Maternal Hemodynamic Effects of Medical Gases and Uterotonics in Obstetrics

Rabow, Sofus

2023

Document Version:
Publisher's PDF, also known as Version of record

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CLINICAL SCIENCES, LUND | FACULTY OF MEDICINE | LUND UNIVERSITY

Printed by Media-Tryck, Lund 2023 NORDIC SWAN ECOLABEL 3041 0903

LUND UNIVERSITY

FACULTY OF MEDICINE

Department of Clinical Sciences, Lund

Lund University, Faculty of Medicine
Doctoral Dissertation Series 2023:99
ISBN 978-91-8021-439-1
ISSN 1652-8220

Maternal Hemodynamic Effects of Medical Gases and Uterotonics in Obstetrics

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LUND
UNIVERSITY

DOCTORAL DISSERTATION
With due permission of the Faculty of Medicine, Lund University, Sweden.
To be publicly defended on September 15, 2023, at 09.00 in Lecture Hall F3, Centralblocket, Skånes Universitetssjukhus Lund

Faculty Opponent
Professor Leiv Arne Rosseland, Oslo University, Norway

Organization: LUND UNIVERSITY

Document name: Doctoral Dissertation **Date of issue** 2023-09-15

Author(s): Sofus Rabow **Sponsoring organization:**

Title and subtitle: Maternal Hemodynamic Effects of Medical Gases and Uterotonics in Obstetrics

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Conclusion: The abovementioned medical interventions have cardiovascular effects that are sometimes quite profound. These effects can be shown with a simple and pain-free methodology. Carbetocin seems to have similar cardiovascular adverse effects compared to Oxytocin. Prudence should be taken when administering these drugs to compromised mothers. Both nitrous oxide and oxygen have vasoconstrictive and possible negative inotropic effects that were more prominent in pregnant women than in nonpregnant controls. Some of the effects seen from nitrous oxide might be due to the oxygen fraction in the gas mixture. Awareness of cardiovascular effects is important when treatment of the mother with oxytocin receptor agonists as well as with nitrous oxide and oxygen is considered. Oxygen treatment should not be used without a precise indication.

Key words: carbetocin, cesarean section, general anesthesia, hemodynamics, hemodynamic monitoring, hyperoxia, nitrous oxide, obstetrical analgesia, oxygen, oxytocics, oxytocin, oxytocin receptors, pregnancy, photoplethysmography, pulse wave analysis, spinal anesthesia, vascular stiffness

Classification system and/or index terms (if any) Supplementary bibliographical information

Language English **ISSN and key title**: 1652-8220

ISBN: 978-91-8021-439-1

Recipient's notes **Number of pages**:88

Price Security classification

Signature Date 2023-08-01

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Cover design by the author

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Printed in Sweden by Media-Tryck, Lund University

Lund 2023

To my family, for putting up with me

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List of Papers

Paper I

Rabow S., Olofsson P. Pulse wave analysis by digital photoplethysmography to record maternal hemodynamic effects of spinal anesthesia, delivery of the baby, and intravenous oxytocin during cesarean section. J Matern Fetal Neonatal Med. 2016 May 26:1-8. doi: 10.1080/14767058.2016.1186162. [Epub ahead of print] PMID: 27145830

Paper II

Rabow, S., Hjorth, U., Schönbeck, S., Olofsson P. Effects of oxytocin and anaesthesia on vascular tone in pregnant women: a randomised double-blind placebo-controlled study using non-invasive pulse wave analysis. *BMC Pregnancy Childbirth* **18**, 453 (2018). https://doi.org/10.1186/s12884-018-2029-1

Paper III

Sofus Rabow, Hanna Jonsson, Emilie Bro & Per Olofsson (2023) Cardiovascular effects of oxytocin and carbetocin at cesarean section. A prospective double-blind randomized study using noninvasive pulse wave analysis, The Journal of Maternal-Fetal & Neonatal Medicine, 36:1, https://doi.org/10.1080/14767058.2023.2208252

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Abbreviations

AI	aging index
Aix	augmentation index
APG	accelerated photoplethysmogram (second derivative PPG)
APGAR	appearance pulse grimace activity respiration
BMI	body mass index
BP	blood pressure
CI	cardiac index
CO	cardiac output
CO_2	carbon dioxide
CRF	case report form
CS	cesarean section
CTG	cardiotocography, cardiotocogram
CVP	central venous pressure
DI	dicrotic index
DPA	digital pulse wave analysis
DPB	diastolic blood pressure
DVP	digital volume pulse wave
ECG	electrocardiogram
EEI	cardiac ejection elasticity index
ETc	left ventricular ejection time compensated
FHR	fetal heart rate
FMD	flow-mediated vasodilatation
FTc	flow time corrected
HIE	hypoxic-ischemic encephalopathy
HR	heart rate
IUGR	intrauterine growth restriction
IV	intravenous
LV	cardiac left ventricle
LVET	left ventricular ejection time
MAP	mean arterial blood pressure
NIBP	non-invasive (oscillometric) blood pressure
N_2O	nitrous oxide (laughing gas)
NO	nitric oxide
O_2	oxygen
OTR	oxytocin receptor
PE	preeclampsia
PH	pulse height
PI	pulsatility index
PP	pulse pressure
PPG	photoplethysmogram
PPH	postpartum hemorrhage

PVR	peripheral vascular resistance
PW	pulse wave
PWA	pulse wave analysis
PWV	pulse wave velocity
RAAS	renin-angiotensin-aldosterone system
RCT	randomized controlled trial
RI	reflection index
ROS	reactive oxygen species
SaO_2	arterial oxygen saturation
SI	stiffness index
SPB	systolic blood pressure
SV	stroke volume
SVR	systemic vascular resistance

Background

Pregnancy and childbirth are physically demanding processes for the woman. The physiological changes in pregnancy, aimed at meeting the demands of the growing fetus and preparing the mother for delivery begin already in early pregnancy, but become more pronounced as pregnancy develops. At term, these changes include a substantial increase in plasma volume, cardiac output, and respiratory workload, as well as vascular, renal, endocrine, and hormonal changes. In some circumstances, these changes are not well tolerated by the mother, as in the presence of pre-existing medical conditions or in case of pathologic development of pregnancy, as in pre-eclampsia or hypertensive disease of pregnancy. Knowledge of these changes is of uttermost importance when taking medical care of women during pregnancy and childbirth.

The physiologically and medically most demanding part of pregnancy for both mother and child is during labor and delivery. During labor, potent analgesia is often needed, and if there is a cesarean section, sufficient anesthesia is needed. These medical interventions have possible adverse effects on both the mother and child. Immediately after childbirth, the uterus must contract to stop and prevent postpartum hemorrhage (PPH). Since PPH is the major cause of maternal fatalities worldwide, and uterine atony is the most common cause of major PPH, most women receive uterotonic drugs to prevent and treat uterine atony. Unfortunately, these interventions have cardiovascular adverse effects on the mother. If pregnancy or delivery are associated with cardiovascular pathologies or major bleeding, additional cardiovascular adverse effects from analgesic, anesthetic, or uterotonic drugs can be detrimental to the mother. For this reason, more focus has recently been put on the hemodynamic effects on the mother from analgesic and uterotonic drugs used during labor and delivery. However, since many mothers are reluctant to accept the sometimes painful, invasive, or potentially harmful methods best needed for the study of hemodynamic changes, knowledge is still scarce.

The aim of this thesis is to investigate and compare maternal hemodynamic effects from common medical interventions during pregnancy. For this purpose, we used noninvasive digital photoplethysmographic pulse wave analysis, ECG, and blood pressure monitoring. The interventions studied were spinal anesthesia and oxytocin during elective cesarean section, general anesthesia and oxytocin during elective suction curettage, carbetocin or oxytocin during elective cesarean section, hyperoxygenation treatment, and nitrous oxide treatment on healthy pregnant and nonpregnant female volunteers.

Introduction

Physiologic changes of pregnancy

Many important physiologic changes occur in the woman during pregnancy. The most obvious change is the growth of the uterus and the fetus inside. To be able to meet the metabolic demands of the fetus and the growing uterus, major changes to the cardiovascular system and to the respiratory workload are taking place during pregnancy, but many other organs are also involved. These changes begin already at early pregnancy, but become more prominent as pregnancy develops. Oxygen demand will increase, making ventilation and respiratory work increase by up to 40%. Cardiac output will rise by 30-40%. Renal blood flow is augmented, and there is an increase in glomerular filtration rate (GFR) of up to 50%. Pathological adaptation to pregnancy can lead to both maternal and fetal morbidity and mortality. In addition, pregnant women are more susceptible to adverse outcomes from diseases that are not dangerous to the nonpregnant. Knowledge of the physiologic changes during pregnancy is of uttermost importance in dealing with the care of the pregnant patient.

Cardiovascular changes

Both the heart rate (HR) and stroke volume (SV) increase during pregnancy. This increases the cardiac output (CO) which is the product of HR and SV. These changes start early in pregnancy and evolve to reach their peak by the end of the second trimester. The blood pressure (BP) is decreased in early pregnancy due to a decrease in vascular stiffness and tone, usually referred to as systemic vascular resistance (SVR) or sometimes called peripheral vascular resistance (PVR). SVR decreases in the first trimester, reaches its lowest during the second trimester, then augments slightly during the end of the third trimester. In the meantime, the plasma volume (PV) increases, and the hemoglobin (Hb) concentration decreases (Figure 1).

According to Duvekot et al.[1] the decrease in SVR precedes and is causative of the increased HR and later also the increased plasma volume. The lowered SVR is probably related to hormonal changes, as it correlates to progesterone and estrogen levels. In addition, the hormone relaxin, produced by the corpus luteum, rises during the first trimester.[2] Relaxin has been shown to have a vasodilating effect on small arterial vessels. It is thought that the relative hypovolemia brought on by the

decreased SVR sets off compensatory renal processes that restore intravascular volume and blood pressure by preserving sodium and water. The principal mechanisms for this are the stimulation of the renin-angiotensin-aldosterone system (RAAS) as well as an increase in angiotensinogen as pregnancy evolves. Angiotensinogen is a substrate for renin.[2]

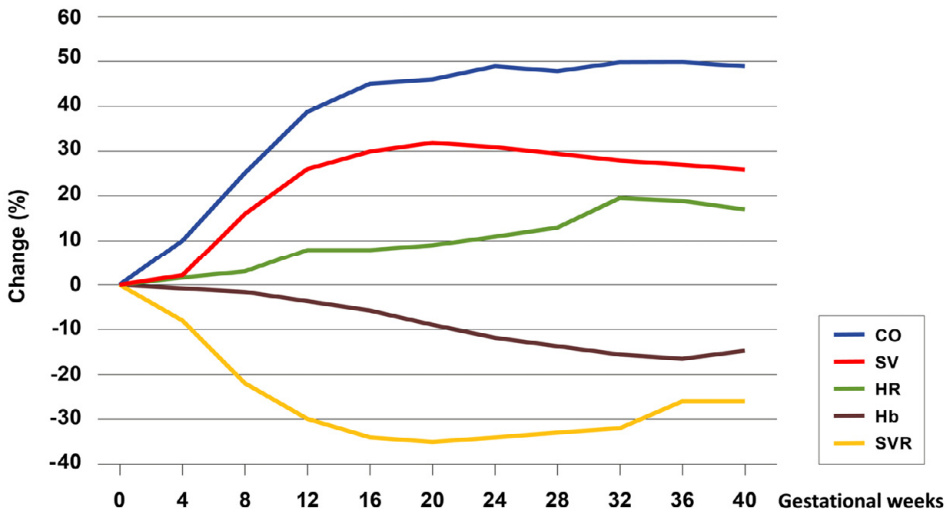


Figure 1. Hemodynamic changes in pregnancy. CO, cardiac output; SV, stroke volume; HR, heart rate; Hb, hemoglobin; SVR, systemic vascular resistance; Weeks, gestational weeks. Modified from Ruys et al., J Cardiol 2013;61: 107-112

The RAAS is to a great deal responsible for the increase of sodium, regulated by the kidney and by appetite and thirst regulation, but also relaxin is involved, stimulating renal blood flow,[3] vasopressin secretion, and drinking.[4–6] The net result in an increase in plasma volume that is larger than the increase in total body sodium, which explains the lower serum osmolality in late pregnancy. Normally, RAAS activation causes not only retention of sodium and water but also vasoconstriction. However, in pregnancy, this response is attenuated due to downregulation of the vasoconstricting angiotensin receptor AT1R and upregulation of the vasodilating receptor AT2R.[4] Further vasodilatory actions are mediated by relaxin, vascular endothelial growth factor (VEGF), nitrous oxide (NO), kallikrein-kinin, and prostanoids.[7] It has been suggested that an imbalance in these vasoactive systems, probably mediated by an abnormal immunological reaction, plays an important part in the development of the hypertensive disorders of pregnancy, such as preeclampsia.

