregnancy, women undergo significant changes with regards to their haemodynamic condition. In pregnant women at term, SVR is reduced, and blood volume and CO are increased by 30% to 50%. Healthy pregnant women generally tolerate these changes well.\textsuperscript{46,47}

The process of birth through the natural birth canal is divided into labour stage 1, with contractions that lead to the gradual opening of the uterine cervix, and labour stage 2, with active pressing during contractions in order to move the foetus downward, including vaginal delivery, the last few contractions leading to parturition. Delivery of the foetus and, usually a few minutes later, of the placenta are followed by the postpartum period.\textsuperscript{48} Haemodynamic changes during this process may be profound, but have only been investigated very little so far. Hence, the literature is sparse and inconsistent.\textsuperscript{18,49} Most studies date back to the period between the 1950s and the 1970s, and some are based on very low patient numbers.\textsuperscript{9-16} To our knowledge, none of the previous studies provided continuous CO monitoring during all labour stages.

A case report based on continuous minimally invasive monitoring described profound decreases in CO and stroke volume (SV), and marked increases in SVR, SAP and HR during the second stage of labour in a pre-eclamptic parturient.\textsuperscript{49} The same monitoring method revealed similar, major haemodynamic changes in three healthy parturients with effective epidural analgesia during contractions in both labour stages (unpublished data from Oslo University Hospital, Rikshospitalet).

Healthy women usually tolerate labour well, but detailed knowledge about the haemodynamic changes during labour and VD is important for optimal management both of healthy parturients and of parturients with reduced cardiac reserve. Severe cardiac compromise is acknowledged as a maternal indication for CD, but for the majority of parturients with cardiac compromise, current guidelines recommend VD.\textsuperscript{1,50-52} While the guidelines emphasise the risk of haemorrhage, infection, thrombosis, and anaesthesiologic complications in case of CD, some authors are concerned that the impact of labour on maternal circulation might be underrecognised.\textsuperscript{17,49}

The idea behind Study II was to examine the challenge that labour poses to maternal circulation. We thought that continuous invasive monitoring in a group of healthy parturients might improve insight into haemodynamic changes during both labour stages and VD. Thorough appraisal of haemodynamics in healthy parturients might be a valuable foundation for clinical judgement regarding, and future research into, physiological and pathological conditions.
1.4 Haemodynamic Monitoring in the Obstetric Context

The most frequently used form of haemodynamic monitoring in parturients is intermittent non-invasive blood pressure measurement. The technique is simple to perform but does not provide data on any other haemodynamic variables, and intervals between measurements are usually one or several minutes.\textsuperscript{27,53} Most studies on the prevention of spinal hypotension during CD are based on intermittent noninvasive blood pressure measurement, which is why they provide limited information on the haemodynamic changes caused by spinal anaesthesia.\textsuperscript{54}

Advanced haemodynamic monitoring measures a wider range of variables, such as CO, SV, and SVR. Techniques of the past involved central venous and arterial catheterisation, and allowed serial single CO measurements using various types of dye dilution. Suffering from disadvantages such as a high degree of invasiveness, a low number of measurements per time, limited reliability for the detection of rapid changes, and high sensitivity to noise,\textsuperscript{18} they have been employed in only a few studies in the obstetric context.\textsuperscript{9-16,55} Hence, haemodynamic pathophysiology during labour, and during vaginal and caesarean delivery, has been sparsely elucidated for a long time.\textsuperscript{18,27,49}

Thanks to the recent development of modern noninvasive and minimally invasive devices, haemodynamic monitoring in parturients has evolved over the past decade.\textsuperscript{53} Modern CO monitors are based on transthoracic or whole-body electrical impedance, finger-cuff plethysmography, ultrasound, or peripheral arterial catheterisation and arterial wave form analysis, facilitating advanced pathophysiological insight while avoiding the risks of historic invasive techniques. Their use in recent studies has improved the evidence base for haemodynamics during CD,\textsuperscript{53,56} but only few single cases have been examined with modern technology during labour.\textsuperscript{53} The minimally invasive device LiDCOplus provides calibrated beat-by-beat data on blood pressure, HR, SV, CO, and SVR, and is valid in detecting rapid changes in haemodynamic trends.\textsuperscript{53,57}

Prior to Study I, only two studies on the prevention of spinal hypotension in healthy pregnant women during CD used continuous minimally invasive haemodynamic monitoring.\textsuperscript{19,32} None of the previous studies on lower limb compression has, to our knowledge, measured blood pressure continuously or examined haemodynamic variables other than blood pressure.\textsuperscript{2,37-41} We are not aware of any previous study that has achieved performing continuous CO measurements during all stages of labour.
2 REVIEW OF THE LITERATURE

2.1 Prophylactic Methods against Spinal Hypotension during Caesarean Delivery

The importance of the prevention of spinal hypotension during CD was emphasised by the Cochrane Collaboration in 2006. They concluded that maternal hypotension has an incidence approaching 100%, and may not only lead to nausea and vomiting, but also to more serious complications, such as impaired consciousness and pulmonary aspiration for the mother, and hypoxia, acidosis, and neurological injury for the baby. Despite intense research over the past decades, however, no ideal preventive technique had been established yet, and spinal hypotension remained a common clinical problem.²

At that time, profound venodilation, with a following reduction of venous return and CO, was considered the primary cause of spinal hypotension, aggravated to some degree by aortocaval compression from the uterus.² Current prophylactic strategies therefore mainly focused on improving venous return to the heart. The spectrum of studied interventions included several variants of maternal positioning to influence distribution of anaesthesia and of circulating blood, various intravenous fluid regimens to enlarge effective blood volume, and different techniques of lower limb compression to minimise peripheral venous pooling. Other studies, by contrast, explored vasoactive drugs. Most of these trials examined ephedrine, and a few trials examined phenylephrine, metaraminol, angiotensin, or dopamine.²

The Cochrane Collaboration assessed 75 randomised controlled trials comparing prophylactic interventions. Whereas most methods had some preventive effect, no single intervention eliminated the need for additional treatment of spinal hypotension.²

Phenylephrine

This pure α₁-adrenergic agonist causes vasoconstriction via stimulation of post-synaptic α₁-fibres, and thereby increases SVR. Its use had already been reported in the 1970s,⁵⁸,⁵⁹ but then generally been avoided for several decades, because of concerns about its potential adverse effects on uterine blood flow.⁶⁰ However, a favourable effect of α₁-adrenergic agonists on maternal blood pressure in a few studies⁶¹-⁶⁴ inspired Ngan Kee et al. to conduct research into α₁-adrenergic agonists. They first examined metaraminol⁶⁵ and then phenylephrine,⁶⁶ showing that it was efficient in preventing spinal hypotension without leading to neonatal acidosis. After a previous Cochrane review had suggested directing future research to a combination of interventions,⁶⁷ Ngan Kee et al. completely averted a decrease in blood pressure by combining a prophylactic high-dose phenylephrine infusion with rapid crystalloid cohydration in 2005.⁶⁸ This study marked a turning point in the prevention of spinal hypotension. Ngan Kee et al. followed up by showing that preventive phenylephrine caused less neonatal acidosis than ephedrine when each of the drugs was used in high doses,⁶⁹,⁷⁰ and by focusing on the dosage regimen of phenylephrine.⁶⁶,⁶⁸,⁷¹-⁷⁴
Most Ngan Kee’s work aimed at keeping the blood pressure close to baseline, by fine-tuning continuous high-dose infusions started at rates around 100 µg/min, lately even by the sophisticated method of closed-loop feedback computer control. However, the price for incidences of hypotension down to 1.9% were concomitantly high incidences of reactive hypertension (up to 47%) and of bradycardia (up to 32%). Ngan Kee accepted these with the argument of unabated maternal wellbeing and excellent neonatal outcomes.

The high-dose approach was questioned in 2008 by Langesæter et al., who introduced a model of weight-based low-dose phenylephrine infusion. A continuous rate of 0.25 µg/kg/min (resulting in doses between 15 µg/min and 25 µg/min), together with moderate crystalloid coload (750 ml NaCl), reduced the incidence of rescuepressor-requiring SHT to 40%, and to 25% when combined with low-dose spinal anaesthesia. While an initial drop in blood pressure was not prevented by either of the regimens, the severity of hypotension was significantly reduced and no reactive hypertension occurred.

More importantly, using continuous minimally invasive monitoring, Langesæter et al. demonstrated that spinal anaesthesia leads to an immediate and profound reduction in SVR, and a compensatory increase in CO. In 2009, Dyer et al. confirmed these findings, also with the use of beat-by-beat monitoring. These two studies contradicted the historic concept, which had postulated that impairment of venous return and, consequently, of CO, were the primary cause of spinal hypotension. The observation that arterial instead of major venous dilation is the main haemodynamic effect of spinal anaesthesia explains the superiority of α₁-adrenergic agonists over methods increasing venous return. This shift in pathophysiological understanding of spinal hypotension was supported by an editorial by Sharwood-Smith and Drummond.

Dyer et al. also demonstrated the haemodynamic effects of therapeutic boluses of 80 µg phenylephrine, which were an increase in SVR of approximately 75%, and a decrease in CO of about 25%, and suggested that phenylephrine boluses should be lower than 80 µg. The authors recommend the use of low-dose phenylephrine, emphasising the adverse impact that reactive hypertension with subsequent bradycardia and reduced CO may have on pregnant women with cardiac risk factors, and, via reduction of uteroplacental bloodflow, on predecitly compromised foetuses. Based on the observation of a strong correlation between CO and HR, HR might serve as a clinical surrogate marker for CO in parturients without advanced haemodynamic monitoring, and should be kept close to baseline during spinal anaesthesia for CD.

In terms of neonatal outcome, Dyer et al. confirmed that ephedrine causes more acidosis than phenylephrine, but reasoned that the extent of this acidosis is probably without clinical significance in healthy neonates. Clinical neonatal outcomes were excellent in spite of umbilical cord acidosis after high doses of ephedrine, and more placental drug transfer of ephedrine than of phenylephrine in previous studies, and both phenylephrine and...
Ephedrine are considered safe for the foetus when used in normal clinical doses in healthy parturients. The most relevant clinical advantages of phenylephrine over ephedrine are thus quicker onset of action, and better restoration of maternal haemodynamics. Vasopressor choice should therefore be guided by maternal circulation. That means using phenylephrine as first-line agent against the typical response to spinal anaesthesia, which is hypotension accompanied by tachycardia, and using ephedrine and an anticholinergic in the rarer case of hypotension and immediate bradycardia.

After Study I had been started in 2009, several trials on different phenylephrine regimens reinforced the evidence in favour of low continuous rates. Using a suprasternal Doppler technique, Stewart et al. demonstrated clinically insignificant improvement of blood pressure stability at the expense of significantly more pronounced reduction in HR and CO (by 20%), when comparing high with moderate and low infusion rates (100 µg/min versus 50 µg/min and 25 µg/min). Their observations were supported by Allen et al., who reported dose-dependent decreases in incidence and severity of hypotension, but corresponding increases in incidence of hypertension (up to 82%) and bradycardia (up to 32%); in conjunction with crystalloid coload, rates of 25 µg/min and 50 µg/min obtained the best overall haemodynamic stability when compared to rates of 75 µg/min and 100 µg/min. A clinically titrated moderate dose regimen (starting at 67 µg/min after moderate crystalloid prehydration) by Cooper et al. generated similar incidences of hypotension and hypertension as the above-mentioned moderate infusion rates.

In 2012, Doherty reported that high-dose phenylephrine infusion (120 µg/min), compared with boluses (120 µg) given in response to blood pressure at or below baseline, resulted in a higher total phenylephrine dose, but in a similar decrease in blood pressure and cardiac output, and in similar incidences of hypotension, hypertension, bradycardia, and nausea. Slightly better attenuation of the initial decrease in blood pressure was achieved by intermittent boluses (5% versus 10% decrease from baseline), the size of which was based on calculations on ED95 from a previous study. Against the background of the haemodynamic changes observed by non-invasive CO monitoring, Doherty contemplated the benefit of an initial bolus dose, but joined authors arguing for low-dose infusion rates.

In 2013, Ngan Kee et al. administered phenylephrine at a moderate start rate (50 µg/min) by a closed-loop titration system, and used suprasternal Doppler ultrasound to assess the prophylactic effect of glycopyrrolate on cardiac output. An increase in HR and CO, but also in incidence of hypertension (44% versus 17%), as well as a decrease in accuracy of blood pressure control, and similarly low incidences of bradycardia, hypotension, and nausea in the glycopyrrolate versus the control group, led to the conclusion that maintaining CO by careful vasopressor titration might be a more advantageous strategy than routine use of anticholinergic drugs for the prevention of bradycardia. Of note, the median phenylephrine rates administered by the computer-controlled system were 31 µg/min and 34 µg/min,
respectively, and 40 µg/min in a study comparing computer-controlled with manually controlled phenylephrine infusion, i.e. rather low continuous doses. Closed-loop systems as investigated by Ngan Kee adjust vasopressor doses based on blood pressure only, and should probably be improved by some algorithmic adjustments such as integration of HR, in regard to overall haemodynamic condition. Because this league of technical sophistication is in any case unlikely to reach widespread clinical availability in the near future, variable-rate infusions based on a clinically guided titration protocol have been recommended as a more realistic clinical approach on a global basis. 

As several recent reviews sum up, studies during the past decade have improved the understanding and management of spinal hypotension considerably. Continuous invasive monitoring has led to the paradigm shift that spinal hypotension is primarily caused by a reduction in afterload due to arterial vaso-dilation, and not by a reduction in preload and CO due to increased venous capacitance. Phenylephrine has been established as the prophylactic and therapeutic vasopressor of choice, and the evidence base on its use is growing, but the debate on the optimal dosing regimen in terms of balancing hypotension against the adverse effects of reactive hypertension, bradycardia and low cardiac output, has not been concluded. Based on publications before the start of Study I, we reasoned that the integration of an initial bolus into a low-dose continuous infusion model could prevent the rapid initial decrease in blood pressure, while avoiding the side effects from higher phenylephrine infusion rates.