Cesarean section

Cesarean section (CS), or cesarean delivery (CD), is the operation by which the child is delivered through a surgical incision in the abdominal wall and in the uterus. It is one of the oldest surgical procedures in history. Originally, this operation was only performed to save the life of the fetus in the case of maternal fatality.[8] It is mentioned in ancient Greek mythology that Asclepius, the God of Medicine, was said to have been born by a cesarean section performed on his dead mother Coronis by his father Apollo.[9] Mythology aside, early records of this mode of delivery have been found in many ancient cultures: in Babylon already in the 18th century BC; in Egypt in 600 BC; in India, Mesopotamia, and ancient Israel.

In ancient Rome, the "lex Regia", a royal law issued in the 600s BC, prohibited the burial of a dead pregnant woman before the extraction of the child from the womb, making post-mortem cesareans obligatory. On the other hand, at the time, no cesarean sections were performed on mothers who were alive, and if so, there are no records of any woman surviving the operation. Subsequently, and contrary to popular beliefs, Julius Caesar could not have been born by cesarean section since his mother, Aurelia, was still alive when he invaded Britain. The term cesarean probably refers either to an earlier Caesar who was a praetor in 208 BC or to the fact that the "Lex Regia" later was referred to as the "Lex Caesarea".[9] Probably, early cesarean sections were not performed by medical professionals but by the clergy. In the Middle Ages, the post-mortem cesarean remained obligatory, mainly in order to save the child's soul through baptism.

In the 16th century, although rarely occurring, cesarean sections slowly became a medical procedure aimed at saving both the woman and the child. The first cesarean section in the British Isles in which the mother survived took place in Ireland in 1738.[10] However, still in the 19th century, maternal mortality rates were at least 75%. By the end of the 19th century, with the development of anesthesia, refined antiseptic technique, and the emerging practice of suturing the uterus, mortality rates fell drastically.[9]

In the late 19th century, the lower uterine incision was introduced, diminishing the risks of hemorrhage and later rupture, and in the beginning of the 20th century, Hermann Pfannenstiel introduced the low horizontal skin incision, in favor of the former lower midline incision. This reduced the risk of wound breakdown, and as a benefit, the incision is more cosmetically appealing. The Pfannenstiel and the modified Joel-Cohen incisions, are the most commonly used skin incisions for cesarean delivery today.[11–13]

General anesthesia became readily available at the end of the 19th century, and was the method of choice up until the 1950s, when there was a shift towards the neuraxial regional anesthesia techniques of spinal and epidural anesthesia. This shift reduced perioperative maternal mortality and morbidity, as general anesthesia in late

pregnancy is associated with significant airway and respiratory complications.[14] Other aspects of improved perioperative care are thrombosis prophylaxis, and better treatment of perioperative bleeding and infections.

As the safety of the cesarean delivery has improved, its indications have broadened from being performed solely post-mortem, via, for example, obstructed labor, placenta previa, fetal bradycardia, and breech presentation, up to today's cesareans on maternal request.[9,11] As a consequence, the rate of cesarean deliveries has risen from a few percent one hundred years ago up to 30-35% in many western world countries today,[15] making it one of the most commonly performed surgical operations of any kind.[16] In general, cesarean delivery is considered very safe, but as a consequence of its increased rate, maternal morbidity and mortality related to long term complications have risen during the last decades.[15] Considering complications, one must also take into account the possible impact of this mode of delivery on the health of the child, as a recent meta-analysis found a higher frequency of respiratory tract infections, asthma, and obesity in children delivered through CS than vaginally.[17]

Spinal anesthesia

Neuraxial anesthesia is the recommended anesthetic procedure for the majority of elective and emergency caesarian deliveries today. Neuraxial anesthesia refers to the application of local anesthesia to the spinal cord either using the spinal (intrathecal) route or the epidural route. Spinal anesthesia is the most common followed by epidural anesthesia top up. The latter is used in emergency or semi emergency cases if the parturient already has a functioning epidural catheter in place, and the former in most other cases. Still, general anesthesia is an option used in some cases but is generally avoided since it is associated with a higher risk of maternal morbidity and mortality than neuraxial blockades.[14] Therefore, general anesthesia is usually only confined to cases where neuraxial anesthesia is contraindicated.[18,19]

The spinal anesthesia is performed by passing a very thin needle into the lumbar sac of the spinal canal, usually at levels L3-4 or L4-5. As the cerebrospinal fluid is identified, a syringe containing a local anesthetic, usually combined with a small opioid dose, is connected to the spinal needle and its contents are injected into the spinal canal. Within minutes, a sensory block in the lower part of the body will be noticed, and soon a motor blockade will also occur. A block of the lower part of the paravertebral sympathetic ganglia will also occur, resulting in small artery vasodilation and a decreased SVR, as well as a slight venodilation. The result is a drop in blood pressure, sometimes causing a sense of vertigo, dizziness, and nausea. At times, a compensatory baroreceptor-mediated increase in HR is seen. The

decrease in blood pressure is sometimes quite profound, and may also have a negative bearing on the child.

To prevent these side effects, treatment with intravenous fluids and vasopressors such as phenylephrine or norepinephrine is part of the routine protocol today.[20] Phenylephrine has been the treatment of choice for many years, used either as intermittent injections or as a continuous infusion. It is a selective alpha-1-receptor agonist, causing vasoconstriction and increased systemic vascular resistance but with no direct inotropic or chronotropic effects. Phenylephrine treatment is associated with maternal bradycardia and sometimes nausea. More recently, norepinephrine has become increasingly accepted for the treatment of hypotension during CS.[21] Having both alpha- and also some beta-receptor effects, one expects norepinephrine to result in fewer episodes of bradycardia in the mother but also be less likely to have adverse effects on fetal acid-base status. The exact extent of the influence of neuraxial anesthesia on the cardiovascular system is multifactorial and dependent on the height of the block, on the alleviation of pain, on the amount of endogenous circulating vasoactive substances, as well as on the level of preexisting emotional and vascular tension and reactivity in the individual.

Uterotonic drugs

The uterotonic drugs are a group of substances with the effect of increasing the contractions and tonus of the uterine smooth muscles. The effects, side effects, and modes of action of the most common uterotonic medications will be described in this section, with a special focus on oxytocin and carbetocin.

Oxytocin

Oxytocin is the primary prophylactic treatment against postpartum hemorrhage (PPH) due to uterine atony today. It is also the first-line treatment when uterine atony is ascertained or suspected.[22] In addition, Oxytocin is used both in the induction of labor after the achievement of cervical ripening and to augment and promote uterine contractions in the active stage of labor when the power or frequency of the contractions are insufficient. [23,24]

Oxytocin is a nonapeptide with a intramolecular ring structure and a C-terminal extension with an amino acid residue at position 8.[23] It is synthesized in the hypothalamus and released into the circulation from the posterior pituitary gland in response to certain stimuli, such as suckling and parturition. But it has also been found to be released in response to hemorrhage, hyperosmolality, fever, physical restraint, and pain.[25,26] In addition, oxytocin can be synthesized in the heart, kidneys,

adrenals, testes, and uterus.[26] Its half-life is 1-6 minutes, but its contractile effects on the uterus last up to 16 minutes.[27]

Oxytocin has been found to have a multitude of effects, both centrally and peripherally. Apart from stimulating uterine contractions, it causes the myoepithelial cells in the alveolar ducts of the female breasts to contract, leading to the ejection of milk. It also has anti-diuretic effects, retaining water in the body.[23] In addition, oxytocin causes vasodilation. In animal and in vitro preparations, it causes cardiac negative inotropy and chronotropy,[28] possibly with a biphasic effect,[29] but quite contrarily, in human studies, short lived positive inotropy and tachycardia have been observed in many studies.[30–33] Some of the negative hemodynamic effects of oxytocin might in fact be ascribed to the preservative chlorobutanol commonly used in oxytocin preparations.[34] Chlorobutanol had negative effects on the contractile force in human trabeculae preparations, while preservative free oxytocin did not. In many studies, it is unclear from the methods section whether the oxytocin used contained chlorobutanol or not.

In recent years, much focus has been on the central effects of oxytocin. Oxytocin has been found to have appetite regulating properties, as well as anxiolytic effects.[35] Oxytocin also seems to have anti-nociceptive effects, probably by activating inhibitory GABA-ergic interneurons.[36] But most research efforts have focused on its behavioral effects. The hormone is often referred to as the "social bonding" hormone, as its effects seem highly influential in the level of maternal-infant bonding as well as in romantic attachments. Maternal post-partum depression scores seem to correlate with lower levels of oxytocin during pregnancy. In fact, altered levels of peripheral oxytocin have been shown to correlate with several neuropsychiatric disorders, and numerous studies have demonstrated that exogenous oxytocin can influence several aspects of social and emotional behavior.[37] Although promising, at least in autism spectrum disorders, nasal spray oxytocin treatment for neuropsychiatric disorders is still in an experimental phase.[38] This is partly due to the fact that oxytocin has a very short half-life both in plasma and cerebrospinal fluid, and does not readily cross the blood brain barrier, making pharmacological preparations difficult.[39]

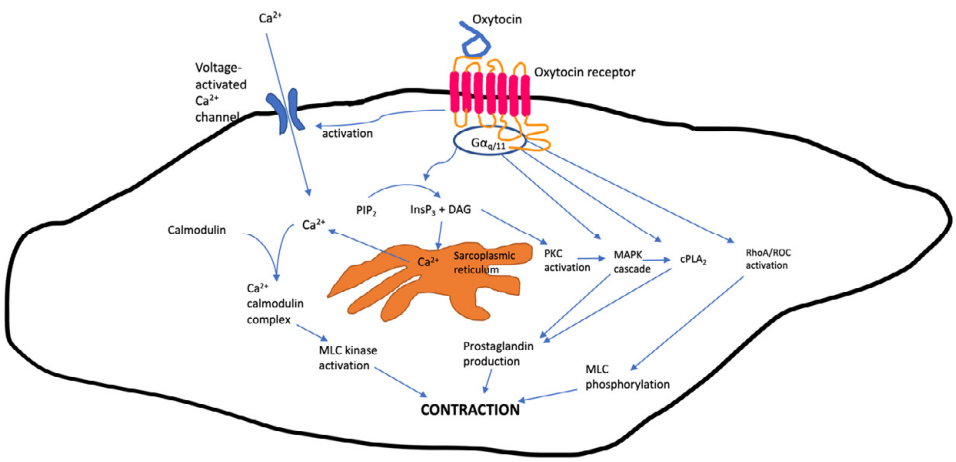
To summarize, oxytocin has a variety of effects in the human body, both peripherally in regulating uterine muscle contractions and milk secretion, also affecting the cardiovascular system and the kidneys, and centrally, regulating many aspects of behavior, emotion, and social interaction.

Receptor physiology and intracellular effects

The oxytocin receptor (OTR) is a G-protein coupled receptor localized in the uterus, mammary glands, heart, kidneys, blood vessels, and brain. The OTR can bind both oxytocin and its structurally similar nonapeptide vasopressin, although the affinity for oxytocin is 10 to 100-fold that of vasopressin. The OTR is also similar to the

vasopressin V1a receptor, both in shape, G-protein coupling, and localization in the vasculature and CNS.[40] In this thesis, the focus will be on OTR effects on the uterus, the heart, and the blood vessels.

In the myometrial cells of the uterus, binding of oxytocin will activate the OTR-coupled $G\alpha_{q/11}$ protein which is in turn coupled to phospholipase C-β (PLC), controlling the hydrolysis of phosphoinositide-bis-phosphate (PIP_2) into inositol-tris-phosphate ($InsP_3$) and diacylglycerol (DAG). These trigger Ca^{2+} release from the sarcoplasmic reticulum.[41] In addition, there is some evidence that oxytocin indirectly augments intracellular calcium ions entry via voltage-operated L-type Ca^{2+} channels (VOCCs). Oxytocin might also cause a decrease in Ca^{2+} efflux. The calcium increase is essential for uterine contraction. In the myometrial cells, calcium ions bind to calmodulin and activate myosin light chain (MLC) kinase, which brings about cross-bridge cycling and the generation of contractile force.[41,42]



Figur 2. The intracellular pathways of myometrial contractions.

The expression of OTRs is probably of greater importance than the plasma levels of oxytocin, during the progress of pregnancy. The OTRs in the myometrium have been shown to increase 12-fold from early to late gestation. In addition, an increase in OTR sensitivity to oxytocin seems to occur during pregnancy. Interestingly, receptor density is greater in the uterine fundus than in the lower segments, causing stronger contractions in the fundus in order to facilitate fetal descent and passage during labor.[41] Post-partum, oxytocin binding sites are down-regulated in the uterus and up-regulated in the mammary glands, in order to stimulate lactation.

Up until recently, there was no consistent evidence of a rise in plasma oxytocin concentration prior to or at the onset of labor. In fact, oxytocin-depleted mice as

well as mothers with malfunctioning posterior pituitary glands have normal labor.[41] But in a recently published review, it is concluded that the oxytocin concentrations rise in a pulsatile pattern during labor, and substantially more so when the baby is born. Oxytocin is then also released into the brain, thus promoting maternal-fetal bonding. Exogenic oxytocin infusions, however, do not cross the blood-brain-barrier, and will not reproduce these neurobehavioral effects.[43]

From an extensive review by Gutkowska et al.[28] we learn that OTRs have been found in the heart and in large vessels. Oxytocin has been shown to exert multiple effects on the heart and vasculature, such as decreased blood pressure, ANP release, negative inotropic and chronotropic effects, parasympathetic neuromodulation, and nitric oxide (NO)-mediated vasodilation. It also has anti-diabetic, anti-oxidant, and anti-inflammatory actions. Oxytocin thus seems to be an important and mostly beneficial hormone in cardiac function, playing parts also in stem cell differentiation, cardiac myocyte survival, and regeneration after ischemic events.[28] Although many of these data stem from experimental models in animal studies, oxytocin has been proposed as a novel therapeutic in heart failure.[44–46]

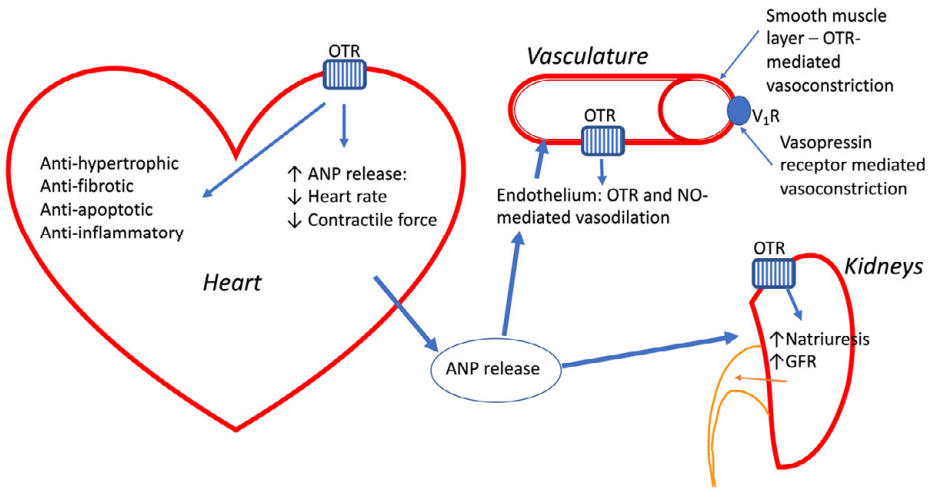


Fig 3. Cardiac, vascular, and renal effects of oxytocin.

The mechanisms for the immediate cardiovascular effects are quite complex. The cardiac effects are related to NO release, ANP release, and centrally mediated parasympathetic activation, slowing down the heart rate. The vascular effects can be both vasodilatory and vasoconstrictive.[47] Vasodilation is mediated by endothelial OTRs, producing a calcium-dependent NO-mediated vasodilation in the studied vascular beds.[48] However, OTRs have also been found to cause vascular smooth

muscle contraction.[47] In addition, at large concentrations, oxytocin acts also on vasopressin receptors, with vasoconstrictive effects. In many human studies, when a rapid intravenous bolus dose of oxytocin is given immediately postpartum during cesarean delivery, one of the immediate effects has been reported to be tachycardia,[30,31,49–52] although the inverse would be expected. Indeed, a decreased heart rate was seen in our studies,[27,53,54] as well as by others.[51,55]

Possible explanations for the diversity of results from in vitro preparations and animal studies include the fact that receptor affinity is lost at high drug concentrations, the diversity of receptor subtype expression in different vascular beds or in different tissue preparations, interspecies receptor subtype differences, and the various oxytocin preparations used.[48] In conjunction, studies on the structurally similar neuropeptide vasopressin have also yielded contradictory results on cardiac effects.[56] Nevertheless, the common belief today is that, at least during cesarean delivery, the hypotensive effects are primary and the tachycardia and increased cardiac output are secondary.[33,49,57] When using phenylephrine as a vasopressor, the increased heart rate and cardiac output from oxytocin are attenuated.[58] In addition, when administering oxytocin more slowly, it seems that both hypotension and the reflective tachycardic response are less prominent.[52] Interestingly, phenylephrine has been found to inhibit both spontaneous and oxytocin-induced uterine contractions in both mouse and human endometrial smooth muscle cells through β2-adrenergic receptor activation.[59]

To add complexity, oxytocin also binds to the structurally similar vasopressin receptors, although with lesser affinity. Oxytocin may thus activate $V_{1a}R$ and $V_{1b}R$, possibly leading to opposite effects than the OTR activation.[39] The $V_{1a}R$ is also expressed in the myometrium, where it exerts similar contractile effects as the OTR.[41] This means that vasopressin also has a saying in uterine contractions in labor, although its exact role remains to be elucidated.

An important clinical problem is OTR desensitization. occurring when prolonged oxytocin infusions are used during labor. This phenomenon increases the risk of PPH as the effect of prophylactic or treatment doses of oxytocin may be substantially decreased. Desensitization seems to occur through the mechanism of receptor internalization and decreased receptor mRNA, and may start within minutes.[25,60] Therefore, it is important for the clinician to have access to and knowledge of other uterotonic drugs that use alternative mechanisms to promote uterine contraction.

In recent years, dose-finding studies have challenged the established standard oxytocin dose of 5 IU, finding an ED_{90} for adequate uterine tone of as low as 0,35 IU for elective cesarean deliveries in healthy mothers. Taken into account the higher ED_{90} for the morbidly obese and possible populational variances, a dose of 1 IU has been suggested as the new standard for uncomplicated elective cesarean deliveries.[61] On the other hand, for intrapartum cesarean deliveries due to labor arrest after

intrapartum oxytocin augmentation, the ED_{90} was found to be 9 times higher, 2,99 IU, illustrating the abovementioned concept of desensitization.

To summarize, oxytocin exerts most of its effects on the OTRs, which are located in the uterus, but also in the vascular endothelium, the heart, and the brain. The OTR is linked to uterine smooth muscle contraction through a complex intracellular pathway resulting in increased calcium ion influx and availability, promoting contractile force. Substantial receptor desensitization can be a clinical problem. In the vascular system, oxytocin have mainly vasodilating properties, resulting in reflex tachycardia. However, animal studies show that the direct cardiac effects of oxytocin are negative inotropic and negative chronotropic, the latter possibly parasympathetically mediated. These effects have not yet been readily demonstrated in humans.

Carbetocin

Carbetocin is a synthetic octapeptide oxytocin analogue, differing in only two amino acid sequences. This modification results in a substantially longer half-life due to better protection from aminopeptidase degradation and disulphidase cleavage. It then also becomes heat stable and does not, like oxytocin, have to be stored in refrigerators. It also results in somewhat modified receptor affinities.[39] Its indication is mainly the prevention of postpartum hemorrhage in cesarean deliveries. A single IV dose of carbetocin results in uterine contractions within 2 minutes, lasting for about 60 minutes. The contractions that result have both a higher frequency and amplitude than those after oxytocin.[39] Oxytocin has a shorter half-life of 1-6 minutes, and its effects only last up to 16 minutes. Therefore, repeated doses or continuous infusions of oxytocin are often needed postpartum to maintain uterine tonus.[27]

In recent guidelines, carbetocin has emerged as an alternative first-line option for the prevention of PPH, both after vaginal and cesarean delivery, especially for high risk women or where cold storage is unavailable.[62] Recent dose-finding studies have challenged the recommended dose of 100 μg for elective cesarean deliveries, establishing the ED_{90} for adequate uterine tone as low as 14,8 μg. On the other hand, for intrapartum cesarean deliveries due to labor arrest after intrapartum oxytocin augmentation, the ED_{90} was 121 μg.[61] Cardiovascular side effects of carbetocin are less examined than those of oxytocin, but a few studies published indicate similar effects.[51,63] Being structurally very similar to oxytocin, one would expect the same multitude of effects in the body from carbetocin. However, there are some differences in receptor affinities, as carbetocin does not seem to activate V1aR or V1bR, but instead acts as an antagonist.[39] These receptor affinity differences may cause a slightly different clinical response than from oxytocin, although this remains to be confirmed in clinical studies.

Methylergometrine

Methylergometrine, also known as methylergonovine, is a semisynthetic alkaloid ergot currently recommended as the second line treatment or prevention of uterine atony, either alone or in combination with other uterotonic drugs.[62,64] The receptor targets are the dopamine D1 receptor, the 5-hydroxytryptamine receptor (5-HT), and alpha adrenergic receptors. The net effect is the influx of Ca^{2+} into the myometrial cells, thus initiating the contraction cascade. The recommended dose is 0.2 mg IM, with an estimated half-life of 3,4 h. The main adverse effects are related to hypertension, as ergot derivates are potent vasoconstrictors. Methylergometrine is therefore contraindicated in chronic or pregnancy-induced hypertensive disorders, and coronary artery disease.[65]

Prostaglandins

Basically, two synthetic prostaglandin analogues are used for the prevention or treatment of uterine atony today, namely misoprostol (prostaglandin E_1) and carboprost (15-methyl-$PGF_{2\alpha}$). They promote contraction by increasing intracellular calcium ions through altered membrane permeability, forming gap junctions, and also by upregulating the oxytocin receptors in the uterus. Prostaglandin derivates are used as second- or third-line treatment, depending on patient comorbidities.[65] Misoprostol is available for the oral, sublingual, or rectal route and is mainly used for the prevention of post-partum hemorrhage (PPH) in situations when other routes or treatment options are less available. It can also be used as second- or third-line treatment of PPH.[62] Misoprostol is given as a single dose, preferably sublingually, and it benefits from not having any absolute contraindications other than hypersensitivity to the drug. The main side effect is fever. Apart from its use in obstetrics, it is a well-known medicine used for the treatment of peptic ulcer disease.[66] Carboprost is used IM, with the adverse effects of possible bronchial constriction and hypotension. It has a quite short half-life and may have to be repeated every 15-90 minutes. A meta-analysis suggests that methylergometrine is slightly more effective as a second line treatment of PPH than carboprost.[67]

Medical gases

Oxygen

Human cells require oxygen to maintain metabolism and life. In the event of no oxygen supply, cell death will occur within minutes. The notion of some gas in the atmosphere necessary for fire and life was thought of already in ancient times, and this was scientifically observed by Leonardo da Vinci. Oxygen is traditionally

claimed to be first discovered in 1774 by Joseph Priestley, who called it dephlogisticated air, although there is evidence that Carl Wilhelm Scheele discovered it just before. Unfortunately his notes on the case were not published until later.[68] Antoine Lavoisier soon contributed with a better understanding of this gas' properties and renamed it oxygène. Medical treatment with oxygen began shortly thereafter, with good results described.[69,70] But in the 19th century, the medical virtues of oxygen treatment seemed to fall somewhat into oblivion, and oxygen therapy often consisted of a few breaths of poorly concentrated oxygen, if any. It was used mainly outside of the medical profession as a "cure-all" and was often quite costly. The first commercial oxygen production began in the late 19th century, eventually resulting in the availability of liquified oxygen.