**Lower limb compression**

In the 2006 Cochrane review, pooling of seven methods for lower limb compression showed a moderate stabilising effect on blood pressure compared to control. Already five decades ago, the idea of impeding blood redistribution to the lower extremities in order to sustain venous return and thus reduce spinal hypotension, had inspired the investigation of inflatable boots during CD. In that study, no positive effect on blood pressure was found, but it was noted that the omission of left uterine displacement may have contributed to the negative findings. Fifteen years later, inflatable splints were shown to reduce hypotension from an incidence of 83% to 48%, but the reliability of the method was considered low. A sequential compression device in combination with thromboembolic deterrent stockings merely led to a small and non-significant reduction in hypotension; however, the study design suffered from serious methodological weaknesses (lack of blinding, unclear randomisation and allocation concealment, and protocol violations concerning vasopressor treatment). Another study found that the same device reduced the incidence of mean arterial pressure hypotension from 92% to 52%.

In 1996, compression stockings were shown to reduce nausea and vasopressor use compared with a control group. The reduction in incidence of hypotension by 29% lacked statistical significance, which was attributed to low power in connection with the small study.
In another trial thromboembolic deterrent stockings were found neither able to prevent hypotension nor to reduce vasopressor need compared with compression stockings, probably because of the lower pressure they exerted. The first study using elastic bandages reduced both the incidence (17% vs 83% control) and the severity of hypotension, measured at one-minute intervals, in 1990, but the sample size was small. The findings were partly confirmed by a larger trial documenting significantly lower incidence (18%) versus the control (53%). According to the authors, the likelihood of hypotension with leg wrapping was one fifth compared to no intervention, both in their own study and in the precedent one on inflatable splints by Goudie. Elastic bandages reduced the incidence of hypotension compared to the control in another larger study at that time (15% versus 54%), and in a very recent one (40% versus 70%), but measurement intervals in both studies were very wide (five minutes). Also a study testing leg wrapping against a control under epidural anaesthesia found the incidence of hypotension to be diminished (23% versus 50%).

The first trial comparing phenylephrine with leg wrapping was performed by Bjørnestad et al., with blood pressure measurements at two-minute intervals, in parturients that were anaesthetised with epidural anaesthesia for CD. Leg wrapping achieved a similar incidence of hypotension as phenylephrine given in three boluses (50 µg) at five-minute intervals, but, owing to the lack of a control group, the magnitude of the methods’ prophylactic effect remains uncertain. Definition of hypotension as a 30% decrease from the baseline complicates the comparison of incidences with the majority of recent publications, as the latter generally refer to a 20% threshold.

2.2 Research on Haemodynamics during Labour and Vaginal Delivery

Hendricks and Quilligan were among the pioneers of haemodynamic research in labouring parturients when they used the pulse pressure method to measure CO in 20 healthy parturients during different labour stages in 1956. They found a 30% rise in CO ‘during effective contractions’, a small drop in CO during ‘bearing down effort without a contraction’, and a possible increase in CO during ‘bearing down effort with a contraction’. They described a continuous rise in baseline CO (i.e. CO ‘at rest’ between contractions) during the first labour stage, a further rise during delivery, and an additional small rise during some minutes postpartum in some of their patients. The authors acknowledged that heterogeneous timing and frequency of measurements, as well as limitations of the monitoring method, impaired the validity of their results. Nonetheless, their study was the first one to examine CO during labour, and represented an important scientific step at the time.

In 1958, Adams and Alexander followed up by using a blue dye dilution technique to measure CO during labour stage 1 in 21 healthy parturients. During contractions, CO increased in 17
of the 21 parturients (by 20%), but in contrast to the study of Hendricks and Quiligan, no cumulative increase in baseline HR, SV, or CO during labour was found.

In 1966, Winner and Romney used green dye dilution for CO measurements in five healthy parturients. During stage 1 contractions, the authors found increases in SAP and HR, and either increases (by up to 25%) or decreases (by up to 20%) in CO. Interestingly, the rises in SAP and HR started prior to palpable contractions. The authors hypothesised that the increases in SAP were due to increased intrathoracic pressure and to smooth vascular contraction that occurred simultaneously with myometrial contractions. Cardiac output measurements during contractions were unreliable because the technique demands steady CO. Under bearing down effort, SAP and HR increased more than during stage 1, but the authors did not succeed in detecting CO at all. Based on central venous pressure (CVP) and right ventricular pressure changes, they postulated that CO diminished during expulsive effort. They further assumed that SV was slightly diminished during contractions, owing to decreased filling or increased emptying caused by tachycardia. As in the study of Adams and Alexander, no cumulative increase was found in the baseline values of any haemodynamic variables. Postpartum measurements were inconsistent between parturients.

In 1966, Hansen and Ueland observed increases in SAP (by 11%), CO (by 15%), and SV (by 25%), and decreases in HR (by 6%) during contractions in early stage 1 in an unreported number of healthy parous women. Using green dye dilution, the authors compared the effect of different analgesic blocks on serial CO measurements. In a subgroup with paracervical and pudendal block, CO at rest increased progressively during labour (by 40%) and postpartum (by 60%), due to increases in both HR and SV. In parturients with caudal analgesia, there was no cumulative change in baseline CO during labour, but a postpartum increase in CO (by 60%) and SV (by 80%).

In 1969, Ueland and Hansen again reported a decline in HR (by 15%), and a rise in CO (by 25%) and SV (by 33%), during first-stage contractions, measured with green dye dilution in 23 healthy women in oxytocin-induced labour. This time, they examined the haemodynamic effect of position in nine of the parturients, and found that changes during contractions were greater in the supine than in the lateral position. Baseline SV and CO, by contrast, were higher in the lateral position. The authors speculated that scopolamine had been the cause of tachycardia and decreases in SV during contractions in previous studies. With 15 single measurements of CO in each of 23 supine parturients, they found an increase in CO (by 15% to 20%) during contractions in labour stage 1. CO and SV were not measured during stage 2 contractions, but CVP and SAP increased during bearing-down effort. Comparing 10 parturients with local analgesia to 13 parturients with caudal analgesia, progressive rises in baseline HR, SV, and SAP during labour were found in the former but not in the latter. A cumulative increase in baseline CO under local analgesia (by 50%) was higher than under caudal analgesia (by 23%). After delivery, CO increased (by 80% versus 60%) in both groups. The authors concluded that caudal block limited the cumulative increase in baseline
CO, but not the increase in CO during contractions or posture changes. They assumed that blood redistribution was the common etiologic factor behind CO changes during contractions, posture changes and postpartum.

In 1970, Lees et al., using green dye dilution in five healthy parturients with epidural analgesia, found a CO rise (by 20% to 30%), together with increased SV and SAP and unchanged HR during stage 1 contractions. Also this group failed to monitor CO during stage 2 contractions. The authors found no cumulative increase in CO during labour, but a postpartum increase in CO (by 40%) due to higher SV. They attributed the rise in CO during contractions to myometrial autotransfusion, the cumulative increase in CO in some of the previous studies to pain, and the postpartum rise in CO to caval relief. They hypothesised that the volume of a possible postpartum autotransfusion is exceeded by the average blood loss during delivery, and hence does not contribute to increased CO.

In 1970, Niswonger and Langmade compared CO, SVR, HR, and CVP during spinal analgesia/anaesthesia in 11 vaginal deliveries and nine caesarean deliveries. Using green dye dilution, they performed five haemodynamic measurements in each parturient; right before and right after induction of anaesthesia, twice (probably at rest) during the period of delivery, and postpartum. They found a decrease in SVR and an increase in CO (by 20%) postpartum. Of note, postpartum measurements were taken some unspecified time after injection of oxytocin. As there were no major differences in haemodynamic values between the groups, they postulated that CD does not reflect an increased ‘cardiac strain’.

In 1987, Robson et al. performed Doppler and cross-sectional echocardiography at three points in time during labour stage 1 in 15 healthy women. Increases in SAP, HR, SV, and CO (by up to 34%) during contractions became greater with the progression of labour. Cumulative increases in baseline SAP, SV, and CO (by 12%) were also observed.

Ten years later, Filippatos et al. questioned the results of all previous studies, pointing out the low validity of dye dilution and Doppler measurements in rapidly changing haemodynamic conditions. He himself used bio-impedance in 10 healthy parturients, and found an increase in CO (by 84%) during stage 1 contractions. This was mainly caused by an increase in SV, which the author attributed to adrenergic stimulation and blood redistribution from the uterus. Measurements during stage 2 contractions failed, because of too much noise. Baseline CO was higher in stage 2 than in stage 1, but did not increase any further after delivery. Filippatos explained the absence of a postpartum increase in CO as being due to blood loss during delivery.

A case report in 2009 described a 50% reduction in CO, a 50% elevation in SVR, a 40% increase in SAP, and up to a more than 85% increase in HR during stage 2 contractions in an almost painfree pre-eclamptic parturient with effective epidural analgesia. Haemodynamic variables were monitored with the LiDCO plus device. To our knowledge, this is the first...
publication based on minimally invasive continuous monitoring, and the first time that CO measurements were achieved during bearing-down effort.

In 2011, using electrical velocimetry, Archer showed higher baseline CO in left than in right lateral position, and increases in CO during a few contractions in a pre-eclamptic parturient.\(^9\)

In summary, there is scarce, conflicting evidence on haemodynamic changes during labour.\(^{18,49}\) Formerly employed monitoring techniques suffered from disadvantages such as a high degree of invasiveness, low frequency of measurements, and limited reliability in unstable haemodynamic conditions.\(^{18}\) These studies represented important scientific progress at the time, and have created basic knowledge of the haemodynamic impact of labour. Continuous measurements with modern minimally invasive technology might help to deepen pathophysiological insight. Successful CO monitoring with LiDCOplus during labour in the published\(^{49}\) and some unpublished cases at Oslo University Hospital inspired us to study haemodynamic changes during the entire course of labour in Study II.
<table>
<thead>
<tr>
<th>Monitoring technique for CO</th>
<th>Parturients analysed (n)</th>
<th>Baseline</th>
<th>Changes during contractions</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>During labour</td>
<td>Post-partum</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CO</td>
<td>CO</td>
</tr>
<tr>
<td>Hendricks and Quiligan 1956</td>
<td>Pulse Pressure 20 parturients with different types of analgesia</td>
<td>Cumulative increase</td>
<td>Small increase in some parturients</td>
</tr>
<tr>
<td>Adams and Alexander 1958</td>
<td>Evans blue dye dilution 21</td>
<td>=</td>
<td>=</td>
</tr>
<tr>
<td>Winner and Romney 1966</td>
<td>Indo cyanine green dye dilution 5 parturients with inhaled, local, and intravenous analgesia</td>
<td>=</td>
<td>Inconsistent</td>
</tr>
<tr>
<td>Hansen and Ueland 1966</td>
<td>Indo cyanine green dye dilution Unspecified n with pudendal block</td>
<td>Cumulative increase up to +40%</td>
<td>+11%</td>
</tr>
<tr>
<td>Ueland and Hansen 1969</td>
<td>Indo cyanine green dye dilution 10 parturients with local analgesia</td>
<td>Cumulative increase up to +50%</td>
<td>+12%</td>
</tr>
<tr>
<td></td>
<td>13 parturients with caudal analgesia</td>
<td>Cumulative increase up to +23%</td>
<td>+10%</td>
</tr>
<tr>
<td>Lees et al. 1970</td>
<td>Indo cyanine green dye dilution 5 parturients with epidural analgesia</td>
<td>=</td>
<td>+40%</td>
</tr>
<tr>
<td>Niswonger and Langmade 1970</td>
<td>Indo cyanine green dye dilution 11</td>
<td>n.r.</td>
<td>+20%</td>
</tr>
<tr>
<td>Robson et al. 1987</td>
<td>Doppler echocardiography 15</td>
<td>Cumulative increase up to +12% in stage 1</td>
<td>n.r.</td>
</tr>
<tr>
<td>Filippatos et al. 1997</td>
<td>Bioimpedance 10</td>
<td>Increase up to +23% in stage 2</td>
<td>n.r.</td>
</tr>
</tbody>
</table>

Exhaustive presentation of the heterogeneous studies would exceed the capacity of this table, thus only a few basic characteristics and findings are displayed. n: number of parturients. Postpartum: the immediate postpartum period. n.r.: not reported. ‘=’: no change. ‘+’: increase. ‘-’: decrease.
3 AIMS OF THIS THESIS

The purpose of this thesis is to improve insight into maternal haemodynamics during caesarean and vaginal delivery.

The aim of Study I was to compare the effect of prophylactic low-dose phenylephrine infusion to the effect of leg wrapping, and to the effect of sham treatment on maternal haemodynamics during spinal anaesthesia for CD. Specific objectives were to:

1. compare the effect of the three interventions on SAP;
2. compare the effect of the three interventions on HR, SVR, SV, and CO;
3. examine the haemodynamic effects of a regimen with an initial phenylephrine bolus before low-dose phenylephrine infusion; and
4. compare the indirect effect of the three interventions on the condition of the newborn, i.e. on Apgar scores, and on umbilical vessel BE and pH.

The aim of Study II was to examine the effect of labour and VD on maternal haemodynamics. Specific objectives were to:

5. compare SAP, HR, SVR, SV, and CO during contractions with baseline values in each labour stage;
6. compare SAP, HR, SVR, SV, and CO during contractions across labour stages;
7. compare SAP, HR, SVR, SV, and CO values at baseline across labour stages; and
8. assess the effect of epidural analgesia on haemodynamics.
4 METHODS

Papers I and II contain thorough descriptions of the respective methods. This section therefore confines itself to a brief summary of the methods, and a few additional details that are not mentioned in the papers.

4.1 Basic Methodological Characteristics

Table 2. Overview of Study Design

<table>
<thead>
<tr>
<th></th>
<th>Study I</th>
<th>Study II</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Population</strong></td>
<td>Healthy parturients at term</td>
<td>Healthy parturients at term</td>
</tr>
<tr>
<td><strong>Sample size</strong></td>
<td>120</td>
<td>20</td>
</tr>
<tr>
<td><strong>Design</strong></td>
<td>Randomized controlled trial</td>
<td>Observational study</td>
</tr>
<tr>
<td></td>
<td>• Double-blinded, parallel group</td>
<td>• Prospective</td>
</tr>
<tr>
<td></td>
<td>• Three treatment arms:</td>
<td>• One cohort</td>
</tr>
<tr>
<td></td>
<td>• Phe: Prophylactic phenylephrine (bolus of</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.25 µg/kg followed by infusion 0.25 µg/kg/min)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Leg: Prophylactic leg wrapping</td>
<td></td>
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<tr>
<td></td>
<td>• Control: Sham treatment</td>
<td></td>
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<tr>
<td></td>
<td>All groups received cohydration with</td>
<td></td>
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<tr>
<td></td>
<td>1000 ml 0.9% saline infusion.</td>
<td></td>
</tr>
<tr>
<td><strong>Primary outcomes</strong></td>
<td>SAP</td>
<td>SAP, HR, SVR, SV, CO</td>
</tr>
<tr>
<td></td>
<td>• Decrease after induction of spinal anaesthesia, prior to delivery</td>
<td>• Change during contractions in each labour stage</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Change during contractions across labour stages</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Change in baseline values across labour stages</td>
</tr>
<tr>
<td><strong>Secondary outcomes</strong></td>
<td>HR, SVR, SV, CO</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Change after induction of spinal anaesthesia, prior to delivery</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Umbilical cord blood gas values</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Apgar scores after delivery</td>
<td></td>
</tr>
<tr>
<td><strong>Monitoring technique</strong></td>
<td>Continuous minimally invasive haemodynamic monitoring by LiDCOplus</td>
<td>Continuous minimally invasive haemodynamic monitoring by LiDCOplus</td>
</tr>
<tr>
<td><strong>Main data material</strong></td>
<td>Repeated haemodynamic measurements</td>
<td>Repeated haemodynamic measurements</td>
</tr>
<tr>
<td></td>
<td>• Analysis period of 13 minutes</td>
<td>• Mean monitoring period of 6 h</td>
</tr>
<tr>
<td></td>
<td>• Mean number of beat-by-beat measurements per variable per parturient in final dataset: 1200</td>
<td>• Mean number of beat-by-beat measurements per variable per parturient in final dataset: 3100</td>
</tr>
<tr>
<td><strong>Main statistical analysis</strong></td>
<td>Linear mixed model</td>
<td>Marginal linear model</td>
</tr>
<tr>
<td></td>
<td>• Analysis of continuous changes as a function of time, modified for non-linearity</td>
<td>• Analysis of continuous changes within strata (baseline, min, max) across labour stages</td>
</tr>
<tr>
<td><strong>Other statistical analyses</strong></td>
<td>One-way ANOVA and pairwise t-test, Kruskal-Wallis and pairwise Mann-Whitney U test, Pearson’s χ² test</td>
<td>Pairwise t-test, Kruskal-Wallis test, Pearson’s χ² test</td>
</tr>
</tbody>
</table>
4.2 Study Population

The target populations of our studies were healthy pregnant women at term, carrying a single healthy foetus that was planned to be delivered by elective CD (Study I) or spontaneous VD (Study II).

The sample size calculation for Study I is described in Paper I. Study II was performed in a convenience sample of 20 parturients. To ensure adequate power before the study start, we estimated the sample size needed for a paired-means test, based on the assumption that the changes during contractions in our sample might be half as pronounced as the changes observed in a previous case report. For changes during contractions, an assumed difference in CO of 25% (1.5 l/min, SD 1.5) from baseline gave an effect size of 1.0. With an \( \alpha \)-level of 0.05, a power level of 95% could be achieved with a sample size of 13 parturients. For the comparison of baselines, a difference of 10% in CO (0.6 l/min, SD 0.7) was considered clinically interesting. With the resulting effect size of 0.85, and an \( \alpha \)-level of 0.05, a power level of 95% could be achieved with a sample size of 17 parturients. The same algorithms were applied for each of the other haemodynamic outcomes, and similar or lower required sample sizes were found. We recruited the intended group size of 20 to compensate for possible dropouts.

The samples were obtained at regional health care institutions with broad demographic coverage in Oslo and surroundings. Participants for Study I were informed and recruited a few weeks prior to their scheduled CD, in the context of routine anaesthesiologic consultation before elective surgery. Inclusion and exclusion criteria were checked; parity status was not considered. Most of the participants were operated on the originally planned date. Scheduled participants who were operated on an earlier than the planned date due to the onset of labour, were not included. Participants for Study II were recruited when they arrived at the labour ward in active labour. Study inclusion was performed at any time of the day. All eligible parous and nulliparous women were asked to participate, but only one parturient at a time could be included.

4.3 Ethical Approval

Both studies were approved by the Regional Committee for Medical and Health Research Ethics of Southern Norway, and by the Data Inspectorate at Oslo University Hospital. Study I, a clinical trial testing medical treatment, was also approved by the Norwegian Medicines Agency, and registered before patient enrolment with the European Union Drug Regulating Authorities Clinical Trials (EudraCT) database and ClinicalTrials.gov.

Both studies were conducted according to Good Clinical Trial Practice and the principles of the Declaration of Helsinki. Participants in both studies gave written consent after thorough oral and written information, prior to their inclusion, and were allowed to withdraw / resign from participation at any time before, during, and after the study.
All study data were de-identified immediately after inclusion of each participant, and stored separately from identifying personal patient information. The collected data was accessible for, and handled by, the investigating research team exclusively.

4.4 Main Haemodynamic Monitoring Method

Continuous haemodynamic measurements were performed with the LiDCOplus monitor (LiDCO Ltd., Cambridge, United Kingdom).91 This is a minimally invasive device able to monitor several haemodynamic variables via a peripheral arterial cannula. The technology is based on pulse power analysis.92 A primary algorithm, PulseCO, continuously calculates beat-to-beat SV by analysing the arterial waveform.93 PulseCO assumes that the input of a mass of blood and the subsequent loss of a mass of blood to the periphery result in a net power change per heartbeat. The employed autocorrelation is a time-based method; in contrast to Fourier analysis, it avoids a frequency approach and thus limits the effects of arterial damping. PulseCO is coupled to a secondary algorithm, LiDCO. The latter uses a single-point lithium indicator dilution system to measure absolute SV, after peripheral intravenous injection of a small single dose of lithium chloride. This absolute SV value is used for calibration of the PulseCO. The LiDCOplus derives beat-to-beat blood pressure, HR, SV, CO, SVR, as well as cardiac index, systemic vascular resistance index, and oxygen delivery from the arterial curve.

4.5 Data Material

Studies I and II consist of two datasets each: one with demographic and single-value clinical characteristics, and one with a large number of longitudinally measured haemodynamic data.

Haemodynamic measurements were registered by the LiDCOplus monitor, and downloaded both as visual ‘.lvu’ files and as ‘.csv’ text files for each parturient.

The haemodynamic raw data for 120 parturients in Study I consist of approximately 3.6 million repeated beat-by-beat measurements in total, 6,000 per haemodynamic variable per parturient. Haemodynamic analyses were run for the first 13 minutes, which equaled the shortest interval from induction of spinal anaesthesia to delivery, and permitted to capture the rapid haemodynamic changes after spinal induction while avoiding the artefacts that delivery, subsequent movement, and uterotonic medication may create. The data for this analysis period in the 112 included parturients consist of approximately 655,000 beat-by-beat measurements in total, i.e. 1,200 per haemodynamic variable per parturient.

The haemodynamic raw data for the entire course of labour in the 20 included parturients in Study II consist of more than 1.8 million repeated beat-by-beat measurements in total. Haemodynamic analyses were run for baselines, and for minima and maxima during contractions that were measured in tilted supine or dorsal lithotomy positions, and that were undisturbed by maternal activities, medical procedures, or obvious noise. The processed dataset, after, according to the criteria described below, cleansing and extraction of analysis
periods, consists of approximately 311,000 beat-by-beat measurements in total, on average
3,100 per haemodynamic variable per parturient.

Preparing the datasets for statistical analysis was a very time-consuming process. Several
rounds of meticulous manual review of the vast amount of measurements were necessary for
definition of analysis periods and cleansing of raw data, prior to final analysis by mathematical
and statistical software. LiDCOview PRO software (LiDCO Ltd.) was used for inspection of
‘.lvu’ files, and Excel version 14.3.2 (Microsoft, Redmond, WA) was used for examination and
processing of ‘.csv’ files.

Individual ‘.lvu.’ files, ‘.csv’ files, and case report forms of each participant were scrutinized
parallel to one another, to ensure that all relevant events (administration of medicines,
changes of position, e.g.) had been registered electronically, with correct coding for type and
point of time.

The individual datasets were then re-examined to identify extreme values and outliers.
Extreme values often occur blockwise, as a result of wire vacillation or arterial line
obstruction.\textsuperscript{94} The LiDCOplus monitor automatically identifies the majority of such corrupted
records, and labels them as ‘bad status’. Thorough manual review of the entire dataset was,
however, necessary to identify unrecognized values outside any reasonable range. In the
event of frequent or prolonged periods with extreme values, exclusion of the entire case due
to low data reliability had to be considered (at this stage). For this first, crude cleanse, cut-off
limits were set for CO at <2 and >20 l/min, for HR at >200 beats/min, for SVRI at >6000
dynes/s/cm\textsuperscript{5}, and in Study II for SAP at <60 mmHg, wide enough to ensure that only clearly
corrupted records would be excluded.

Another review of all individual files was dedicated to identifying single-point values with
sharp deviation from the adjacent beat-to-beat values. Such artefacts may be caused by, e.g.,
extra or skipped heartbeats, or sudden movements.\textsuperscript{94} The cut-off limits were set individually
for each patient file, based on clinical discretion.

In Study I, these cleansing steps were performed using MATLAB version R2013a (The
MathWorks, Natick, MA). Remaining artefacts were eliminated by running an artefact removal
algorithm described by Deegan et al.\textsuperscript{95} and were replaced using nonlinear interpolation. The
uneven sampled beat-to-beat dataset was transformed into sliding averages with a window
size of ten seconds and a slide of five seconds. The purposes of this transformation were
smoothing the data and reducing the number of observations for a given period of time. After
completion of the cleansing and transformation processes, the final dataset was read into the
statistical software, and the randomisation codes were released by the hospital pharmacy.
Individual traces were merged into one summarising graph per treatment group, and group
comparisons were performed using linear mixed models.
In Study II, cleansing was performed using Excel software. The final dataset was constructed by extraction of repeated individual baseline values from each stage, and repeated individual minima / maxima during contractions from each stage, based on the criteria described in the data analysis section in Paper II. Summary measures were calculated in Excel, and the final dataset was read into the statistical software for analysis of haemodynamic changes during the different stages of labour by marginal linear models.

### 4.6 Statistical Models

Descriptive data were analysed with appropriate tests for single-point comparisons (1-way ANOVA and pairwise t-test, Kruskal-Wallis and pairwise Mann-Whitney U test, Pearson’s χ² test) in SPSS (Version 22.0; IBM Corp Armonk, NY, USA) in both studies.

Haemodynamic data were analysed with a linear mixed model (SPSS) in Study I, and with a marginal linear model (Stata Statistical Software: Release 14; StataCorp. 2015, College Station, TX, USA) in Study II.

The linear mixed model was used for analysis of continuous changes in haemodynamic variables as a function of time, with treatment groups as fixed factors. Baseline differences were adjusted for by excluding the main effect of the group from the model. The dynamism in haemodynamic trends was accounted for by introducing a quadratic effect of time (uncentred). Dependencies in the data and inhomogeneous variances among the groups were handled by introducing a random intercept and a random effect of time. Adjustment for multiple between-group comparisons was handled ad modum Bonferroni.

The marginal linear model was used to assess haemodynamic changes across stages, by strata (baseline, minimum, maximum). Stage, parity, epidural analgesia, and oxytocin infusion were treated as fixed factors; epidural and oxytocin infusion could vary within parturients during the course of labour. Within-subject correlation was allowed for by using the robust variance estimator for estimation of standard errors. Sensitivity analyses were performed by running the same marginal linear models without adjusting for any factors other than stage.
5 SYNOPSIS OF RESULTS

Figure 1 shows patient numbers and group allocation in Study I.

For Study II, the logistic organisation of study inclusion prevented identification of the total number of eligible parturients during the enrolment period. Non-inclusion of parturients assessed for eligibility was mainly due to either latent, advanced, or induced labour. Approximately one third of the eligible parturients that were informed about the study declined taking part, because of reservations against participation in research projects or against arterial cannulation during labour. Of the 20 included parturients, 19 were followed until the early postpartum period, and one was lost to follow-up during late stage 1 because of obstetric indication for caesarean delivery.
5.1 Results of Study I

1. SAP was highest in the phenylephrine group (phe), with
   - less continuous SAP decrease than in leg (p = 0.013) and control (p < 0.001)
   - less maximal SAP decrease than in leg (p = 0.031) and control (p < 0.001)
   - shorter duration of decreasing trend in SAP than in leg and control
   - lower incidence of hypotension than in control (p = 0.016).

   SAP was higher in the leg wrapping group (leg) than in the control group (control), with
   - less continuous SAP decrease than in control (p < 0.001).

2. All groups had a rapid decrease in SVR, and a rapid increase in SV, HR, and CO. The respective initial changes were followed by a gradual inverse trend. Comparing groups,
   - continuous SVR was higher in phe than in leg (p < 0.001) and control (p < 0.001)
   - continuous SV was higher in phe (p = 0.001) and leg (p < 0.001) than in control
   - continuous HR was lower in phe than in leg (p = 0.002) and control (p = 0.002)
   - continuous CO was lower in phe (p < 0.001) and control (p = 0.001) than in leg.

3. There was no reactive hypertension in any of the groups. The incidence of bradycardic episodes was lower in phe (2.6%) than in leg (5.3%) and control (8.3%), but the difference was not statistically significant. Maximal decrease in CO was 5% below baseline in phe and similar between groups (p = 0.72).

4. Apgar and umbilical blood gas values were within normal range and without significant between-group differences, except for lower umbilical artery lactate in phe (2.2 mmol/l) than in control (2.6 mmol/l; p = 0.007), and lower umbilical vein lactate in phe (1.75 mmol/l) than in leg (1.9 mmol/l; p = 0.035) and control (2.1 mmol/l; p < 0.001).