A pioneering case of successful continuous oxygen therapy to a patient with pneumonia came from Dr. Albert Blodgett in 1890.[69,71] From his article there is an interesting quote: 'The dealer who supplied the gas was astonished at the amount required, and, thinking to do me a service, sent me a cautionary message, implying that no human being could possibly stand so great an amount of oxygen, on account of the dangerous degree of stimulation to the system and the increased combustion of tissue.' From there on, via the works of Fick, Bert, and Haldane, the modern rational use of oxygen evolved, unfortunately catalyzed by the gas poisonings of World War I.

The current use of oxygen (O_2) therapy and treatment covers an immense number of clinical situations. Chronic long-term treatment is rare in numbers, but still, quite a few patients in the late stages of chronic obstructive pulmonary disease (COPD) have chronic low-dose oxygen therapy. In most other cases, oxygen treatment is indicated for potentially reversible emergency situations or in pre-oxygenating situations before induction of anesthesia. In emergency and pre-hospital medicine, many patients receive O_2 therapy as a routine, often without checking if hypoxemia is present or not.[72] Common cases where O_2 is routinely administered are pulmonary disease, cardiac disease, septic shock, trauma, hemorrhagic shock, toxic gas exposure, intoxications, and other states of altered consciousness, including anesthesia, post-operative and post-anesthesia situations, or basically any other state of serious or potentially serious physical ill-being. Hyperbaric oxygen (HBO) treatment is rare but optional in selected cases. In obstetrics, oxygen has been recommended for the treatment of non-reassuring fetal status when suspected from a pathologic cardiotocogram or signs of fetal acidosis.[73]

Despite the potentially lifesaving effects of O_2 therapy, concerns have been raised about O_2 toxicity. Casual or sluggish use of supplementary oxygen may result in hyperoxygenation. Hyperoxygenation has been shown to have quite a few short-term and long-term negative effects.[74] The long-term effects are related mainly to the production of reactive oxygen species (ROS) that are involved in a multitude of potentially organ damaging processes, including bronco-epithelial injury, DNA-damage, and uncoupling of mitochondrial respiration.[75] The short-term effects are

vasoconstriction, decreased microcirculation, alveolar damage and atelectasis, and potentially worsening myocardial infarction and stroke.[72,76,77]

Cardiovascular short-term effects

Probably the first study focusing only on the circulatory effects of oxygen was made by Parkinson in 1912,[78] He described a modest decrease in heart rate (HR) of about 6 % on average, occurring within minutes during oxygen inhalation in 12 healthy volunteer students. This finding has since then been confirmed by several studies. In 1962, Daly and Bondurant conducted a study on 15 normal male subjects,[79] measuring HR, blood pressure (BP), and cardiac parameters using an indocyanine green hemodilution method. They found that oxygenation resulted in a decreased heart rate and cardiac index (CI) a slightly increased blood pressure, an increased systemic resistance, but no change in stroke index. They also found an almost linear relationship between the increase in oxygen concentration (between 15 and 100%) and the decrease in HR. Since atropine administration attenuated the decrease in HR and CI, it was assumed that the decrease in HR was vagus-dependent, and the decrease in CI was rate-dependent. These findings have been confirmed by other works[80].

A very recent study using PPG in the emergency department, found that hyperoxygenation caused a slight increase in BP, a slight reduction in CO, no change in SV, and a quite large increase in SVR.[81] A recent review came to similar conclusions, concerning healthy volunteers.[82] Oxygen inhalation reduces CO by approximately 10% and increases systemic vascular resistance (SVR) by 11-12%. HR decreased and BP slightly increased. In heart failure patients, however, the response seems more pronounced, with a CO reduction of 15%, mainly due to a reduction of stroke volume (SV), and a greater increase of SVR of 25%. In patients with sepsis, hemodynamics were unaffected by hyperoxia, probably due to generalized vasoplegia. In five of the six included studies, hyperoxia did not improve systemic oxygen delivery. There is some heterogeneity between studies that is believed to be due to different methods for oxygen delivery, unblinded study designs, and the use of measuring methods with low reproducibility. Nevertheless, available data support the notion that the use of superfluous oxygen in the absence of hypoxemia should be discouraged.[72,75,82,83]

On the subject of circulatory adverse effects from oxygen treatment on pregnant women, very few studies are published. There is a study from Polvi et al. examining the effects of hypoxia and hyperoxia for 10 minutes each on 10 healthy women in late pregnancy.[84] They used doppler flow parameters to calculate the pulsatile index (PI) from both fetal and maternal vessels. Hyperoxia decreased FHR but had no effect on the mother on these measurements. A study by Litchfield et al. used bio-impedance to evaluate the hemodynamic response from approximately 40% O_2 (8 L/min via Venturi mask) on healthy full term pregnant women.[85] Despite the rather low O_2 flow, they observed a small decrease in CI and a small increase in SVR, but no changes in stroke index, HR, or MAP. A recent study by McHugh et al. used a

NICOM device to measure the hemodynamic response from 10 minutes of hyperoxygenation in both nonpregnant and third trimester pregnant women.[86] They used a non-rebreather mask, delivering 12 L O_2/min. In the pregnant group, they found a fall in HR, CO, and CI coupled with a rise in SVR. BP did not change. Interestingly, these changes did not occur in the nonpregnant group. The study did not include sham inhalations of room air as a control, but subjects were their own controls in a before-and-after fashion.

To conclude, pregnant women seem to respond to hyperoxygenation in similar ways as the rest of the population, with an increased SVR and a decreased CO, but their response seems to be more profound and easily provoked. The number of studies is still scarce, and more research is needed.

Obstetric use

For years, maternal hyperoxygenation has been used in labor when signs of fetal distress have been present. At times, it has also been used prophylactically, with the aim of better fetal outcome. Fetal monitoring usually consists of fetal heart rate (FHR) monitoring, most commonly using cardiotocography (CTG), and fetal acid base status sampling from the fetal scalp when the former shows signs of distress. In low resource settings, only auscultational FHR is available, but otherwise, CTG is the cornerstone of fetal surveillance in modern obstetrics.[87]

During fetal life, oxygen must be transported from the atmosphere to the fetal cells. Fetal gas exchange is totally dependent on the function of the placenta, placental and umbilical blood flow, and maternal-fetal concentration gradients. Maternal respiration, circulation, and oxygen transport, as well as fetal circulation and hemoglobin, are all of uttermost importance for fetal oxygenation. In the case of hypoxia, anaerobic metabolism may produce energy for a limited period of time, but this will result in the accumulation of intracellular lactic acid. The lactic acid will eventually diffuse into the circulation, resulting in lactic acidosis.[88] Umbilical cord blood gas analysis immediately post-partum is the only way to quantify the degree of fetal acidosis just before birth. There is an association between low pH (< 7,05) and high base deficit (BD) (>10 mmol/L) and adverse short-term outcomes in the newborn. Severe newborn acidosis is also associated with low Apgar scores at 1 and 5 minutes. Low 5-minute Apgar scores are correlated with worse short- and long-term neurological outcomes.

It is important to recognize that some degree of hypoxemia occurs in almost all fetuses during labor, and that there is, to date, no notion of to what extent these episodes have impact on the future health of the baby. Transient fetal hypoxia significantly reduces or decelerates FHR, mediated by arterial chemoreceptors in the carotid sinus and aortic arch.[89] These chemoreceptors send signals to the brain stem, from where cardiovascular and endocrine responses are distributed. In this fetal chemoreflex, a raised fetal blood pressure is included, in order to maintain

oxygenated perfusion into the vascular beds most essential for survival. In long-term or chronic hypoxia, the chemoreflex is not sustained. Instead, other compensatory mechanisms occur, the nature of which is complicated and not fully understood. The responses to long-term hypoxia include adaptive physiologic changes, but in some or severe cases, responses include intrauterine growth retardation (IUGR), possible cell damage due to the formation of ROS, and possible bacterial translocation from the mother to the fetus as a result of increased placental maternal-fetal permeability.[89]

Severe intrapartum hypoxic events may lead to hypoxic-ischemic encephalopathy (HIE). This diagnosis includes metabolic acidosis, low Apgar scores, imaging evidence of cerebral edema, changes in muscular tone, suckling movements, seizures, or coma. HIE is divided into three grades, of which grade 1 usually comes without sequelae, whilst in grade 3, the majority die or develop long-term sequelae.[88]

The most common cause of intrapartum fetal hypoxia is decreased blood circulation during uterine contractions. In normal labor, this always occurs to some extent, as contractions compress the maternal blood vessels to the placenta, as they run through the myometrium. If the umbilical cord is compressed at some point, this will worsen the situation. Excessive uterine activity, either spontaneous or iatrogenic through oxytocin stimulation, is often responsible for decreased fetal oxygenation. Much less common reasons for decreased fetal oxygenation are maternal factors, such as respiratory distress resulting in maternal hypoxia or other blood gas abnormalities, or maternal decreased blood pressure due to aortocaval compression, neuraxial or general anesthesia, or pathologies involving the cardiovascular system. Even more rare, but imminently life threatening reasons for fetal hypoxia are placental abruption, uterine rupture, or severe mechanical complications of delivery.[88]

In the case of detected or suspected fetal distress, treatment goals are to optimize O_2 delivery to the fetal cells. The most common measures for doing so depend on the probable cause. Most often, it is sufficient to suppress uterine contractions by administering tocolysis, but sometimes there is also a need to optimize maternal respiration and circulation. This is usually accomplished by giving oxygen to the mother and by putting her on her left side to relieve any potential aortocaval compression, as well as any umbilical cord or fetal head compression. If a low BP is still present, discontinuation of epidural anesthesia (if present) is advised, and intravenous fluids and vasopressors are administered. If there are other causes of respiratory or cardiovascular unease, these should, of course, be promptly diagnosed and treated.[90]

The use of oxygen in the uncompromised mother for the sole reason of fetal distress has been scrutinized and criticized in many studies lately. In the situation of a normoxic mother, it is currently not clear if the fetus benefits from maternal hyperoxygenation. In fact, the opposite might be true.[91]

The rationale for oxygen treatment for intrauterine resuscitation, in the case of nonreassuring FHR tracings, originates from several small studies, where positive effects on secondary outcomes were seen. For example, in a 1971 study, mothers were exposed to O_2 for 60 minutes during labor, but the only outcome was better fetal scalp pO_2.[92] There is a study on mothers receiving Entonox (50% N_2O in O_2) or pethidine as analgesia during labor, that shows an increased number of episodes of maternal desaturation in the group receiving both pethidine and Entonox.[93] Interestingly, mothers not taking any analgesic medication also had episodes of desaturation. A study from 1993 where 12 laboring mothers were given 100% O_2 and their fetuses were monitored with fetal SaO_2 showed us that fetal oxygenation rose in response to maternal hyperoxygenation, but the maximum response took approximately 9 minutes to occur.[94] These mothers had epidural analgesia and no opioid medication, and no signs of hyperventilation.

Many other studies have addressed the subject, for example, Aldrich et al. found increased cerebral oxygenation from maternal hyperoxygenation,[95] while Sorensen et al. came to a different conclusion. In a fetal lamb experiment, the maternal arterial pO_2, fetal liver pO_2, and the blood oxygen level dependent (BOLD) magnetic resonance imaging (MRI) tissue signals from the fetal liver, spleen, and kidney were clearly correlated when the ewes were exposed to normoxic, hypoxic, and hyperoxic conditions.[96] However, the BOLD signals from the fetal brain remained unchanged, which the authors attribute to efficient autoregulation to protect the fetal brain from hyperoxia, in analogy with the brain-sparing effect to protect from hypoxia.