![Figure 2. Continuous SAP during 13 minutes after spinal anaesthesia for CD, Study I](image-url)
Figure 3. Continuous SVR during 13 minutes after spinal anaesthesia for CD, Study I

Figure 4. Continuous SV during 13 minutes after spinal anaesthesia for CD, Study I

Figure 5. Continuous CO during 13 minutes after spinal anaesthesia for CD, Study I

More detailed results are presented in Paper I, and in the appendix.
5.2 Results of Study II

5. Haemodynamic changes during contractions were profound in all labour stages. The primary change was followed by a short inverse change before baseline was restored. Percentages below are mean maximum changes for the entire cohort.

During stage 1 contractions, the primary direction of changes varied between parturients. Compared to stage 1 baseline values,

- SAP increased in all parturients; maximum increase: 25% (from 136 to 171 mmHg);
- HR increased in all parturients; maximum increase: 39% (from 83 to 115 beats/min);
- SVR increased in most parturients, but decreased in some; maximum increase: 24%;
- SV decreased in most parturients, but increased in some; maximum decrease: 18%;
- CO increased in most parturients, but decreased in some; maximum increase: 52%.

During the peak of stage 2 contractions, the direction of changes was the same in all parturients. Compared with stage 2 baseline values,

- SAP increased by 36% (from 136 mmHg to 185 mmHg);
- HR increased by 52% (from 86 beats/min to 131 beats/min);
- SVR increased by 88% (from 1124 dynes/s/cm$^5$ to 2110 dynes/s/cm$^5$);
- SV decreased by 44% (from 77 ml to 43 ml);
- CO decreased by 32% (from 6.6 l/min to 4.5 l/min).

6. The extent of haemodynamic changes during contractions increased along the course of labour, and was greatest in stage 2 and during delivery.

7. Baseline values were similar throughout labour, and postpartum, for all haemodynamic variables.

8. The effects of epidural analgesia were minimal and non-significant for all haemodynamic variables.
Figure 6. Haemodynamic changes during labour, representative trace
Extract from late stage 1 (flags 42-50), stage 2 (flags 78-87) with delivery (flags 88-99), and early postpartum stage in one of the parturients.

Figure 7. Haemodynamic changes during labour, representative trace.
Extract from stage 2 (flags 23-47) with delivery (flags 48-59), and early postpartum stage in one of the parturients, in the right panel of the figure. In the left panel of the figure, flags 40-46 from the right panel are displayed in enlarged view.

More detailed results are presented in Paper II, and in the appendix.
6 METHODOLOGICAL CONSIDERATIONS

6.1 Basic Methodological Characteristics
Both studies examined the haemodynamic variables SAP, SVR, SV, HR, and CO in healthy parturients at term, using the minimally invasive monitoring method LiDCOplus, which resulted in large datasets with an excessive amount of longitudinal measurements. However, different modes of delivery and outcomes of interest in the two studies required unlike designs. For the comparison of possibly minor haemodynamic differences between three treatment arms in Study I, a large sample size and randomised, controlled double-blind design were chosen. For demonstration of profound haemodynamic changes from baseline during contractions in one cohort in Study II, a smaller sample size and prospective observational design were appropriate.

Since CD is relatively quick and follows a consistent sequence of events, the measurement period per participant in Study I was rather short (around one hour), and a predefined identical time interval was analysed in all parturients. By contrast, duration of labour and VD is less predictable, and may take many hours. In Study II, the measurement period per participant was hence longer (mean six hours), and varied between parturients (range of between two and 15 hours); data for analysis were extracted from a different number of time intervals for each parturient.

6.2 Study Population
The majority of participants in both studies were of Caucasian Norwegian origin. Apart from slight differences in age and body height, descriptive characteristics in both samples are similar to previous studies cited in our papers. Due to minor anatomical or physiological variations, the incidence of spinal hypotension, the haemodynamic reaction to prophylactic methods, and haemodynamics during labour might differ slightly between ethnic populations. We are, however, not aware of any major factors related to the composition of our study population that would limit the generalisability of our findings to the target population of healthy pregnant women at term in Norway, Europe, or on different continents.

The fact that participants were recruited a few weeks prior to inclusion in Study I allowed the parturients time for taking their decisions, and facilitated smooth preparation and logistic organisation of their study enrolment.

In Study II, direct succession of recruitment and inclusion in the study demanded a quick decision from the parturients, when active labour had started. This, and the uncertain duration of labour for each participant posed considerable logistic challenges to the investigator. A high number of parturients who did not meet inclusion criteria (predominantly because of advanced or induced labour), declined participation (mainly because of reservations against arterial cannulation or against taking part in research projects), or had exclusion criteria (pre-existing disease, or language problems preventing informed consent) led to a great deal of
time spent in the labour wards without successful inclusion of participants. Advance recruitment might have been desirable, both for participants and investigator, but would have required dayround availability of study staff, as it is impossible to predict the exact onset of spontaneous labour.

6.3 Ethical Aspects
In both studies, the use of minimally invasive monitoring required radial artery cannulation. This procedure may cause transient local pain, and potential complications include haemorrhage, nerve injury, local infection, and permanent ischaemic damage due to arterial injury or thrombosis. The overall risk of these complications is, however, very low, and arterial line placement is generally considered safe. Benefits of an arterial line include increased patient safety through continuous haemodynamic monitoring, and the possibility for taking multiple blood samples without the need for repeated vascular puncture. In all participants, contraindications for arterial line placement (e.g. signs of inadequate blood circulation to the hand, local injuries, anticoagulation, and history of conditions that increase the risk of thrombosis or impaired vascular flow such as Raynaud’s syndrome or thromboangiitis obliterans) were excluded before the procedure was carried out.

Receiving no specific prophylaxis against spinal hypotension, the control group in Study I was likely to develop a high incidence of spinal hypotension. However, continuous invasive blood pressure monitoring and a strict rescue pressor protocol ensured immediate identification and treatment of hypotension. In view of heterogeneous clinical practice with regards to monitoring intervals and prophylactic interventions, we considered a pure placebo group as justifiable in our study.

With continuous haemodynamic monitoring and constant presence of the investigating anaesthesiologist, participants in both studies had closer clinical follow-up during their CD or during labour, respectively, than non-participants.

6.4 Main Haemodynamic Monitoring Method

Choice of technology
We used the LiDCOplus monitor, because it is currently the only minimally invasive device that provides calibrated continuous data, and is valid in detecting rapid changes in haemodynamic trends. LiDCOplus is considered an appropriate device for obstetric anaesthesiologic research, and has been used in several recent studies in obstetric patients. Its reliability has been validated also in the setting of changing SVR, and its accuracy has been shown to be similar to pulmonary arterial catheter measurements in pre-eclamptic parturients. An editorial claiming limited reliability of the LiDCOplus during rapidly changing haemodynamics was based on the misconception that the method depends on pulse contour analysis using the Fourier principle. In fact, LiDCOplus employs pulse power analysis, which is a much more robust algorithm.
Alternative haemodynamic monitoring techniques include both invasive and non-invasive devices with different features. LiDCOrapid is an advanced version of PulseCO, with high trending reliability but limited accuracy due to the lack of proper calibration. Flotrac/Vigileo (Edwards Lifesciences, Irvine, California, USA) is a minimally invasive method based on pulse contour analysis. Its algorithm does not provide true continuous real-time data, its accuracy is limited due to lacking the possibility for proper calibration, and its reliability in tracking changes is restricted, particularly in settings with rapid changes in SVR. PiCCO (Pulsion Medical Systems, Munich, Germany) and pulmonary artery catheters are highly accurate, but do not provide continuous monitoring, and due to their invasiveness and the related discomfort and higher risk of complications, they are not an option for research in healthy parturients.

Among non-invasive monitoring methods, echocardiography is inappropriate for continuous monitoring. Suprasternal (SupraQ Cardiac Function Monitor, Deltex Medical Limited, Chichester, UK; USCOM Ultrasonic Cardiac Output Monitor, USCOM Limited, Sydney, New South Wales, Australia) and transoesophageal (CardioQ-ODM, Deltex Medical Limited, Chichester, Sussex, UK) aortic Doppler velocimetry devices provide beat-to-beat records of several haemodynamic variables and have been used in obstetric studies, but there are concerns about limited measurement accuracy and inter-observer variability. In addition, the suprasternal techniques are unsuitable for continuous use, and transoesophageal monitoring requires sedation or general anaesthesia. The accuracy of devices based on transthoracic or whole-body electrical resistance, i.e. classical bio-impedance, electrical cardiometry or electrical velocimetry (ICON and AESCULON Systems, Osypka Medical GmbH, Berlin, Germany) and bio-reactance (NICOM, Cheetah Medical, Portland, Oregon, USA), is limited, as is their ability to track rapidly changing trends. Moreover, the reliability of these devices is rather easily affected by diathermy, surgical manipulation, changes in peripheral vascular resistance, or patient position. Modelflow via finger-cuff plethysmography (Finometer and Portapres, Finapres Medical Systems, Amsterdam, the Netherlands) provides convenient beat-by-beat monitoring, but accuracy and precision are limited, particularly during changes in SVR, body temperature, or volume state.

Limitations of LiDCOplus
Reliability may be reduced during highly irregular arterial rate and treatment with muscle relaxants or lithium, but none of these factors pertained to any of our participants.

Because of possible minor drift in terms of accurate interpretation of absolute stroke volume, recalibration of the LiDCO device every 8 to 12 hours is recommended. Recalibration during advanced labour with frequent contractions and constantly shifting haemodynamics might be unreliable, and was therefore not carried out. In participants with longer duration of labour in Study II, measured stroke volume might thus differ slightly from the true absolute...
values. Since drift is unidirectional, this would not affect the extent of haemodynamic changes during contractions. Labour went on for more than eight hours in five parturients, and the mean duration of labour was below the recommended recalibration interval; thus the reliability of baseline measurements across stages should not be significantly diminished either. In Study I, the monitoring period was less than two hours per parturient.

LiDCO traces may be disturbed by movement, or kinking of the arterial line. Outliers and artefacts were much more frequent during labour in Study II, due to significant movement or valsalva effort, than in the relatively calm setting of elective CD in Study I. Parturients were continuously encouraged to keep their body as still as possible and their upper limb relaxed, during as many contractions as possible, also under bearing-down effort during stage 2 and delivery, and postpartum. Most parturients managed this generally well, but did move or clench their hands during a number of contractions. Artefacted measurements were not included in the final dataset.

6.5 Analysis and Presentation of Data
Preparing the haemodynamic datasets for statistical testing was the most time-consuming part of the data analysis in both studies. To ensure high reliability of the final datasets, each of the extensive raw data files was reviewed meticulously several times, for stepwise cleansing of artefacts by different criteria, and for data extraction.

Analysis period
The analysis period in Study I was a single continuous interval, with a relatively narrow time window from spinal induction to delivery of the newborn. In Study II, data extraction was complex, owing to long-lasting heterogeneous progression of labour, varying frequency and duration of contractions, changes of position, and noise during movement and obstetric procedures. Because of different cervical dilatation at study inclusion, the starting point for haemodynamic analyses varied between parturients. The total analysis period included data from multiple time intervals, the amount of which also varied between parturients. These time aspects affected the choice of statistical models for Studies I and II.

Statistics
Analysis of the vast longitudinal haemodynamic datasets required advanced statistical models in both studies. Statisticians with expertise in the field of repeated measurements therefore advised us on the choice, execution, and interpretation of the respective appropriate models.

Both the linear mixed model and the marginal linear model are extensions of ordinary linear regression that are suited to dealing with complex longitudinal data.

We chose the linear mixed model for Study I because it allows correlation of observations within subjects, and between clustered subjects, even in the case of changing variability. The
model also permits varying intra- and inter-individual spacing of measurements by flexible, regression-based handling of time,\textsuperscript{112-115} and allows modelling of more than one error term by inclusion of both fixed and random effects.\textsuperscript{112,114} Fixed effects are caused by explanatory variables that have systematic predictable influence on the outcome,\textsuperscript{115} such as treatment group. Random effects arise from non-systematic, unpredictable causes.\textsuperscript{115} The additional flexibility requires complex specifications to be incorporated,\textsuperscript{112} and the relevant details of our model are described in Paper I and section 4.6. Adjustment for multiple group comparisons is generally recommended, and in view of the relatively low number of group comparisons, we considered the Bonferroni correction as appropriate.\textsuperscript{116,117} Adjustment for multiple testing of several outcome variables is controversial\textsuperscript{116,117} and was not performed.

In general, the marginal linear model is less flexible than the linear mixed model, but also less complex, and thus suitable for analysis of unclustered longitudinal data\textsuperscript{114} as in Study II. Like the linear mixed model, the marginal linear model accounts for correlation of repeated observations within subjects and assumes independency between subjects. It also allows for a different number of repeated observations per subject, but does not require fixed starting points nor identical analysis periods in all subjects. Since inter-parturient heterogeneity in timing and amount of measurements per labour stage precluded the use of a common time axis for analyses, we categorized the observations according to cervical dilatation and stages in Study II. The detailed specifications incorporated in the model are described in Paper II and section 4.6. Study II was not primarily designed for comparison between parturients with and without epidural analgesia, but approximately half of the 1,366 summary measures per haemodynamic variable in the final dataset were from observations with epidural analgesia. For parturients with epidural analgesia, the dataset includes observations of haemodynamic data prior to initiation of epidural analgesia. Hence, assessment of epidural analgesia as an independent factor in the marginal linear models was feasible. To study the impact of epidural analgesia as a possible modifying or confounding factor, sensitivity analyses were carried out by running the same model without epidural analgesia as an independent factor.

\textit{Presentation of results}

The different structure of analysis periods offered different options for presentation of results in the two studies. Merging individual traces into one summarising graph was suitable for the 13-minute period analysed for all parturients in Study I. A merged graph would not have been meaningful in Study II, because duration of labour stages, and duration and frequency of contractions varied considerably within and between parturients. A graph based on interpolation of summary measures would not have provided any additional information to the presented tables. Instead, we present extracts from representative raw data traces, which we believe are a useful visual supplement from a clinical perspective. These extracts do not reflect overall group values, but they illustrate the typical, verbally described haemodynamic changes, and provide an intuitive clinical impression of maternal haemodynamics during the different stages of labour.
6.6 Validity

Validity reflects how closely a given inference approximates the truth. In science, this may only be achieved if the chosen measures, design, and samples are appropriate for answering a particular research question.\textsuperscript{118}

The internal validity of a study reflects whether derived conclusions on causal relationship between tested factors and observed effects in the study population are adequate.\textsuperscript{118} To maximise internal validity, systematic and random errors need to be minimised.\textsuperscript{119}

Systematic error, also called bias, describes measurement inaccuracy into one consistent direction due to flaws that persist throughout the entire experiment.\textsuperscript{120} Such flaws may occur during different stages of a study, and should be limited by thorough planning.\textsuperscript{119} Systematic errors are generally divided into the three main categories of selection bias, information bias, and confounding. They may be sub-classified by different criteria. Different types of studies are prone to different main- and subtypes of systematic errors.\textsuperscript{119} Systematic errors with relevance for our studies will be considered in the following section.