An interesting study from Thorp et al. from 1995 randomized 86 mothers without signs of fetal distress to receive O_2 therapy of 10 L/min continuously or no treatment during the second stage of labor.[97] The net result from oxygenation was a significant *deterioration* of umbilical blood gases at birth. A similar study, but with low flow O_2 of 2 L/min was recently conducted in China, detecting no difference between the groups in umbilical pH or FHR tracings.[98] A Cochrane review from 2012 concluded that evidence was insufficient for the support of maternal oxygen therapy in case of fetal distress or for prophylactic use during the second stage of labor. Since then, several publications have discouraged the use of maternal hyperoxygenation for fetal distress, at least in category II CTG patterns. [99,100] This has not passed without debate, with the argument that there is evidence of improved fetal oxygenation from maternal hyperoxygenation, especially in hypoxic fetuses, and that evidence of harmful effects on the fetus is only theoretical.[101]

In the last 5 years, to my knowledge, three randomized controlled studies addressing the subject have been published,[102–104] but they all only include category II FHR tracings, a category that is intermediate and includes a variety of possible tracings not necessarily indicative of significant fetal hypoxia.[105] In fact, up to 80% of laboring women have category II FHR at some point during labor.[106] From a descriptive study on 2251 parturients with category II FHR, we learn that two thirds of these women recover to category I within 60 minutes with relatively simple

measures.[107] In this study, only 3,4% underwent CS and 4,2% instrumental vaginal delivery within 60 minutes from the observed FHR pattern. 75% of women with category II FHR received O_2 treatment, but since there was no randomization and no control group, we cannot know for sure if the improvement in FHR was due to the O_2 supplementation.

The randomized studies addressing the subject of maternal hyperoxygenation for intrauterine fetal resuscitation in category II FHR tracings all came to the conclusion that this intervention did not alter umbilical lactate.[102–104] One study showed some improvement in FHR tracings and fewer epistotomies,[104] with the weaknesses that 39% of the included women delivered within 15 minutes of enrollment and that 33% removed their oxygen mask due to discomfort. The two other studies, made on the same subjects, showed room air to be non-inferior compared to 10 L/min O_2 regarding umbilical cord blood gases and mode of delivery,[102] and no improvement in FHR tracings in the treatment group.[103] A weakness of these studies is that they did not include cases of established or severe hypoxia, as in category III FHR. A review from 2021 concludes that better-powered RCTs are needed to thoroughly assess both short- and long-term neonatal morbidity in response to maternal hyperoxygenation for the treatment of suspected fetal hypoxia.[100]

The problem of the formation of ROS from hyperoxygenation has been addressed by Khaw et al. in an RCT comparing O_2 to room air for mothers during elective CS.[108] They found a slight increase in umbilical cord pO_2, but also an increase in oxygen free radical activity in both the mother and fetus. On the other hand, when repeating the study during emergency CS, no difference in lipid peroxidation occurred.[109] Of importance is that oxidative stress seems to be generally increased in pregnancy and even more so in preeclampsia.[110] This suggests that hyperoxygenation could be more harmful in preeclamptic patients.

To summarize, routine obstetric use of supplementary oxygen for the treatment of nonreassuring FHR in the normoxic healthy mother is probably not useful, although there is no clear clinical evidence for it to be harmful either. The potentially harmful effects of ROS on both the mother and the baby are insufficiently examined. Maternal adverse cardiovascular effects from hyperoxygenation may be unsuitable for the compromised patient. Until there is better understanding, the recommendation is to avoid unnecessary hyperoxygenation.

Nitrous Oxide

Nitrous oxide (N_2O) is a colorless gas used as an analgesic and anesthetic adjunct since the mid-19th century, making it one of the longest-lasting medications in clinical use today. Joseph Priestley, who was also the first to describe oxygen, initially characterized it in 1772. Priestley named this gas “nitrous air”.[111] Humphry Davy was a pioneer in his discovery of some of the analgesic and anesthetic properties of the

gas, through a long series of experiments on both animals and on himself at the beginning of the 19th century. Unfortunately, he did not quite realize its full potential at the time. [112,113] The first public demonstration of the analgesic effects of N_2O was made by the dentist Horace Wells in 1845. This was, however, considered a failure, and the use of ether gained more popularity. In the 1870s, N_2O found its place in dentistry, and in the 1930s it replaced chloroform for labor analgesia.[114]

N_2O has the favorable effect of very rapid uptake and elimination, but it does not produce complete anesthesia. This makes it very suitable for short-lasting, painful events such as labor contractions, dentistry, and similar processes. Its fast action and elimination are due to its very low tissue solubility and excellent blood-gas coefficient. Its uptake and elimination are solely pulmonary, thus, not dependent on liver or kidney function, nor does it interact with other medications.[115] Its mode of action on the central nervous system is complex, but it is now believed to be through antagonism of the NMDA and the AMPA-kainate subtype glutamate receptors. However, opioid, GABA, and noradrenergic pathways are also involved in its actions, as is the blocking of voltage-dependent calcium channels via free radicals.[116–119] There are reports of N_2O stimulating endogenous opioid release from the periaqueductal gray area (PAG) in the midbrain, leading to modulation of pain processing in the spinal cord through descending inhibitory pathways.[119]

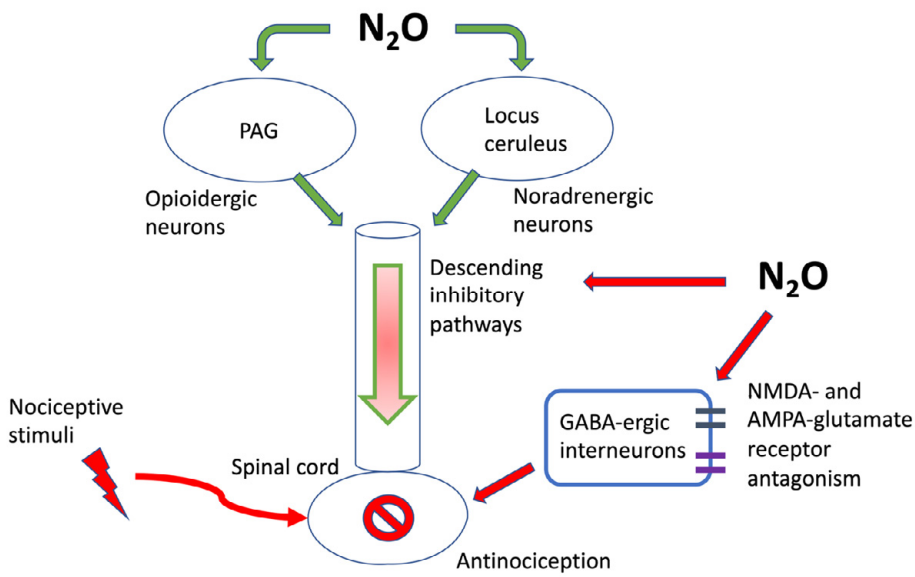


Figure 4. A schematic overview of the major mechanisms for the anti-nociceptive effects of nitrous oxide.

The current use of N_2O is during general anesthesia, during labor, in dentistry, and for painful procedures of short durations such as venipunctures, emergency orthopedic fracture reduction, laceration repairs, and so forth, especially in pediatric care. It is considered safe and effective also in pre-hospital settings for short, painful procedures.[120] Due to its effect on the NMDA receptor, N_2O is believed to have the ability to dampen opioid-induced hyperalgesia and thus reduce post-operative opioid consumption.[121,122] In analogy with the NMDA antagonist ketamine, N_2O also seems to have potential for the treatment of chronic pain and depression.[123,124] This is perhaps a case of historic recurrence, since already Humphrey Davy discovered the psychotropic and euphoric effects of N_2O, and up to the first half of the 20th century, there were several reports on N_2O being used therapeutically in psychiatry.[125] But at least in part, adverse effects from long-term use diminished its popularity. Subsequently, the proposal of N_2O as an anti-depressive treatment has been criticized on behalf of potential serious adverse effects from long-term use (more of which are explained below).[126]

Adverse effects and side effects from N_2O must be divided into short-term and long-term effects. Short-term effects emerge almost immediately and dissolve very quickly as the use ceases. Considering subjective side effects, the most popular are undoubtedly euphoria, uncontrollable laughter, and psychotropic experiences. However, many patients experience mostly nausea, headaches, loss of control, and sedation. Luckily, these side effects resolve within minutes as the gas is eliminated.

With the use of N_2O comes the phenomenon called “diffusion hypoxia”.[127] This happens as the diffusion of N_2O from the bloodstream to the alveoli is faster than that of oxygen, replacing all the alveolar gas with N_2O and (briefly) resulting in hypoxia. The inverse occurs at the start of the inhalations, making the patient hyperoxic. If another volatile anesthetic is present, this occurs for that gas as well. This phenomenon is also called the “second gas effect”. There is some data indicating that carbon dioxide is also rapidly eliminated this way, creating a short-lasting hypocapnia after the N_2O inhalation is stopped. This could theoretically induce a short period of hypoventilation. However, the clinical importance of this is very small, at least as long as N_2O is mixed with O_2 in the recommended concentrations (at least 30% O_2, usually 50%). Today, all medical devices for the administration of N_2O should be equipped with a hypoxia blockage device with a minimum set O_2-level.[128] On the other hand, hypoxia may be a serious problem in abuse situations. It is notable that if N_2O is combined with systemic opioid medication during labor, the incidence of respiratory depression is higher than from opioids alone.[93,129]

Another important side effect of N_2O is its propensity to expand in closed air-filled spaces, making it contraindicated in cases such as emphysema, pneumothorax, ileus, middle ear surgery, pneumocephalus, air embolus, or intracranial hypertension.

Long-term adverse effects are, for the most part, only related to chronic exposure, either occupational or due to abuse. Longer exposure (months) can result in vitamin B12 (cobalamin) deficiency. This happens because N_2O oxidizes the vitamin B12 cobalt ion, hindering its function as a coenzyme for methionine synthase and L-methyl-malonyl-coenzyme.[130] These enzymes are essential for the maintenance and synthesis of the myelin sheath, and their deficiency can result in subacute combined degeneration (SCD) of the spinal cord. Symptoms include peripheral neuropathy, abnormal proprioception, spastic paraparesis, and autonomic disturbances. Vitamin B12 deficiency may also have effects on the bone marrow, causing megaloblastic anemia and neutropenia.[131,132] Thus, long-term clinical use of N_2O is discouraged. If vitamin B12 deficiency is known or suspected, cobalamin deficiency may occur after shorter exposure times. In those situations, the use of N_2O is contraindicated. The regained popularity of N_2O as a party drug in recent years has unfortunately brought the aforementioned rare complications to date.[133] However, regarding the very long clinical experience with the gas and when following the current recommendations for its use, N_2O is considered very safe.

Cardiovascular effects

The results from studies of the hemodynamic effects of N_2O are not completely unanimous. Many studies are small, unblinded, and non-randomized. Quite a few were performed under general anesthesia during surgery, with many confounding factors. Review articles tend to blend results from in vitro and animal studies with those from human in vivo studies. In a 1972 study, effects from 40% N_2O during 30-45 minutes were compared to nitrogen (on the same patients) using ultra-low-frequency ballistocardiogram and dye-dilution technique on 10 healthy volunteers.[134] The study protocol was quite complicated, starting off with some kind of preparation phase where the volunteers "got familiar" with breathing N_2O. Then there was a two-phase experiment with the measurements. N_2O was shown to cause a decrease in HR, BCG, and CO, but not BP. The TPR increased accordingly. In a study by Lichtenthal in 1977, three different modes of gas delivery were compared to a control group while measuring the effects on circulation in 22 healthy volunteers.[135] They found a decrease in HR and BP. On 8 of these subjects, they also performed echocardiographic and pulse wave analysis for the calculation of left ventricular (LV) function. No change in any index of the LV function was found.