Random error is the term for variability in measurements from unknown and unpredictable causes, such as limited precision of measuring instruments, or changes in the environment that are beyond the control of the investigator. This type of measurement inaccuracy varies in size and direction, corresponding to normal distribution, when repeating the measurement.\textsuperscript{121} Hence, random error decreases with increasing sample size, and can be estimated by statistical analysis. Common measures of random error include standard deviation and confidence intervals.\textsuperscript{120}

The external validity of a study reflects the applicability of conclusions from the study population to the relevant target population,\textsuperscript{122} as well as to a broader population or to different settings.\textsuperscript{118} Internal validity, adequate composition of the study sample by appropriate inclusion and exclusion criteria, suitable study setting and timing, and avoidance of certain types of systematic errors, all are imperative for external validity.\textsuperscript{122}

**Internal Validity in Study I and II**

*Selection bias*

Selection bias occurs when a study sample or group is not representative of the target population.\textsuperscript{119} As discussed under point 6.2, we think that our samples correspond reasonably well to our target population.

In Study I, selection bias between treatment groups was minimised by randomisation. Concerning Study II, we assume that the somewhat heterogeneous haemodynamic changes mirror actual pathophysiological diversity between parturients, but a much larger sample would be needed to exclude the possibility that selection bias contributed to the observed variability. Apart from that, inferences regarding effects of epidural analgesia might be biased if
parturients requesting epidural analgesia were systematically different from those wishing to cope without analgesic treatment.

In Study I, we excluded eight participants. In view of the low number of excluded cases compared to the total number of participants in each group, and of the reasons for their exclusion, bias created by exclusion of cases should not be relevant. Case exclusions were performed before breaking the randomisation codes. Study I had no loss to follow-up. In Study II, owing to varying cervical dilatation at study inclusion, the number of participants in early stage 1 was slightly lower than during the later stages. For one participant who needed CD, only stage 1 measurements are included. The total number of longitudinal measurements was high enough for valid statistical analysis, and marginal linear models allow for a varying number of observed subjects per stage.

**Information bias – General**

Information bias may arise from various pitfalls during data collection. One frequent subtype is misclassification bias, caused by incorrect classification of exposure, or by flawed detection of effects. The general risk of detection bias was minimised in both studies by using a validated and observer-independent technique for continuous minimally invasive haemodynamic monitoring. In Study I, the general risk of detection bias was further minimised by double-blind controlled design. Specific limitations of the employed monitoring technique, and other possible sources of misclassification, are discussed below.

**Information bias – Validity and Reliability of Measurements**

The accuracy of LiDCOplus is similar to pulmonary arterial catheter measurements. Pulmonary arterial catheter, which is considered the gold standard device for haemodynamic measurements, has an approximate accuracy of 10% to 20%. Thus, a minor degree of uncertainty remains concerning the proximity of measured to true values. Correct calibration of the pressure transducer inside the arterial cannula is a prerequisite for accurate LiDCO measurements, and was therefore performed with great care in both studies.

LiDCOplus has shown high precision in following trends. As discussed in section 6.4, we assume that effects of possible drift are negligible in both studies.

LiDCOplus has been validated for use in rapidly changing haemodynamic conditions and in obstetric patients, but has not been used for studies during labour so far. In Study II, the device provided apparently undisturbed traces even during intense contractions and physical effort, but in some parturients, a number of measurements during the peak of bearing-down effort were obviously compromised and thus excluded. Simultaneous use of LiDCOplus, peripheral artery Doppler and Doppler echocardiography might help to distinguish effects of peripheral vasoconstriction from compromised cardiac output during bearing down.
Stage 2 baselines were analysed until the period immediately prior to delivery. Baseline values during delivery were not analysed, because pauses between delivery contractions were too short to achieve repeated stable baseline readings. Delivery comprises the last few contractions leading to parturition of the newborn, i.e. a short time span only.

In the cases where arterial pressure traces were artefacted during the peaks of delivery contractions, undisturbed arterial curves and stable LiDCO readings reappeared immediately after the last bearing-down effort. Thus, analysis of postpartum data was considered valid, and inclusion of repeatedly measured postpartum baseline values was performed according to the same criteria as for stage 1 and stage 2 baselines.

Blood gas values were measured with the same calibrated instruments, and within a time frame of three years and of one year in the respective studies, thus laboratory variation should not be of major concern.

*Information bias – Missing values*

Haemodynamic analyses are exclusively based on measurements that were defined as reliable. As described under 4.5, 6.5 and in Paper II, the dataset was cleansed from corrupted values, during significant movement or maximal expulsive effort during delivery in Study II, for instance. The true haemodynamic changes from baseline during corrupted, hence excluded, peak segments of stage 2 contractions are unknown (i.e. missing), and might thus either be similar, or more significant, or less significant than the adjacent included measurements. The latter seems improbable, in view of the considerable changes prior to, and the increased physical strain during, maximal expulsive effort. We assume that the presented mean maximum changes during stage 2 and delivery might underestimate the true mean maximum changes to some degree.

We did not measure haemodynamic baselines prior to the onset of labour in Study II. Pre-labour baselines might be different from baseline measurements during labour and postpartum. The aim of Study II was the assessment of haemodynamic changes after the onset of active labour, hence pre-labour baselines were not relevant.

A considerable number of missing values may limit valid interpretation of umbilical cord blood gas values in both studies. The missing values are mainly due to an insufficient amount of blood in several samples, which in turn may be caused by blood wastage during manipulation of the umbilical cord, or by coagulation before blood aspiration was attempted. The amount of missing values differed considerably between groups in Study I, and between nulliparous and parous in Study II, but we cannot draw any conclusions on whether this is due to coincidence or to any specific factors.

*Information bias – Observer variation*

As described above, haemodynamic measurements with LiDCOplus are observer-independent. In Study I, calculation of cut-off limits for rescue pressor boluses and continuous
registration of relevant events (rescue pressor, nausea, delivery) into the LiDCO device and the case report form followed a standardised instruction. The same investigator and the same scientific assistant followed all participants, and ensured consistent adherence to the study protocol. In Study II, one single investigator followed all participants, without a scientific assistant. The labour setting sometimes posed logistic challenges, particularly in parturients with high levels of pain and stress. Therefore, the risk for missing registration of individual events was higher than in Study I. Contractions were registered manually into the LiDCO device, based on the tocometry report by the midwife. Accuracy in reporting the onset of contractions might have varied between the respective midwives. This kind of observer variation, and the absence of the possibility for correlation of uterine pressure and haemodynamic values, introduce some uncertainty with regard to the timing of haemodynamic changes during contractions. This potential source of error could have been avoided, if synchronised tocometry had been part of our study data.

Data were cleansed following clear and predefined criteria, as described under 4.5, and in Papers I and II. The final step of cleansing individual artefacts was performed by clinical discretion, and in spite of high concentration and meticulous work, a minor risk of missing individual artefacts or excluding some non-artefact ed values remains.

Data of both studies were analysed with advanced statistical models, according to the advice of experts in the field of complex repeated measurements. The appropriateness of analyses and quality of results were verified by the same experts.

Information bias – Flawed detection of treatment effect
In Study II, incorrect assessment of volume status or efficiency of epidural analgesia was theoretically possible. In that case, identification of effects caused by epidural analgesia or oxytocin infusion might be thwarted. We consider it improbable that major error was introduced by this potential source of misclassification or detection bias, but, as expounded in section 7.2, our study design prohibits definite conclusions about the haemodynamic effects of epidural analgesia in any case.

Confounding and effect modification
In Study I, the risk of confounding was limited by randomisation, and a strict study protocol that avoided variation with regards to exposure (rescue pressor, for instance).

As Study II examined parturients presenting for spontaneous delivery, a certain heterogeneity with regards to duration of labour and exposure (mobilisation, oral intake, epidural analgesia, oxytocin infusion, and obstetric procedures) could not be eliminated. In order to reduce confounding from these elements, only measurements taken in tilted supine or dorsal lithotomy position, in the absence of significant movement and obstetric or other procedures, were included in the final dataset. In order to detect possible effect modification, we included epidural analgesia, oxytocin infusion, and parity as factors in the statistical analysis, and ran additional sensitivity analyses for these factors.
Differences between findings in Study II and findings in previous haemodynamic studies during labour might partly be due to insufficient internal validity in the former studies, owing to confounders or to the use of unreliable and intermittent monitoring methods; pathophysiological variability between parturients presumably also plays a role (see section 7.2). However, it is impossible to exclude that undetected confounders might exist in Study II. Large and complex studies would be needed to definitely answer these questions.

**Random errors**

Random errors are less likely in large samples such as in Study I than in small samples such as in Study II. As measures of uncertainty, standard deviation and confidence intervals help to evaluate random error in a sample. Narrow confidence intervals indicate high precision of estimates. Low standard deviations suggest little variation.120 Confidence intervals and standard deviations are displayed in the result tables for each study.

**External Validity**

As discussed in section 6.2, we think that participants in both our studies represent the target population of healthy parturients around term reasonably well. Subject to internal validity, our findings should hence be generalisable to healthy parturients outside of our study. We did not measure socio-demographic characteristics in our parturients, but it seems unlikely that possible participation bias would have a major influence on haemodynamic outcomes. However, selection bias is hard to measure, and some uncertainty may remain.
7 DISCUSSION OF RESULTS

This Ph.D. project investigated maternal haemodynamics during caesarean delivery in Study I, and during vaginal delivery in Study II. The project was not designed for comparison of haemodynamics across the two studies, and does not permit any conclusions on maternal circulation during caesarean versus vaginal delivery. Our findings are therefore discussed separately for each study, with a summary of the respective discussion sections in Papers I and II, and a few additional considerations.

7.1 Discussion of Study I

Study I showed that an initial bolus followed by low-dose phenylephrine infusion has a better prophylactic effect than leg wrapping against spinal hypotension during caesarean delivery. Study I is the third study evidencing with continuous invasive monitoring that a rapid decrease in SVR and a compensatory increase in CO are the main haemodynamic derangements induced by spinal anaesthesia. Study I is the first trial using continuous invasive monitoring to compare a prophylactic strategy directed at the venous side with one exerting its main effect on the arterial side of the vascular system. The data indicate that venodilation contributes, to a minor degree, to spinal hypotension.

Prophylactic Effect of Phenylephrine and Leg Wrapping on Blood Pressure

Less continuous SAP decrease in the phenylephrine group compared with the leg wrapping and control groups, and less mean maximal SAP decrease (-10 mmHg) as well as a lower incidence of hypotension in the phenylephrine compared with the control group, demonstrate that the incidence and severity of hypotension were reduced best in the phenylephrine group. Comparing leg wrapping with control, continuous SAP decrease was significantly less, but neither mean maximal SAP decrease (-20 mmHg versus -31 mmHg) nor the incidence of hypotension (58% versus 75%) were significantly different. By the end of the analysis period, group traces show a similar SAP decrease in the leg wrapping and control groups. Leg wrapping thus had a moderate preventive effect on spinal hypotension, which is in line with conclusions by the Cochrane Collaboration, based on seven previous studies on lower limb compression.2 Neither our phenylephrine regimen nor leg wrapping caused reactive hypertension, and the incidence of bradycardia was minimal in both groups. That means leg wrapping had no advantage over low-dose phenylephrine concerning these side effects. Study I is the first comparison of phenylephrine and lower limb compression during spinal anaesthesia for CD. Demonstrating that the prophylactic effect of our low-dose phenylephrine regimen is superior to leg wrapping, Study I supports phenylephrine infusion combined with crystalloid cohydration27 as the first-line choice for prevention of spinal hypotension during caesarean delivery. In settings where phenylephrine is not available, lower limb wrapping may be used as an alternative means of hypotension prophylaxis.
The Phenylephrine Regimen

Our phenylephrine regimen, an initial bolus (0.25 μg/kg, i.e. median dose 20 μg, range from 15 μg to 28 μg) followed by low-dose infusion (0.25 μg/kg/min, i.e. median rate 20 μg/min), did not completely avert the rapid vasodilation caused by spinal anaesthesia. However, it achieved a lesser decrease in SVR, a lower incidence of hypotension, and less maximum decrease in SAP than a previously studied regimen using the same continuous low-rate infusion without an initial bolus. Quicker stabilisation of blood pressure by bolus dosage than by continuous infusion of phenylephrine in a previous trial supports the addition of an initial bolus to a low-dose infusion regimen. The bolus in that study was higher than ours (120 μg), but administered on therapeutic instead of prophylactic indication. Since intermittent haemodynamic monitoring may miss the peak effect of an administered bolus, the frequently recommended bolus size of 100 μg or more might be too high. The only study that monitored the haemodynamic effects of phenylephrine boluses continuously suggests that a bolus of 80 μg is too large because it may lead to an intermittent overshoot in SVR with concomitant CO depression. Since our bolus of 20 μg was too small to completely prevent the initial decrease in SVR, the optimal dose for an initial bolus prior to low-dose infusion is probably somewhere between 40 μg and 60 μg.

Reactive hypertension and baroreceptor mediated sinus bradycardia are known side effects of phenylephrine. Several recent studies have attempted to optimise phenylephrine regimens in order to avoid these adverse effects, while improving the prevention of hypotension and related symptoms. Intermittent boluses prevent hypotension effectively, but continuous infusion has been shown to stabilise blood pressure closer to baseline, to keep the incidence of nausea lower, and to require less physician interventions than bolus-based administration. High-dose phenylephrine infusions (100 μg/min to 120 μg/min), combined with cohydration, may completely avoid hypotension, but lead to high incidences of hypertension (up to 80%) and of bradycardia (up to over 30%). Recent suggestions for clinical practice include variable rate infusion regimens with a moderate start dosage (50 µg/min or 0.75 µg/kg/min) and subsequent rate adjustment by clinically monitored variables. From a clinical perspective, this may seem more reasonable than the rigid rates of many trial protocols, but a perfect titration algorithm has not been reported yet. Hitherto studied variable-rate infusions attained lower incidences of hypotension (<15%) than our (42%) and other low- or medium-dose regimens, but caused some reactive hypertension (6-35%). Intermittent monitoring may fail to detect rapid changes in blood pressure, hence it is possible that studies based on intermittent monitoring underestimated the respective incidences of hypotension and hypertension.

With an incidence of bradycardia of 2.6% and no reactive hypertension, our regimen had fewer adverse effects than previously studied variable-rate and low- or medium-dose infusions (incidences of hypertension of between 10% and 40% and of bradycardia of between 8% and 15%). Based on these and our own findings, we assume that a
higher initial bolus than in our study, added to low-dose infusion or to variable-rate infusion with a low start dosage, might help to further optimise the balance between prevention of hypotension and avoidance of side effects.

The Leg Wrapping Technique

In spite of our strict wrapping protocol, coload instead of preload, and the same definition of hypotension as in previous studies, we were not able to reproduce the low incidence of hypotension (15% to 18%) reported for leg wrapping groups in some of the limited number of previous trials. In view of our strict wrapping protocol, it seems unlikely to us that the quality of compression in our leg wrapping group might have been lower than in previous studies. Besides, the incidence of hypotension in the control groups of previous trials was also lower than in our control group. In the light of the rapidly changing haemodynamic condition after spinal onset, we presume that intermittent non-invasive monitoring (with up to five-minute intervals between measurements) in the historic studies may have missed hypotensive episodes that continually invasive monitoring would have detected. In a recent study, continuous non-invasive blood pressure monitoring revealed a 91% incidence of hypotension during CD, whereas intermittent measurements at three-minute intervals only detected a 55% incidence in the same patients.

One might contemplate whether the choice of a different lower limb compression method would have led to better haemodynamic outcomes than leg wrapping. In previous studies, alternative techniques for lower extremity compression have shown varying success. A sequential compression device reduced hypotension incidence from 92% to 52%, i.e. to a similar incidence as in our leg wrapping group. Other studies were either not able to reduce hypotension significantly, e.g. by inflatable boots, compression stockings, or thromboembolic deterrent stockings, or the reliability of the study methods was low, e.g. in studies on inflatable splints or a sequential compression device in combination with thromboembolic deterrent stockings. Manual application of elastic bandages is simple and, despite the absence of the possibility to monitor and fine-tune the exerted pressure, has been pointed out as the most effective technique among different methods of lower limb compression. In light of these findings, and of the recent insight that spinal hypotension is mostly due to arteriolar rather than venous vasodilation, we consider it unlikely that an alternative lower limb compression technique would have stabilised maternal blood pressure significantly better than leg wrapping did in our study.
Effect of Phenylephrine and Leg Wrapping on Overall Haemodynamics

In all treatment groups, the decrease in SAP was preceded by a sudden and profound decrease in SVR, and a compensatory increase in HR, SV, and CO. Study I thus confirms that spinal anaesthesia causes prompt arterial vasodilation with a marked decrease in afterload, in keeping with the past years’ fundamental change in pathophysiological understanding of spinal hypotension.\textsuperscript{19,32} Notwithstanding the consistently limited success of preventive strategies stabilising venous circulation,\textsuperscript{45,125} and the fact that impaired venous return with a significant reduction in CO is no longer considered the primary cause of spinal hypotension during CD, lower limb compression has been continued in a number of institutions, and has been recommended by some authors, even very recently, as the primary prophylactic method against spinal hypotension.\textsuperscript{44} The observation that phenylephrine, but not leg wrapping, counteracted the decrease in SVR in Study I clearly demonstrates that the alpha\textsubscript{1}-agonist phenylephrine prevents spinal hypotension in a more physiological manner than lower limb compression. A survey on current clinical practice in Europe revealed that, in 2012, only 20\% of clinicians used prophylactic vasopressor against spinal hypotension during CD.\textsuperscript{26} Modern haemodynamic management of spinal hypotension is probably implemented more widely in clinical practice today, but we are not aware of any up-to-date survey. Our findings are another piece of evidence in support of phenylephrine as first-line prophylaxis.

The paradigm shift that not venous but arteriolar vasodilation is the main reason for spinal hypotension has more or less eliminated mention of venodilation from the pathophysiological debate during recent years. It is therefore an interesting observation that the initial increase in SV was more pronounced in the leg wrapping group than in the control group. This may imply that spinal anaesthesia causes minor venodilation, which to a lesser extent also contributes to hypotension. Continuously higher SV in the leg wrapping group compared with the control group, in spite of similarly low afterload in both groups, indicates that venous recruitment by leg wrapping may help to stabilise preload.

In spite of higher SVR in the phenylephrine group compared with the leg wrapping group, SV was similar in both groups. This observation may indicate that phenylephrine generates a higher preload than leg wrapping does. The finding that SV remained above baseline when SVR was restored to baseline indicates that the preload increase in phenylephrine patients persists.\textsuperscript{126} Our results therefore imply that phenylephrine restores blood pressure not only by its action on the arterial but also on the venous side of the vascular system. The physiological mechanism for this may be alpha-agonist-mediated splanchnic venous recruitment by phenylephrine. This would be in keeping with the literature describing that constriction of preportal veins by low phenylephrine doses shifts blood centrally.\textsuperscript{28,29,127-129}
The rapid and prominent increase in CO was caused by increases in SV and HR, following the sudden decrease in afterload in all three groups. The subsequent gradual reduction in HR was most pronounced in the phenylephrine group. Lower continuous HR and CO in the phenylephrine than in the leg wrapping group indicate that cardiac effort was less in the former. These findings underline that phenylephrine, by counteracting arterial vasodilation and baroreceptor-mediated tachycardia, and simultaneously maintaining preload, has a more favourable effect on the overall haemodynamic condition than leg wrapping does. Several recent publications suggest that HR may serve as a clinical surrogate marker for CO, and may help to guide titration of phenylephrine in healthy parturients during spinal anaesthesia for caesarean delivery.27,32,35

One frequently raised concern about phenylephrine is that it may cause reflex bradycardia, and a concomitant decrease in CO, particularly when higher doses are used. A study comparing prophylactic infusion of noradrenaline to phenylephrine with the aim of preventing bradycardia and a decrease in CO, found a lower incidence of bradycardia (defined as HR<60 bpm) and a slightly higher mean HR in the noradrenaline group.130 However, with relatively higher doses needed to keep blood pressure equally stable, lower SVR, and a lasting increase in CO by almost 20% above baseline after the first five minutes, noradrenaline did not have a superior overall haemodynamic effect compared to phenylephrine. Bradycardia and an associated decrease in CO are often the result of overtreated blood pressure, hence a β-effect as from noradrenaline is usually unnecessary in healthy parturients.77 With our phenylephrine regimen, CO was restored to slightly below baseline. The incidence of bradycardia was minimal, and, in view of mildly tachycardic baseline values, the gradual decrease in heart rate to 10 beats/minute below baseline was probably of physiological benefit.

According to the classic baroreceptor reflex concept, hypotension is the direct cause of reflex tachycardia after spinal induction.131 In our study, the HR increase in all three groups occurred prior to hypotension. We therefore think that other cardiovascular reflexes might play a role, or that the initial increase in HR might be a direct response to reduced SVR, i.e. that the reflex receptor fibres are sensitive to changes not only in pressure, but also in resistance.

The principal goal during spinal anaesthesia for CD is ensuring maternal and foetal safety and wellbeing by maintaining haemodynamics close to resting physiological baselines.35 Permissive hypotension around 10% below baseline has been suggested as a specific goal in order to warrant sufficient stabilisation of blood pressure whilst preventing side effects from phenylephrine, i.e. bradycardia and a significant decrease in CO.19 With a mean decrease in SAP of 8% from baseline, no reactive hypertension, a minimal incidence of bradycardia, and a very slight reduction in CO, our regimen came close to this goal. As stated above, however, we think that a higher initial bolus added to low- or variable-rate phenylephrine infusion might achieve an even better balance.
Neonatal Outcome

All umbilical cord blood gases and Apgar values were within normal range, and pH, BE, and Apgar were similar in all groups, indicating that the maternal haemodynamic condition and rescue-pressor doses were well tolerated by newborns in all three groups. Lower umbilical artery and vein lactate in the phenylephrine group might suggest slightly less metabolic stress than in the leg wrapping and control groups.

In view of the excellent neonatal outcomes even in the placebo group, some might question the importance of maternal haemodynamic prophylaxis. First of all, continuous monitoring and a strict treatment protocol in case of hypotension contributed to prevention of prolonged severe hypotension, and of possible neonatal impairment, in our study. Second, while short-lived hypotensive episodes generally do not harm healthy babies in low-risk deliveries, they may exacerbate the condition of compromised infants who, due to prenatal impairment or complicated delivery, already are at risk of acidosis and intrapartum hypoxia.\textsuperscript{22,42,132} Hence, optimising maternal haemodynamics during CD, and avoiding any other contributions to potentially negative outcomes, are the safest working principles in regard to neonatal condition.\textsuperscript{42,132}

Due to a good ‘safety margin’ between uterine blood flow and foetal oxygen demand under normal physiological conditions, healthy foetuses usually tolerate some reduction in blood pressure or CO well.\textsuperscript{35} Previous studies have shown good clinical neonatal outcomes after high doses of ephedrine leading to maternal tachycardia and umbilical acidosis,\textsuperscript{42,60,69,70} and after high-dose phenylephrine infusions leading to maternal bradycardia and hypertension.\textsuperscript{68,74,75} These findings underline that maternal circulation, rather than umbilical pH or Apgar scores, should be the primary focus of vasopressor choice and general anaesthetic management.\textsuperscript{27,57}
7.2 Discussion of Study II

Study II demonstrated a profound impact of spontaneous labour and vaginal delivery on maternal haemodynamics in healthy parturients. This is the first study monitoring maternal haemodynamic changes continuously during all labour stages in a cohort of healthy women. The data show that contractions induce considerable haemodynamic changes starting early in active labour, and question whether epidural analgesia has a major effect on these changes.

Haemodynamic Baseline Values in Stages 1 and 2

Similar baseline values across stages for all haemodynamic variables in Study II imply that progression of labour has no major effect on haemodynamics during rest between contractions. Previous studies have provided controversial results on whether progressing labour leads to a cumulative increase in resting CO \(9,12,14,18\) or not.\(^{10,11,15}\) This discrepancy might be due to the use of non-continuous or unreliable monitoring techniques,\(^{18}\) or perhaps to confounders such as intravenous administration of different fluids or medicines during the course of labour. However, a larger sample size than ours would be needed to detect minor differences in baselines between labour stages.

Haemodynamics during Contraction

Stage 1 contractions generated considerable changes in all haemodynamic variables, and these changes increased slightly between early and late stage 1. During stage 2 contractions and delivery, haemodynamic changes were more uniform and more substantial than during stage 1, with prominent increases in SAP, HR, and SVR, and profound decreases in SV and CO in all parturients. A variety of mechanical, neurophysiological, and endocrine factors may affect haemodynamic changes during labour.\(^{11}\) Their investigation was beyond the scope of our project, and previous evidence is sparse, hence the pathophysiological interactions behind our findings remain speculative.

During stage 1 contractions, increases in SAP in our parturients were greater than the increases in blood pressure \(11,12,14,15\) reported by most authors in the past. During stage 2, increases in SAP in our parturients were more prominent than during stage 1, and of similar extent as in three previous studies reporting blood pressure during stage 2.\(^{11,12,14}\) Blood pressure responses during labour may depend on pain and stress, but possibly also on neurohumoral control independent of pain.\(^{11,133,134}\)

The increases in HR during stage 1 contractions in Study II were greater than previously reported increases in HR.\(^{10,11,17,18}\) One former research group found decreases in HR during contractions, which they ascribed to the baroreceptor reflex.\(^{12,13}\) We did not observe a primary decrease in HR during contractions in Study II, but the initial increase was often followed by a short decrease before values returned to baseline. Tachycardia during contractions was more prominent in stage 2 than in stage 1, and also more prominent than in two previous studies describing HR during stage 2.\(^{11,14}\)
While stage 1 contractions caused either increases or decreases in SVR, stage 2 contractions led to considerable increases in SVR in all parturients. In view of blood pressure increases\textsuperscript{11,12,14,15} and adrenergic activation\textsuperscript{133,134} during labour, the decreases in SVR during contractions in some of our parturients, in the absence of epidural analgesia, were rather unexpected. Most previous studies did not explicitly report on SVR, but one author group also found decreases in SVR during stage 1 contractions.\textsuperscript{15} There is an increasing body of evidence on reflex systems and local biochemical agents controlling SVR under stress and exercise.\textsuperscript{135} The pathophysiology of SVR regulation during labour is not elucidated yet, and might be an interesting subject for future research. For instance, progressively increasing levels of intrinsic norepinephrine during labour, as well as maximal catecholamine levels at the time of delivery, and their rapid decline directly after delivery have been shown,\textsuperscript{133} but neither the exact timing pattern of catecholamine secretion during progressing labour, nor the possible effects on haemodynamics have been investigated so far. Other studies found progressive increases in oxytocin and prostaglandin,\textsuperscript{136} and pulsatile secretion of intrinsic oxytocin at several-minute intervals during labour.\textsuperscript{136,137} Since bolus administration of synthetic oxytocin reduces SVR,\textsuperscript{138} it might be interesting to study whether intrinsic oxytocin pulses significantly affect maternal haemodynamics. In general, we suppose that cardiovascular reflexes\textsuperscript{131,139-142} contributed to the spectre of observed haemodynamic changes in our parturients. Beyond that, it might be instructive to examine potential correlations between haemodynamic changes and uterine pressure.