Per Hohner and Sebastian Reiz, in a review from 1994,[136] describe the known effects of N_2O on the cardiovascular system: N_2O has an attenuating effect on baroreceptor-mediated tachycardia. It has a mild depressant effect on the myocardium, seemingly more pronounced in patients with heart disease. A probable explanation is that N_2O inhibits transsarcolemmal calcium ion entry. However, N_2O seems to increase sympathetic tone, thus masking some of the cardiodepressant effects. At the date of that review, there was a weak association between N_2O and intraoperative myocardial ischemia in certain patient populations, but there were no prospective

data to support this. Later on, mainly studies on the effects of N_2O on cerebral blood flow and metabolism were published, not so much on cardiovascular effects. However, there is a study from 2004 comparing the effects of N_2O with Xenon during general anesthesia.[137] They found a moderate decrease in MAP and LV systolic function. In order to establish the cardiac risk from adding N_2O to general anesthesia, the POISE subgroup post-hoc analysis came out in 2013,[138] not showing any difference if N_2O was given or not during surgery. A year later, the ENIGMA-II study was published.[139] This is a large RCT randomizing 7112 patients with known or suspected cardiac disease having non-cardiac surgery to receive N_2O or not during general anesthesia. There was no difference in cardiovascular complications or perioperative infections between the groups. This confirms the current statements that N_2O may be safely used and should not be abandoned in clinical practice.[114,128,129,140]

Maternal and fetal side effects

The main side effects described above also apply to pregnant women. However, due to the altered physiology of pregnant women, a few special notes must be made. As the use of N_2O in pregnancy other than during labor is rare, the focus will be on the adverse effects and side effects during labor on both the mother and the fetus. N_2O during labor is usually administered without special anesthetic surveillance, like oxygen saturation, ECG, and intermittent BP measurements. Years of experience and many clinical studies have concluded its safety nevertheless.[129] The main adverse effects in labor use are, as previously mentioned, nausea, vomiting, dizziness, drowsiness, and dysphoria. Another common problem in labor is the incorrect timing of the N_2O inhalations, causing pain - analgesia "phase shifting". As it takes at least 30 seconds to have some analgesic effect and a few minutes to reach maximum effect, the analgesic effect is not always reached during the painful contractions. In fact, often the full effect comes slightly after the painful stimuli. If this happens, the parturient will have insufficient analgesia and experience mostly side effects. Adequate guidance and counseling in breathing technique and timing are essential for the efficacy of N_2O analgesia in labor. This said, one must be aware that N_2O is one of the fastest-acting analgesics available.

For the comparison of N_2O to other analgesics available during labor, research quality is poor in general, and study heterogeneity is large.[141] N_2O is more efficient than placebo, probably more efficient than TENS, (but has more side effects). It is equally efficient as opioids, but opioids are associated with more maternal and fetal side effects. It is not as efficient as epidural analgesia, but it is less invasive, less staff consuming, and interferes less with the labor and delivery process.[142,143] There is no evidence of N_2O affecting uterine activity, labor progress, or mode of delivery.[128]

Studies are heterogeneous on the subject of oxygen desaturations. It is unclear if N_2O actually increases desaturation episodes more than if unmedicated. This is quite

clearly shown in a well-made, albeit small, study by Griffin et al.[144] They also showed that the episodes of lower SaO_2 (<94%) were not accompanied by any change in FHR. Concerning fetal adverse effects from maternal use of N_2O during labor, there is no correlation in Apgar score, umbilical blood gases, or neonatal behavior.[145] Concerning long-term effects on the baby, methionine synthase inhibition has been a theoretical concern, and robust data are lacking, but so far, there has been no evident association with any adverse fetal outcomes. The nature of circulatory effects in pregnant women is still not sufficiently validated.

Environmental side effects

The environmental effects of N_2O are a major concern and drawback, much discussed today. Nitrous oxide is a major global contributor to the greenhouse effect, and the chemical life in the atmosphere is quite long (114 years). However, most N_2O is produced in agriculture and through natural biological processes. The medical proportion of the total N_2O emissions is very low, just 0,1% of the total amount of US greenhouse gas emissions in 2012.[146] If N_2O should be withdrawn from clinical use, other pharmaceuticals must be used instead. In that case, the potential pollutive effects of these medications and their metabolites must be included in the balancing act of deciding what medication to recommend. Propofol, for example, an alternative to volatile anesthetics, is highly toxic to aquatic organisms and may cause long-term effects in the aquatic environment.[147] Some authors promoting the abolishment of N_2O have conflicts of interest.[146,148] One must remember that N_2O is a very cheap medication, and no major pharmaceutical company can profit from its use. In addition, destruction facilities are now being installed in many hospitals, reducing up to 99% of N_2O at a low energy cost.[149–151]

Nevertheless, the use of N_2O should be with care, using proper ventilation, closed circuits, minimal fresh gas flow, and tight-fitting masks. Central piping systems should be properly maintained, or even abandoned, to minimize leakage. Concerning general anesthesia, the additive analgesic and anesthetic effects of N_2O can often be readily replaced by intravenous agents such as remifentanil and ketamine. Still, in obstetrics and for other short-lasting painful procedures, however, it is definitely a safe and important medication today.

Pulse wave analysis

Pulse wave physiology

The peripheral pulse wave originates from the contraction of the left ventricle (LV) of the heart. As the ventricle contracts, the aortic valve opens, and a volume of blood (the stroke volume, SV) rushes out from the LV into the ascending aorta. Here the

pulse wave meets the present blood in the aorta and the aortic vascular wall, and then it propagates further towards the periphery of the vascular tree. With each pulse stroke, the arterial wall deforms in the circumferential, longitudinal, and radial directions, with the circumferential movement being the predominant one. This is referred to as the aortic wall compliance, whose magnitude is determined by factors like the circulating blood volume, atherosclerosis, catecholamine levels, and other vasoactive molecules. Compliance also decreases with age. The compliance (C) is defined as the change in volume (ΔV) divided by the change in pressure (ΔP):

$$C = \Delta V / \Delta D$$

The compliance is largest in the aorta, and decreases in the peripheral vessels, reaching its minimum in the femoral and saphenous arteries.[152] This leads to increased systolic pressure as the pulse wave approaches the periphery. The pulse pressure (Pp) is defined as the systolic BP minus the diastolic BP, which in turn is dependent on the stroke volume (SV) divided by the compliance:

$$Pp = SV / C$$

The diastolic BP is determined by the LV relaxation, the integrity of the aortic valve, and the systemic vascular resistance (SVR). The SVR is referred to as the resistance in the small vessels, which is regulated by sympathetic activity, local humoral factors, and blood flow autoregulation.[153] The actual arterial pulse wave is a blend of multiple forwardly ejecting waves, and the distortion of the reflecting waves from the periphery. The reflections differ depending on where in the vascular tree they originate (Figures 5 and 6).

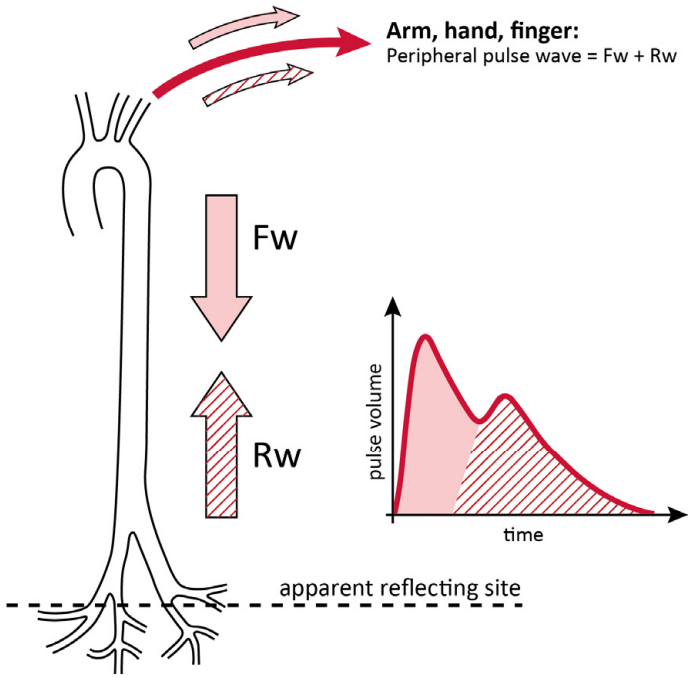


Figure 5. The propagating (forward) wave (Fw) and the reflecting wave (Rw) in the vascular tree, and how they constitute the pulse wave.

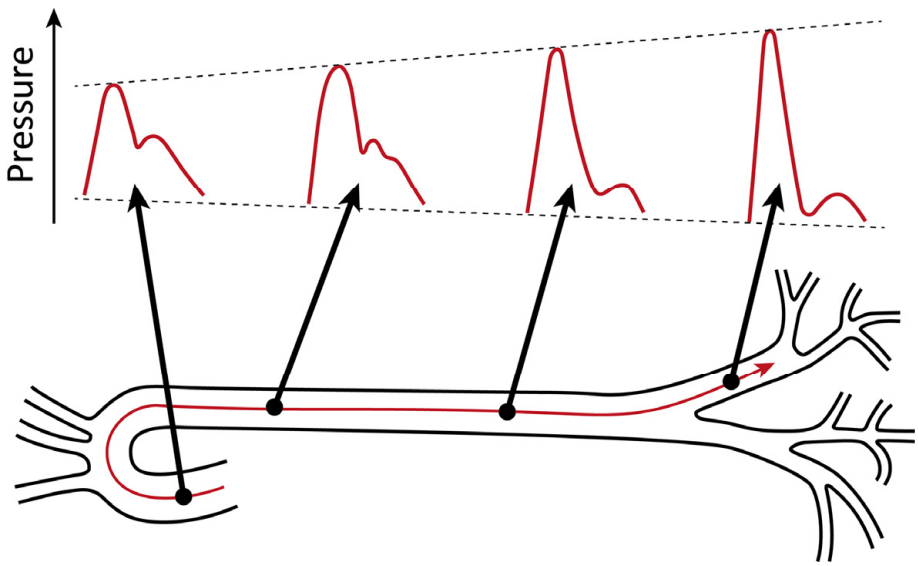


Figure 6. The shape of the pulse wave throughout the vascular tree. Systolic blood pressure increases as the wave travels peripherally, as seen in the increased amplitudes of the pulse wave.

Principles of pulse wave analysis

Arterial compliance (stiffness), SVR, and cardiac output (CO) may be determined or approximated by analyzing the pulse wave. The most accurate estimations require multiple invasive access points or cumbersome technology. Methods can be divided into invasive, minimally invasive, and non-invasive types. Invasive and minimally invasive methods may be calibrated externally, internally, or be non-calibrated, while non-invasive systems are usually not externally calibrated. External calibration usually involves some kind of transpulmonary hemodilution technique and requires both an arterial catheter and a central venous catheter. Internally calibrated systems use nomograms for an approximative calibration. In non-invasive applanation tonometry, performed by holding a sensor above a major artery and registering the contour of the pressure pulse wave, pulse wave velocity can be calculated using two different measuring points, usually the carotid-femoral distance. Carotid-femoral applanation tonometry is quite cumbersome and requires trained staff, but it is considered the gold standard for the measurement of arterial stiffness.[154] Other methods include finger volume clamp methods and finger photoplethysmographic methods.[153] The photoplethysmographic method evaluates the volume pulse wave, while the tonometry methods analyses the pressure wave form. The volume curve is closely related to the pressure curve with a simple transfer function.[155] Examples of how the shape of the curve change in relation to altered hemodynamics are seen in figure 7.

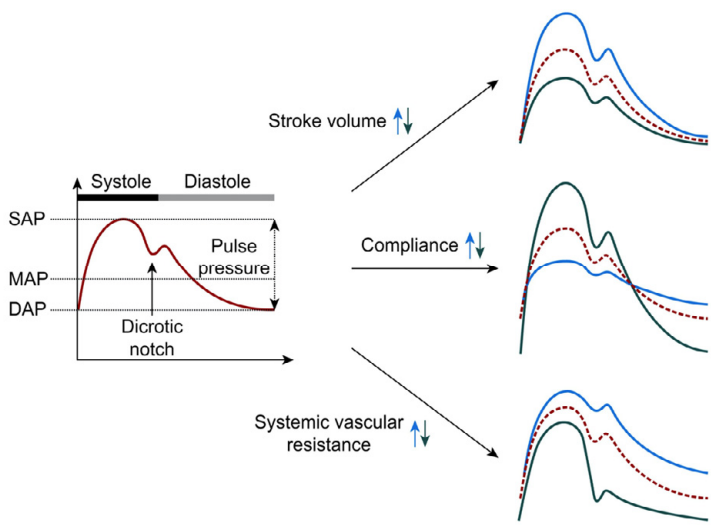


Figure 7. How changes in stroke volume (SV), compliance (C), and systemic vascular resistance (SVR) affect the shape of the pulse wave. The color of the arrow that denotes the direction of change corresponds to the color of the pulse wave form. From Saugel et al., British Journal of Anaesthesia, 126 (1): 67-76 (2021) with kind permission.