Study II showed that SV may either increase or decrease during stage 1 contractions, and thus confirms both the rises in SV observed by most authors,\textsuperscript{12-15,17} and the declines in SV observed by a few others.\textsuperscript{10,11} Stage 2 contractions, by contrast, generated decreases in SV in all our parturients, and these were more profound than the decreases during stage 1. To our knowledge, no previous study has achieved reliable SV measurements during stage 2 contractions before. Decreases in SV might be caused by concomitant increases in afterload, or, since there were cases with parallel decreases in SV and afterload during stage 1 in Study II, by reduced filling time due to tachycardia, or by decreased venous return due to caval compression.\textsuperscript{90} Increased intrathoracic pressure during bearing-down effort reduces venous return,\textsuperscript{9} and did probably contribute to the significant extent of decreases in SV during stage 2. Increases in SV have mainly been ascribed to blood redistribution from the contracting uterus,\textsuperscript{9,10,14,15,18,143} but this hypothesis remains to be confirmed, as direct evidence for the volume and clinical effect of autotransfusion seems to be absent. Alternatively, catecholamine-mediated cardiac stimulation,\textsuperscript{11,18,143} splanchnic recruitment, or other cardiovascular mechanisms\textsuperscript{127,128} might contribute to increases in SV.

The mean increase in CO of around 50\% during stage 1 contractions in Study II was larger than the increases of 20 \% to 30\% observed in most earlier studies.\textsuperscript{9-15,17} One study revealed an 84\% increase in CO, but the authors doubted whether their measurements by bioimpedance were reliable.\textsuperscript{18} Decreases in CO during stage 1, as detected in some of our
parturients, have only been observed by one other research group. The considerable decreases in CO during stage 2 in our parturients confirm findings described in a recent case report. The increases in CO in Study II were the result of either concomitantly increased HR and SV, or of increased HR and decreased SV. The decreases in CO occurred either during the entire contraction or only during the peak of contraction, as a result of increasing HR being outweighed by decreasing SV.

Except from the recent single case with similar haemodynamic changes as parturients in Study II, reliable CO measurements during bearing down have so far not been reported in any other study. Almost all previous studies were based on dye dilution techniques, the reliability of which depends on stable CO during an ongoing measurement. Several seconds pass from injection of the dye agent to appearance of the dilution curve, and the recording takes around half a minute. Beat-by-beat monitoring with LiDCO plus in Study II illustrates that, during ongoing contractions, important haemodynamic changes may occur within only a few seconds. The reliability of bio-impedance and Echo Doppler measurements, too, is restricted during brisk haemodynamic fluctuations. Inconsistent findings on CO and SV in the early studies have mainly been assigned to non-continuous, unreliable monitoring techniques, as well as to differences in posture, intravenous fluids and administered medicines. However, continuous invasive monitoring in Study II revealed some haemodynamic inter-parturient variability, which we assume may be an additional reason for conflicting previous evidence.

The LiDCO plus technique enabled continuous haemodynamic measurements during the entire course of labour, including delivery. In some parturients, however, LiDCO traces showed extreme haemodynamic values, or brief disruptions at the time of peak effort during several stage 2 and delivery contractions, even though the arterial cannulas were patent and the parturients’ upper limbs relaxed. Since this phenomenon was observed in a few individual stage 2 contractions when no voluntary valsalva effort was performed, we assume that intense vasoconstriction may have played a role in these cases.

Study II provides some new evidence, but numerous questions remain concerning the profound haemodynamic changes and the observed inter-parturient variability, and more research is needed to deepen understanding of haemodynamics during contractions. Future studies should investigate larger samples, and use synchronised continuous haemodynamic and tocodynamic monitoring. Studies with sophisticated design, including advanced blood sampling protocols, would be needed in order to shed more light on whether, and to what extent, endocrine changes affect haemodynamics at different moments during progressing labour.
Haemodynamics during Labour with Epidural Analgesia

Marginal linear model analyses of haemodynamic data by labour stage revealed small non-significant effect estimates for epidural analgesia. Furthermore, haemodynamic analyses yielded similar results when including and excluding epidural analgesia as independent factor. Epidural analgesia was titrated to reduce pain while maintaining motor function in our study. Effectiveness of epidural analgesia was verified by reduction of both pain scores and sensitivity to cold. However, since neither of them was included in the marginal model analyses, limited longitudinal effect must be considered as a possible reason for the absent influence on haemodynamics. Two previous studies using relatively higher epidural doses than those in Study II, reported mild\textsuperscript{14} or no\textsuperscript{12} effect of caudal analgesia on haemodynamic changes during contractions, but the reliability of their results might be limited, due to intermittent and possibly unreliable haemodynamic monitoring techniques. Considering that estimates for the effect of epidural analgesia on baseline SVR in Study II were close to the significance level, a decreasing effect of epidural analgesia on baseline SVR might have been detected using similar epidural doses in a larger sample. This would be in line with the clinical understanding that sympathetic blockade by epidural analgesia may lead to some degree of vasodilation.\textsuperscript{144} Epidural analgesia may also transiently reduce maternal blood pressure, but most studies have assessed the overall incidence of hypotension (5\% to 30\%) as a side outcome, without reporting blood pressure during the course of labour.\textsuperscript{144} Both the intended analgesic and the adverse effects of epidural analgesia are subject to dosage. Local anaesthetic regimens providing near-complete sensory block may impede mobility as well as bearing-down ability, and induce considerable hypotension.\textsuperscript{144}

Our study was not suited to quantifying the influence of epidural analgesia on pain and haemodynamics, but in light of the above-described findings, we question whether epidural analgesia dosed to reduce pain but maintain motor function has a major effect on haemodynamic changes during contractions. Anxiety, stress, and pain have been the main postulated causes for increasing HR, SVR, and SAP during contractions,\textsuperscript{134} but the actual effect of these factors or of analgesic treatment on haemodynamic changes has never been determined. Previously observed similar norepinephrine levels in parturients with and without epidural analgesia,\textsuperscript{133} increases in SAP prior to subjectively perceived contractions,\textsuperscript{11} and significant haemodynamic changes in a parturient with epidural analgesia and little pain\textsuperscript{49} indicate that other factors than pain might contribute to increases in HR, afterload, and blood pressure during contractions.

Comparison of haemodynamics between parturients with and without epidural analgesia in large randomised, controlled trials would be interesting and valuable, but challenging practical aspects, and high drop-out rates due to cross-over from control to epidural analgesia should be expected and taken into account in the study planning.
Haemodynamics Postpartum

Similar baseline values as in stages 1 and 2, and the absence of a significant increase in SV and CO, directly postpartum are in contrast to some of the early studies which reported an important increase in resting CO during the first few minutes after delivery. Our observations therefore question the common belief in a major increase in venous return after delivery, caused by autotransfusion from the contracted uterus, and corroborate doubts about this theory expressed by other authors. The conjecture that an intravenous oxytocin bolus might have led to the increase in CO in the respective ancient studies received support from a recent publication reporting increases in SV after a postpartum bolus of either oxytocin or carbetocin, but not after placebo, during CD. Postural changes and the relief of caval compression have been postulated as alternative causes of a postpartum increase in CO. The fact that all of the patients in the carbetocin study were in the supine position with left lateral tilt during the complete monitoring period rather supports the oxytocin hypothesis. Routines of oxytocin administration are not described in all of the historic studies, but an oxytocin bolus immediately after delivery is reported in some of the studies with a postpartum increase in CO. In our study, oxytocin was administered intramuscularly a few minutes after delivery, and was therefore unlikely to exert any haemodynamic effect within the monitoring period.

Labour has a profound impact on maternal circulation, and may last several hours, but early postpartum haemodynamic values and good general condition suggest that the circulatory impact of labour was well tolerated by parturients in Study II. Late postpartum and longterm cardiovascular outcomes were not assessed.

Clinical Value of Haemodynamic Monitoring during Labour

Knowledge about typical haemodynamic changes during labour may be a valuable basis for clinical assessment and management of parturients, particularly in case of unexpected adverse events. Since we examined healthy women, we cannot draw any conclusions on behalf of compromised parturients. Evidence on haemodynamics in healthy parturients might, however, have a potential indirect value for clinical considerations and future research in pathological conditions. Acute cardiac events, and diagnosed or undiagnosed pre-existing cardiac disease, are among the leading causes of maternal mortality. While healthy parturients tolerate labour generally well, haemodynamic implications of VD in parturients with cardiac compromise are controversial. In consideration of obstetric benefits and avoidance of surgical complications, current guidelines recommend VD for the majority of parturients at cardiac risk. The potentially deleterious effects of high myocardial workload on the compromised heart are well known, but most authors state that limiting valsalva effort and duration of the second stage by assisted delivery, and limiting pain by epidural analgesia, are efficient means to reduce maternal haemodynamic stress, and thus the risk of adverse outcome. Reliable evidence is sparse, and to our knowledge, no study has quantified the haemodynamic effect of epidural analgesia, or of normal and limited
pushing during second-stage contractions in healthy or compromised parturients. Neither has our project, but Study II shows that haemodynamic changes may be profound already in the first labour stage, and questions whether moderately dosed epidural analgesia significantly reduces maternal cardiovascular stress during contractions. We think that the observed haemodynamic fluctuations might have the potential to aggravate the condition of parturients at cardiac risk, and point up the need for future research in this population.

**Neonatal Outcome**

A high number of missing values limits the interpretability of umbilical cord blood gases in Study II, but the Apgar values indicate good clinical neonatal outcome.

**7.3 Comment across Studies I and II**

This Ph.D. project investigated maternal haemodynamics during spinal anaesthesia for caesarean delivery in Study I, and during vaginal delivery in Study II, but the project was not suited for assessment of haemodynamics across the two studies. Haemodynamics during VD and CD obviously differ in some general points. The exact pathophysiological mechanisms behind the haemodynamic changes during labour are complex, and not entirely understood, but intrinsic adrenergic stimulation likely plays a role.\textsuperscript{133,134} Conversely, iatrogenic inhibition of sympathetic pathways is responsible for the haemodynamic changes during spinal anaesthesia for CD.\textsuperscript{22} While hypotension therefore is a major concern during CD,\textsuperscript{22} contractions during VD are usually accompanied by intermittent hypertension.\textsuperscript{11,12,14,15}

The limited extent and duration of haemodynamic changes during CD in the phenylephrine group in Study I may seem to constitute less cardiovascular stress than the profound haemodynamic fluctuations during the protracted course of labour in Study II, but our project design does not permit any valid conclusions on this matter, and haemodynamic outcomes of CD and VD have never been compared by reliable advanced monitoring techniques in any previous study. Both haemodynamic management during CD and the haemodynamic impact of labour were seemingly well tolerated by the healthy participants and neonates of Studies I and II, respectively. Implications of both VD and CD on circulation in compromised parturients are controversial.\textsuperscript{1,52,146,148} Several contemporary authors have pointed at the importance of solid haemodynamic understanding\textsuperscript{146} and the necessity of high-quality prospective studies providing evidence upon which to base future clinical practice in both healthy and compromised parturients.\textsuperscript{49,148,149,151} We think that the profound haemodynamic impact of first- and second-stage contractions in Study II underline the need for future research into short- and long-term cardiovascular outcomes of vaginal delivery compared to haemodynamically well-managed caesarean delivery, particularly in parturients at cardiac risk.
8 CONCLUSIONS

1. Low-dose phenylephrine infusion is superior to leg wrapping and to no intervention for preventing spinal hypotension during CD. Leg wrapping has a limited preventive effect on spinal hypotension compared with no intervention.

2. Study I confirms that spinal anaesthesia induces a rapid decrease in SVR, and a compensatory increase in HR, SV, and CO. Study I indicates that there is also modest venodilation after induction of spinal anaesthesia. The reduction in afterload is counteracted by phenylephrine but not by leg wrapping. Both phenylephrine and leg wrapping contribute to the maintenance of preload. In summary, phenylephrine has a more favourable effect than leg wrapping on the overall haemodynamic condition.

3. A phenylephrine regimen consisting of a small initial bolus (0.25 µg/kg) followed by low-dose infusion (0.25 µg/kg/min) stabilises SAP, and restores HR and CO to levels slightly below baseline, without clinically significant adverse effects. The initial decrease in SAP is attenuated but not completely prevented by this regimen, hence the initial phenylephrine bolus should probably be increased.

4. Both prophylactic low-dose phenylephrine infusion and leg wrapping are well tolerated by healthy newborns of healthy mothers.

5. During labour, stage 1 contractions cause prominent increases in SAP and HR, and either increases or decreases in SVR and SV. Cardiac output may either increase or decrease, depending on the relative extent of changes in SV and HR. During stage 2 contractions, the changes are more uniform, with pronounced increases in SAP, HR, and SVR, and profound decreases in SV and CO in all parturients.

6. Haemodynamic changes during contractions are profound, both in early and late active labour. The extent of maternal haemodynamic changes is most substantial during bearing-down effort in stage 2. The haemodynamic impact of labour is probably stronger than formerly shown.

7. Progress of labour itself has no major influence on haemodynamic baselines. Stable SV and CO in the immediate postpartum period query the common belief that delivery itself leads to a significant myometrial autotransfusion.

8. Our findings question whether epidural analgesia significantly minimises the effect of contractions on maternal circulation.
9 CLINICAL IMPLICATIONS

Based on the findings in Study I, the combination of prophylactic phenylephrine infusion and cohydration should remain the method of choice for prevention of spinal hypotension during CD. Phenylephrine is a more efficient and a more physiological approach to prevention of spinal hypotension than leg wrapping, hence institutions still using leg wrapping as first-choice prophylaxis should change their protocols to using phenylephrine. Leg wrapping may serve as an alternative prophylactic method, in settings where phenylephrine is not available.