Photoplethysmographic digital pulse wave analysis

The pulse waves can be assessed by measuring the pulse in the finger by passing light through the tissue. This method was used as early as the 1930s by Alrick Herzman.[156] To generate a pulse curve, the method employs variations in light absorption according to the blood content during the cardiac cycle. The continuous absorption represents the tissue and the non-pulsatile blood volume, while the pulsatile component increases the light absorption as it passes the probe. This pulse wave is often referred to as the digital volume pulse (DVP) and its waveform as the photoplethysmogram (PPG).[157] The amplitude of the PPG can be affected by temperature and sympathetic nervous system activity, as they affect local tissue perfusion, but the shape of the volume curve appears to be primarily influenced by the conditions of the systemic circulation.[156,158] This is comparable to what is known about the radial pressure wave form. The contour analysis of the waveform was introduced already in 1941 by Dillon and Hertzman, evaluating the waveforms on both healthy and hypertensive volunteers.[159] Several studies have subsequently been published, addressing the changes of the curve according to the effects of different vasoactive drugs, age, hypertension, atherosclerosis, sympathetic activity, stress, pain, and anesthetic depth, among others. [160–163]

The amplitude of volume pulse in relation to the continuous light absorption component is an important measure of peripheral vasoconstriction. The terminology differs, this measure can be called systolic amplitude, systolic peak amplitude, perfusion index (PI, or Perf.), or pulse height (PH).[161,163–165]. Similar to the arterial waveform, the variations of the amplitude during ventilation can be a useful measure of the patient's intravascular volume status.[165,166] PPG waveform variations during respiration have also been proposed to be useful in the monitoring of the respiratory rate using a fusion of baseline wander, amplitude variations, and frequency variations.[167]

On the crude PPG waveform, The first wave indicates the start of systole, the second wave the percussion, or forward wave, the next wave the reflected or tidal wave, followed by the dicrotic notch indicative of the end of systole, and finally the dicrotic wave (figure 8). The tidal wave (T) is often just a slight inflection or change of slope of the curve (figures 11 and 12). These waves are sometimes denoted differently by different authors. Indices derived from the internal relations of these waves can be used for the pulse wave analysis. The stiffness index (SI) and the reflection index (RI) are used in some studies.[168] The SI is the ratio of the height of the patient and the time between the systolic (P) and diastolic (D) peaks, $h/\Delta T$, indicating large artery stiffness. The RI is the ratio of the height of the diastolic and systolic peaks and correlates with the tonus of small to medium-sized arteries. The RI has been shown to change in response to the administration of vasoactive drugs, and these changes occur before changes in BP or HR.[156] Other indices derived from the PPG are ejection time (S – C, or t_{sys}), elasticity index (P/T), and dicrotic index (C/PH).

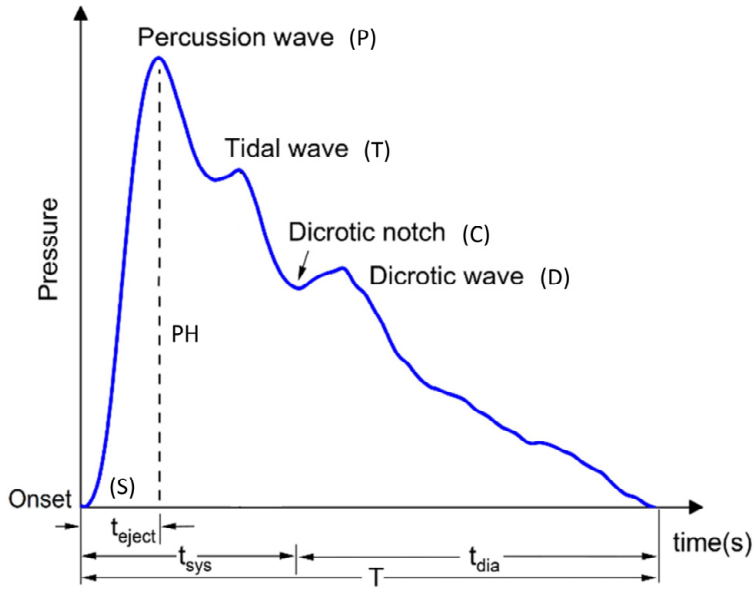


Figure 8. An example of a digital pulse waveform, consisting of the onset (S), percussion wave (P), tidal wave (T), dicrotic notch (C), and a dicrotic wave (D). Pulse height (PH) denotes the systolic amplitude. Modified from J. Chen et al. Micromachines 2021, 12, 569, with kind permission.

Acceleration plethysmogram (APG)

Investigators in Japan have developed the use of the second derivative of the PPG, referred to as the acceleration plethysmogram (APG). (Figure 9).[169,170] In publications, this is called the 'accelerated plethysmogram', or the 'second derivative plethysmogram' (SDPTG). Here, the term APG will be used, as proposed by Elgendi in 2012.[157]

From the APG, five wave points are easily distinguished, named a-e. The a point is of the early systolic positive wave, b the early systolic negative wave, c the late systolic reincreasing wave, d the late systolic redecreasing wave, and e the early diastolic positive wave, that represents the dicrotic notch. (figure 9).[163] Sometimes the e-point is claimed to represent the closure of the aortic valves, the *incisura*. However, as the pulse wave recording is elongated from the aortic root, this *incisura* is strongly diminished, and the dicrotic notch is more likely to be related to the vascular resistance of the peripheral vessels.[171] The heights of the different wave components can be described as the ratios *b/a*, *c/a*, *d/a*, and *e/a*. Particularly *d/a* has been related to arterial blood pressure, arterial stiffness, and the effects of vasoactive drugs, where a decrease suggests increased vascular stiffness. An increase of the *b/a* ratio has been particularly related to age and large artery distensibility, while the inverse applies for *c/a* and *e/a*.[163] The Ageing Index (AI) can be calculated using the formula *(b-c-d-e)/a* and correlates to

carotid distensibility, age, hypertension, and the estimated risk of coronary heart disease.[163] A study by Takazawa examining the PPG after the administration of vasoactive drugs told us that *d/a* was readily changed by vasoactive substances, while *b/a*, *c/a*, and *e/a* were not.[169] This was caused by the change of the reflection wave; vasoconstriction in the arterioles from angiotensin resulted in an early return of the reflected wave, while vasodilation with nitroglycerin resulted in the inverse. These results have later been reproduced by Millaseau.[172]

A study by von Wowern,[164] comparing the Meridian™ DPA with applanation tonometry, shows that the variables best suited for estimation of LV function are *b/a*, EEI, and ETc, for large arteries tonus EEI, and for small arteries tonus DI and DDI. The global variable AI shows a good repeatability and the best correlation to the augmentation index (AIx), which is a global measurement of arterial compliance.

ETc, ejection time compensated, is a true cardiac variable. It corresponds to the HR-corrected LV ejection time (LVETc) by tonometry and echocardiographic measurements, and to flow time corrected (FTc) in esophageal doppler waveform analysis.[164,173,174] However, according to von Wowern et al. repeatability of ETc was fairly poor, probably due to difficulties defining the end of systole from the curve.[164] The DPA-variable pulse height (PH) was not evaluated in the von Wowern study, but this has been done in many other publications, although, as previously mentioned, its terminology is inconsistent. PH and the perfusion index (PI), which denotes the ratio of the amplitude of the pulsatile component to the non-pulsatile component, both correlate to stroke volume, vascular tone, and local peripheral vasodilation.[162,165]

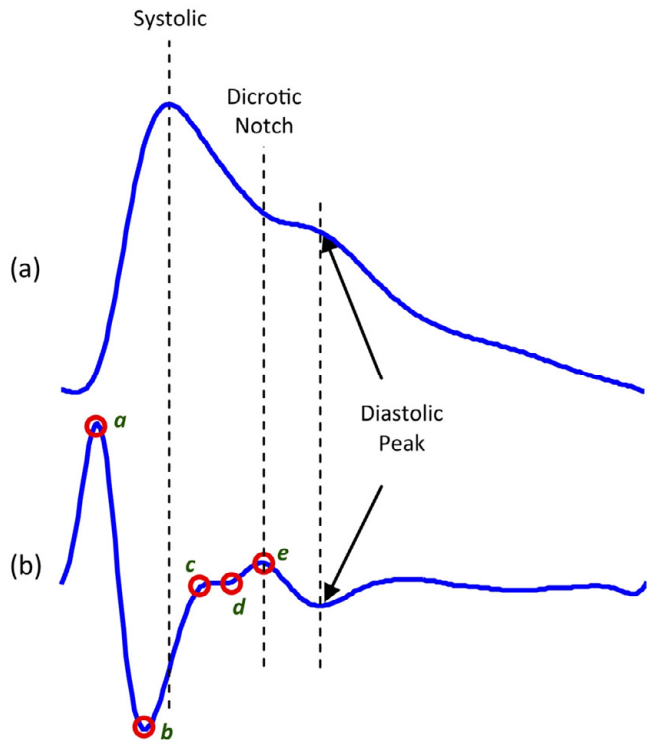


Figure 9. The PPG (top) and the corresponding second derivative, the APG, with its indices a-e (below). By kind permission from Elgendi et al. Biomedical engineering online, 2014, 13:139

Different DPA methods

There are many different devices available for the analysis of the peripheral pulse wave. These devices often use very different technologies, being more or less invasive, sometimes using interchangeable terminology, and sometimes not. One reason is that developers have different ideas of what they want to measure. Quite different approaches may be used if the device is aimed at the evaluation of cardiac output or the screening of arterial stiffness and cardiovascular risk factors. There are very few studies evaluating the methods against each other, and the results are inconsistent concerning interchangeability between devices and indices. Indices from devices using similar technology correlate better than those from devices using different technologies.[175] Devices developed with similar measurement goals also seem to have better interchangeability.

A description of some of the different variables and indices seen in research output is displayed in Table 1, including both invasive and non-invasive technologies.

Table 1. Some commonly used devices for pulse wave analysis and their terminologies.

Device name	Meridian DPA	ClearSight	Pulse Trace	SphygmoCor	FinaPres	USCOM	NICOM	LiDCOrapid	CardioQ	Flo-trac Vigileo
Invasivity	Non-invasive	Non-invasive	Non-invasive	Non-invasive	Non-invasive	Non-invasive	Non-invasive	Arterial line	Esophageal probe	Arterial line
Calibration	none	None or length	n/a	Length	Internal, (gender, age length, weight	Internal (Length, weight)	Internal, (gender, age length, weight	Internal	Internal	Internal, (gender, age length, weight)
Technique used	Plethysmographic pulse wave analysis, PPG and APG	PPG + pressure cuff combination	PPG	Applanation tonometry pulse wave analysis	Finger pressure cuff pulse wave analysis	Transcutaneous doppler	Chest bio-reactance	Radial artery pulse wave analysis	Esophageal doppler of the aortic waveform	Radial artery pulse wave analysis
Output Aims	Vascular stiffness, cardiovascular risk estimation	Cardiac output	Vascular stiffness, cardiovascular risk estimation	Vascular stiffness, cardiovascular risk estimation	Vascular stiffness, cardiovascular risk estimation	Cardiac output	Cardiac output	Cardiac output	Cardiac output	Cardiac output
Major cardiac variables	ETc, EEI	CO, SV	n/a		CO, SV, LVET	ET% (ejection time percent) Ftc (Flow time corrected) SV, CO, CI	CO, CI, SV, VET (ventricular ejection time) TFC[a]	CO, CI SV, SVV, PPV	CO, CI, SV, SD (stroke distance) PV (pulse velocity) FTc	SV, CO, SVV (stroke volume variation)
Major vascular varables	PH, *b/a*, *d/a*, DI, AI	SVR	SI, RI	Aix, PWV (pulse wave velocity	SVR	Vpk (Peak velocity) MD (minute distance) SVR	TPR (MAP/CO), TPRI (MAP/CI)	-n/a	SVR	SVR
Correaltion/ validation	Applanation tonometry	Thermodilu-tion, Echocardio-graphy,	Applanation tonometry		n/a	Swan-Ganz Picco	Swan-Ganz	Swan-Ganz	Swan-Ganz	Swan-Ganz

[a] Thoracic fluid content

Aim of study

The aim of this thesis is to investigate and compare maternal hemodynamic effects from common medical interventions during pregnancy with suspected or well-known cardiovascular adverse effects. The specific aims of each study, presented as papers I–V, were:

Paper I

To investigate the effects of oxytocin during elective cesarean section on cardiac left ventricular (LV) ejection function and systemic arterial stiffness. The secondary objectives of the study were to investigate the hemodynamic effects of spinal anesthesia and the delivery of the baby.