Adding an initial bolus to low-dose phenylephrine infusion can be recommended in order to improve haemodynamic stabilisation, while keeping the incidence of adverse effects low. A higher bolus dose than in our study, probably between 40 μg and 60 μg, might help to further optimise the prevention of the initial decrease in blood pressure. The negative effect of phenylephrine on HR and CO is of physiological benefit when used in low doses, as it reduces cardiac effort. However, it is important to keep in mind that high doses of phenylephrine may induce hypertension, bradycardia, and an unreasonable degree of cardiac output depression, and should therefore be avoided.\textsuperscript{27,57}

In general, Study I substantiates that preventive and therapeutic means against spinal hypotension should primarily focus on stabilising afterload, and on keeping heart rate and cardiac output close to baseline, hence limiting maternal cardiac effort.\textsuperscript{27,57}

The observation that transient moderate maternal haemodynamic imbalance is well tolerated by healthy newborns confirms that maternal circulation, rather than neonatal outcome, should be the primary focus of prophylactic strategies against spinal hypotension.\textsuperscript{27}

Study II, indicating that haemodynamic stress during stage 1 may be more substantial than previously assumed, and being the first study to evidence the considerable CO changes during expulsive effort in stage 2, underlines the importance of realistic appraisal of every parturient’s tolerance for profound haemodynamic fluctuations, at an early point during labour. A cardiovascular burden as observed in Study II is usually well tolerated by healthy parturients, but might have the potential to worsen the condition of women with cardiac disease, and to promote circulatory complications in predisposed parturients. A parturient’s resilience to significant intermittent hypertension and CO depression during bearing-down effort should receive particular consideration in clinical decisions on mode of delivery, or on management of expulsive effort, for instance. The threshold for continuous minimally invasive monitoring in parturients at risk should probably be low.

Until future studies provide valid evidence, clinicians should arguably not rely on epidural analgesia to eliminate the haemodynamic impact of contractions.

Based on our personal experience, the LiDCO\textsuperscript{plus} may prove useful for future haemodynamic research during labour.
10 FUTURE RESEARCH

The pathophysiology and management of spinal hypotension during CD in healthy parturients are well elucidated by now. A few questions remain, concerning:

- which mechanism leads to the rare presentation of hypotension and accompanying bradycardia in direct response to spinal anaesthesia;\(^3,35\)
- the exact dose-related effects of phenylephrine on venous return\(^35\) and uterine blood flow; and
- the effect of blood pressure and CO on uterine blood flow.\(^81\)

Future haemodynamic research in the context of CD should concentrate on circulation in parturients with preeclampsia, cardiac disease,\(^27,31\) or other pathologies. Of interest are i.a.:

- the haemodynamic effects of spinal anaesthesia in pre-eclampsia;
- optimal vasopressor and general clinical management during CD in pre-eclampsia, cardiac disease,\(^27\) or vasopressin depletion;\(^152\)
- the effects of oxytocin receptor agonists in pre-eclampsia;\(^98\) and
- the effects of phenylephrine on uterine blood flow in placental insufficiency.\(^36,81\)

There are many unanswered questions concerning the complex interactions of mechanical, neurophysiological, endocrine, and external factors that may influence haemodynamic changes during labour. Large studies with sophisticated design would be needed in order to draw definite conclusions. Of interest are the detailed haemodynamic effects of i.a.:

- the uterine tone;
- positioning and volume state;
- epidural analgesia, remifentanil analgesia, and labour augmentation; and
- neuro-endocrine factors (intrinsic oxytocin, catecholamines, and cortisol, for example).

Future research should focus on parturients with pre-eclampsia or cardiac disease. Randomised, controlled trials may be difficult both from a practical and ethical perspective, hence observational studies are more realistic. To obtain data that are as complete and valid as possible, continuous haemodynamic monitoring should be used.\(^53,57,153\)
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APPENDIX

Study I

Table 3. Neonatal Characteristics in Study I

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<th>Phe (n = 38)</th>
<th>Leg (n = 38)</th>
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<td>2.2 [0.6]</td>
<td>2.3 [1.0]</td>
<td>2.6 [0.8]</td>
<td>0.031 ^K</td>
<td>21 / 18 / 31</td>
</tr>
<tr>
<td>PCO₂</td>
<td>7.35 [1.14]</td>
<td>7.40 [0.97]</td>
<td>7.77 [1.34]</td>
<td>0.343 ^A</td>
<td>16 / 13 / 25</td>
</tr>
<tr>
<td>PO₂</td>
<td>2.15 [0.88]</td>
<td>2.11 [0.85]</td>
<td>1.83 [0.76]</td>
<td>0.507 ^A</td>
<td>16 / 13 / 25</td>
</tr>
<tr>
<td><strong>UV</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>pH</td>
<td>7.344 [0.034]</td>
<td>7.358 [0.027]</td>
<td>7.353 [0.041]</td>
<td>0.138 ^A</td>
<td>13 / 5 / 11</td>
</tr>
<tr>
<td>BE</td>
<td>-1.10 [2.1]</td>
<td>-1.70 [1.5]</td>
<td>-1.60 [1.1]</td>
<td>0.595 ^A</td>
<td>18 / 8 / 28</td>
</tr>
<tr>
<td>Lac</td>
<td>1.75 [0.4]</td>
<td>1.9 [0.3]</td>
<td>2.1 [0.5]</td>
<td>0.001 ^K</td>
<td>21 / 11 / 31</td>
</tr>
<tr>
<td>PCO₂</td>
<td>5.78 [0.79]</td>
<td>5.66 [0.72]</td>
<td>6.10 [0.81]</td>
<td>0.050 ^K</td>
<td>18 / 8 / 28</td>
</tr>
<tr>
<td>PO₂</td>
<td>3.66 [0.94]</td>
<td>3.98 [1.12]</td>
<td>3.39 [1.21]</td>
<td>0.056 ^A</td>
<td>18 / 8 / 28</td>
</tr>
</tbody>
</table>

Data are presented as median [interquartile range]. ^ = 1-Way-Anova. ^K = Kruskal-Wallis. ^U = Mann-Whitney U. Apgar 1 and 5 are scored 1 and 5 minutes after delivery. UA = umbilical artery; UV = umbilical vein; BE = base excess in mmol/l; Lac = lactate mmol/l; PCO₂ = partial pressure of carbon dioxide in kilopascal; PO₂ = partial pressure of oxygen in kilopascal. Statistically significant intergroup differences for UA Lac between groups Phe and Control (0.007 K), and for UV Lac between groups Phe and Control (0.000 K), Phe and Leg (0.035 K), Leg and Control (0.026 U).

Study II

Table 4. Neonatal Characteristics in Study II

<table>
<thead>
<tr>
<th></th>
<th>All (n = 20)</th>
<th>Nulliparous (n = 11)</th>
<th>Parous (n = 9)</th>
<th>P Value</th>
<th>Missing results per group (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Apgar 1</strong></td>
<td>9 [6-10]</td>
<td>9 [6-10]</td>
<td>10 [8-10]</td>
<td>0.18</td>
<td>1 / 1 / 0</td>
</tr>
<tr>
<td><strong>Apgar 5</strong></td>
<td>10 [9-10]</td>
<td>10 [9-10]</td>
<td>10 [10]</td>
<td>0.36</td>
<td>1 / 1 / 0</td>
</tr>
<tr>
<td><strong>UA</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>pH</td>
<td>7.210 [0.118]</td>
<td>7.208 [0.077]</td>
<td>7.221 [0.175]</td>
<td>0.84</td>
<td>6 / 4 / 2</td>
</tr>
<tr>
<td>BE</td>
<td>-4.5 [4.4]</td>
<td>-5.7 [2.6]</td>
<td>-2.2 [3.9]</td>
<td>0.09</td>
<td>7 / 5 / 2</td>
</tr>
<tr>
<td>Lac</td>
<td>5.4 [3.5]</td>
<td>6.0 [4.4]</td>
<td>4.7 [3.2]</td>
<td>0.42</td>
<td>8 / 6 / 2</td>
</tr>
<tr>
<td>PCO₂</td>
<td>7.83 [2.54]</td>
<td>7.22 [-]</td>
<td>7.99 [2.70]</td>
<td>0.54</td>
<td>11 / 8 / 3</td>
</tr>
<tr>
<td>PO₂</td>
<td>2.38 [1.28]</td>
<td>2.38 [-]</td>
<td>2.57 [1.33]</td>
<td>0.54</td>
<td>11 / 8 / 3</td>
</tr>
<tr>
<td><strong>UV</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>pH</td>
<td>7.319 [0.089]</td>
<td>7.319 [0.113]</td>
<td>7.343 [0.092]</td>
<td>0.60</td>
<td>5 / 3 / 2</td>
</tr>
<tr>
<td>BE</td>
<td>-4.7 [5.3]</td>
<td>-5.7 [2.9]</td>
<td>-2.1 [4.2]</td>
<td>0.05</td>
<td>6 / 4 / 2</td>
</tr>
<tr>
<td>Lac</td>
<td>4.70 [3.60]</td>
<td>5.50 [5.00]</td>
<td>4.00 [2.20]</td>
<td>0.57</td>
<td>7 / 5 / 2</td>
</tr>
<tr>
<td>PCO₂</td>
<td>5.48 [1.66]</td>
<td>5.68 [2.01]</td>
<td>5.48 [1.55]</td>
<td>0.94</td>
<td>10 / 7 / 3</td>
</tr>
<tr>
<td>PO₂</td>
<td>3.73 [1.59]</td>
<td>3.64 [1.57]</td>
<td>3.89 [1.99]</td>
<td>0.95</td>
<td>10 / 7 / 3</td>
</tr>
</tbody>
</table>

Data are presented as median [interquartile range]. P-values are from Mann-Whitney U for Apgar Values, and from independent samples t-test for umbilical cord blood gas values. Apgar 1 and 5 are scored 1 and 5 minutes after delivery. UA = umbilical artery; UV = umbilical vein; BE = base excess in mmol/l; Lac = lactate mmol/l; PCO₂ = partial pressure of carbon dioxide in kilopascal; PO₂ = partial pressure of oxygen in kilopascal.
Table 5. Effect of Epidural Analgesia on Haemodynamics in Study II

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>During contractions</th>
<th></th>
<th></th>
</tr>
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<tbody>
<tr>
<td></td>
<td></td>
<td>Minimum</td>
<td>Maximum</td>
<td></td>
</tr>
<tr>
<td></td>
<td>mean</td>
<td>95% CI</td>
<td>p</td>
<td>mean</td>
</tr>
<tr>
<td>CO (l/min)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Crude value</td>
<td>ref</td>
<td>-0.2, 0.7</td>
<td>0.3</td>
<td>ref</td>
</tr>
<tr>
<td>Effect of Epidural</td>
<td>0.2</td>
<td>-0.2, 0.7</td>
<td>0.3</td>
<td>0.06</td>
</tr>
<tr>
<td>SV (ml)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Crude value</td>
<td>ref</td>
<td>-2, 6</td>
<td>0.3</td>
<td>ref</td>
</tr>
<tr>
<td>Effect of Epidural</td>
<td>2</td>
<td>-2, 6</td>
<td>0.3</td>
<td>2</td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Crude value</td>
<td>ref</td>
<td>-4, 6</td>
<td>0.6</td>
<td>ref</td>
</tr>
<tr>
<td>Effect of Epidural</td>
<td>1</td>
<td>-4, 6</td>
<td>0.6</td>
<td>3</td>
</tr>
<tr>
<td>SVR (dynes/s/cm²)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Crude value</td>
<td>ref</td>
<td>-154, 1</td>
<td>0.06</td>
<td>ref</td>
</tr>
<tr>
<td>Effect of Epidural</td>
<td>-76</td>
<td>-154, 1</td>
<td>0.06</td>
<td>3</td>
</tr>
<tr>
<td>SAP (mmHg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Crude value</td>
<td>ref</td>
<td>-2, 9</td>
<td>0.2</td>
<td>ref</td>
</tr>
<tr>
<td>Effect of Epidural</td>
<td>3</td>
<td>-2, 9</td>
<td>0.2</td>
<td>3</td>
</tr>
</tbody>
</table>

Mean values are estimated effects of epidural analgesia on the reference crude mean value. Each haemodynamic variable was analysed separately within each stratum (baseline, minimum, maximum), with marginal linear models that allowed for dependency between repeated measures within parturients. The model assessed the haemodynamic variables as dependent factors, and stage, parity, epidural analgesia, and oxytocin as independent factors. SVR: systemic vascular resistance; SAP: systolic arterial pressure. Epidural = epidural analgesia. CI: confidence intervals. P: P-value. P values <0.05 were considered statistically significant.

Table 6. Effect of Epidural Analgesia on Pain and Sensory Level in Study II

<table>
<thead>
<tr>
<th>Parturients with Epidural (n=12)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>NRS during contractions before start of Epidural</td>
<td>7.4 (1.3)</td>
</tr>
<tr>
<td>NRS during contractions after start of Epidural</td>
<td>3.8 (2.0)</td>
</tr>
<tr>
<td>Reduction in NRS after start of Epidural</td>
<td>3.6 (1.9)</td>
</tr>
<tr>
<td>Sensory level after start of Epidural</td>
<td>9 (1)</td>
</tr>
</tbody>
</table>

Data are presented as mean (SD). Comparison of NRS before and after start of epidural analgesia was performed with paired samples t-test (significance level = 0.05). NRS = numeric rating scale for pain (0-10). Epidural = epidural analgesia. Sensory level indicates the uppermost thoracic dermatome with bilaterally reduced sensitivity to cold, measured by ethyl chloride spray within the first hour after start of epidural analgesia.
<table>
<thead>
<tr>
<th>Page</th>
<th>Line</th>
<th>Original Text</th>
<th>Type of Correction</th>
<th>Corrected Text</th>
</tr>
</thead>
<tbody>
<tr>
<td>30</td>
<td>6 to 10</td>
<td>Original text will not be changed. Variables are listed in row order: CO, SV, SVR, HR, SAP</td>
<td>Cpltf</td>
<td>Original text remains unchanged. Variables are listed in row order: SAP, HR, SVR, SV, CO</td>
</tr>
<tr>
<td>30</td>
<td>13 to 17</td>
<td>Original text will not be changed. Variables are listed in order: CO, SV, SVR, HR, SAP</td>
<td>Cpltf</td>
<td>Original text remains unchanged. Variables are listed in row order: SAP, HR, SVR, SV, CO</td>
</tr>
<tr>
<td>57</td>
<td>20</td>
<td>positioning and volume state</td>
<td>Cor</td>
<td>positioning and volume state;</td>
</tr>
</tbody>
</table>

This Errata List displays corrections between the original version and the printed version of the PhD Thesis “Haemodynamics during Vaginal and Caesarean Delivery in Healthy Parturients”. Cpltf: correction of page layout or text format. Cor: Correction of text.
Am Abend wird man klug für den vergangenen Tag, doch niemals klug genug für den der kommen mag.

*Friedrich Rückert (1788-1866)*

Tonight, you are wise for the day that has gone, but not yet wise enough for the day that will come.

*Free translation after Friedrich Rückert*