Paper II

To investigate whether oxytocin affects both large and small arteries, and cardiac LV ejection function, during elective surgery in early pregnancy. Secondary aims were to investigate the above-mentioned effects of the induction of general anesthesia.

Paper III

To investigate whether there are differences in cardiovascular effects between oxytocin and carbetocin up to 1 h after treatment. Secondary aims were differences in uterine tonus, bleeding, and subjective side effects.

Paper IV

To investigate the hemodynamic short-term effects of 100% inhaled oxygen, in third trimester pregnant women and in healthy female nonpregnant controls of fertile age

Paper V

To investigate the hemodynamic short-term effects of 30% and 50% inhaled nitrous oxide, in third trimester pregnant women and in healthy female nonpregnant controls of fertile age

Methods

The studies upon which this thesis is based were conducted on five different study groups. All participants were female: three groups in late pregnancy, one group in early pregnancy, and one nonpregnant group. In all five studies, the pulse wave analysis was performed by the Meridian DPA (Meridian Co., Ltd. Korea, and Salcor AB, Uppsala, Sweden) and the output automatically transferred to a spread sheet file on an attached laptop computer (HP 625, Hewlett Packard, Solna, Sweden). The oxygen saturation, heart rate, ECG ST-index, and non-invasive oscillometric blood pressure (NIBP) were assessed from the anesthetic surveillance machines available for the specific study, either the Philips Intellivue MP70 (Philips Healthcare, Stockholm, Sweden), or the Dash 4000 Pro monitoring system (GE Medical Systems Information Technologies, Danderyd, Sweden), and manually entered in the case report form (CRF) for each subject at each evaluation time point. This data was then manually transferred to the spread sheet file.

Digital pulse wave analysis

The pulse wave analysis variables used in these studies were extracted from the Meridian DPA output. The principles of the technique are described in the introduction. The specific technology, output, and terminology for the Meridan DPA will be explained in this section. The Meridian is a non-calibrated, non-invasive, operator-independent digital pulse analyzer that analyzes both the crude PPG and the second derivative PPG, denoted the APG. Its output consists of 16 variables plus the HR. The variables are described in table 2.

In this specific setting we only used the variables recommended by the works of von Wowern et al.[164] as previously mentioned, namely PH, DI, EEI, and ETc, from the PPG, and *b/a*, *d/a*, and AI from the APG. The interpretations of change of these variables are described in table 3. The device samples the PPG during approximately 70s and generates an analysis report output sheet, shown in figure 12. It can also export all values to a spreadsheet file on an external computer.

Fig 10. The Meridian DPA™ device

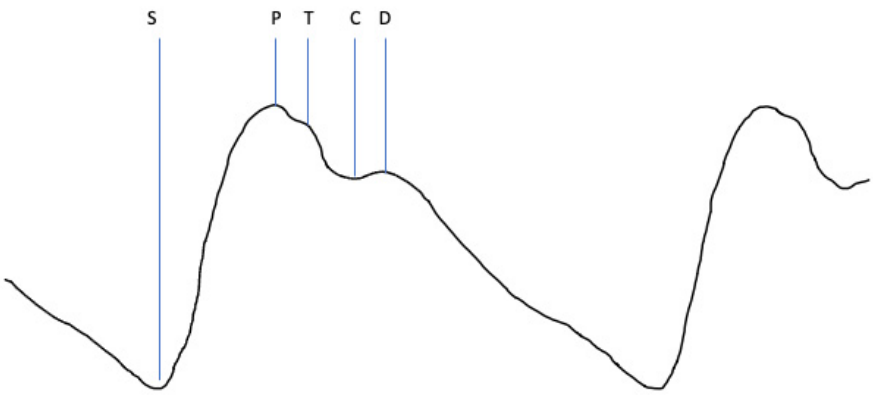


Figure 11: The Meridian PPG and its terminology. The S-wave indicates the start of systole, the P-wave the percussion, or forward wave, the T-wave the reflected or tidal wave, the C-wave the incisura, or the end of systole, and the D-wave, the dicrotic wave .

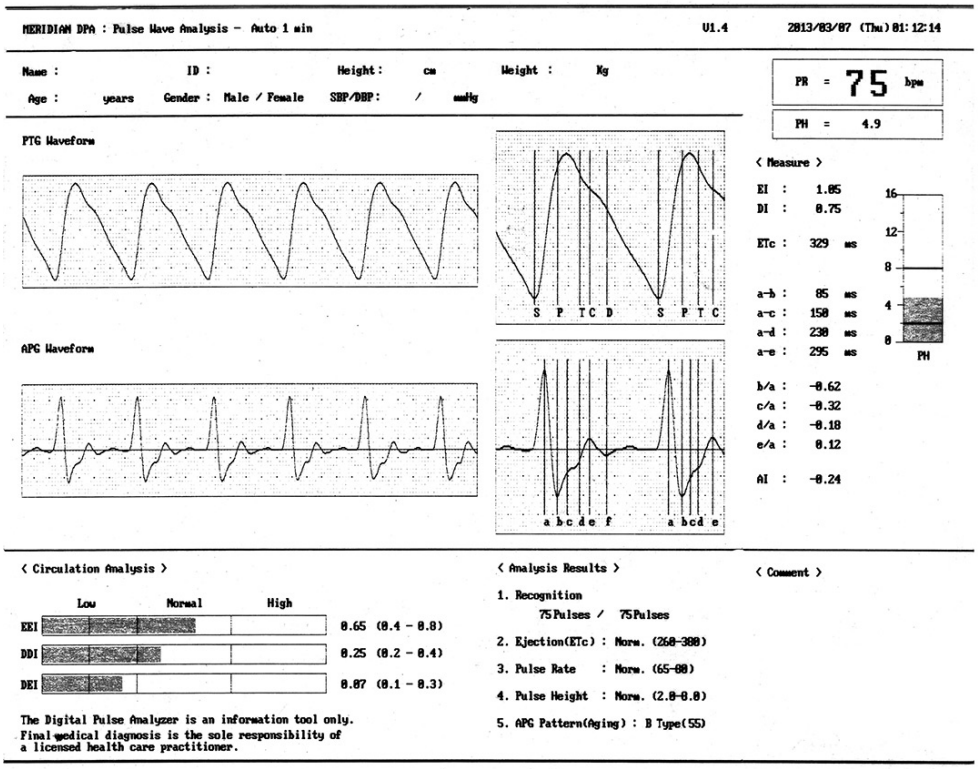


Figure 12. Sample of the Meridian DPA analysis report. From digitalanalyzer.com

Table 2. Variables provided by the Meridian DPA™ system, and how they are computed. The variables used in this thesis are marked in bold. By kind permission from E. von Wowern.

Variable	Formula	Interpretation
Pulse height (PH)	P - S	Amplitude of the pulse, an indicator of perfusion, stroke volume, vasomotor tone, and volume loading. Affected by all factors that affect perfusion and is thus a sensitive but not specific measure of circulatory change.
Ejection time compensated (ETc)	$\frac{S - C}{\sqrt{HR/60}}$	Time in milliseconds for the left ventricular ejection of blood adjusted to heart rate (HR) by the Bazett formula. Affected by left ventricular performance and aortic valve disease.
Elasticity index (EI)	P/T	An indicator of left ventricular ejection power and central arterial stiffness/compliance.
Cardiac ejection elasticity index (EEI)	(P/T) x (-*b/a*)	An indicator of left ventricular ejection power and central arterial stiffness/compliance.
Dicrotic index (DI)	C/PH	An indicator of peripheral vascular resistance/constriction
Dicrotic dilatiation index (DDI)	(PH-C)/PH = 1-DI	An indicator of peripheral vasodilation
Dicrotic elasticity index (DEI)	D–D'/C	An indicator of arteriolar dilatation/constriction
b/a	*b/a*	The acceleration of blood flow from S to P (early systolic phase), an indicator of left ventricular power or central arterial compliance.
c/a	*c/a*	Positive wave in late systole, related to arterial stiffness and age.
d/a	*d/a*	The intensity of the reflected wave and thus the augmentation of aortal pressure, indicating afterload and likely the effects of vasoactive agents.
e/a	*e/a*	Positive wave in early diastole, related to age
Ageing index (AI)	*(b-c-d-e)/a*	A composite index of global arterial stiffness or vascular "age".
a-b, a-c. a-d, a-e		Time intervals from peak to peak. No clinical interpretation[176]

Table 3. Interpretations of changes in the DPA parameters used in the study.

Variable	Interpretation of increase	Interpretation of decrease
PH	Increased peripheral perfusion, increased SV, decreased vasomotor tone	Decreased peripheral perfusion, decreased SV, increased vasomotor tone
ETc	Increase in LV ejection time, Decreased afterload, decreased SVR, increased preload	Decrease in LV ejection time, Increased afterload, increased SVR, decreased preload
EEI	Increase in LV ejection power, large artery vasodilatation	Decrease in LV ejection power, large artery vasoconstriction
DI	Peripheral vasoconstriction	Peripheral vasodilatation
b/a	Large artery vasoconstriction, decreased LV ejection	Large artery vasodilatation, increased LV ejection
d/a	Small artery vasodilatation	Small artery vasoconstriction
AI	Global arterial vasoconstriction, decreased compliance	Global arterial vasodilatation, increased compliance

Method for paper I

Study population and setting

The study was performed in the operation theatre at the Clinic for Gynecology and Obstetrics, Skåne University Hospital, Lund. The included women were scheduled for elective caesarean sections, and recruited consecutively. This was in part a feasibility study, to evaluate the study protocol. Included women had singleton pregnancies, were healthy and and had given their informed consent to participate.

Specific method description

Spinal anesthesia, cesarean section, and oxytocin are thoroughly described in the introduction. Digital photoplethysmographic pulse wave analysis was used, and this method is described at the beginning of this chapter.

Study protocol

All measurements were made in the supine position, with a slight left lateral tilt on the operating table. Each evaluation involved the manual notes of the NIBP, ECG ST index, and SaO_2 from the anesthesia surveillance system, as well as the readings from the Meridian DPA apparatus. Patients had their baseline evaluation (T0) after 5 minutes of rest. Then spinal anesthesia was performed, and the next evaluation was made just before the start of surgery (T1). T2 was made just after the delivery of the baby but just before oxytocin administration. The oxytocin dose was 8,3 µg IV, given during 60s. T3 was made 1 minute after oxytocin administration. T4 was made 5 minutes after oxytocin administration.

Method for paper II

Study population and setting,

The study was performed in the operation theater at the Clinic for Gynecology and Obstetrics, Skåne University Hospital; Malmö. The study group consisted of healthy pregnant women, with a gestational age below 12 weeks, scheduled for elective vacuum aspiration under general anesthesia. 54 patients were asked to participate, and 51 were randomized.

Study protocol

The patients were randomized to two different treatment sequences: either oxytocin first and placebo second (OP) or the inverse (PO). All measurements were made in the lithotomy position, and the patient remained in this position for the whole procedure. Injections were blinded to all staff involved. The oxytocin dose was 1 mL (8,3 µg, 5 IU), and the placebo was NaCl 0,9%, 1 mL. Assessments were made

before and after the induction of anesthesia and before and after the two injections (figure 13). Surgery was halted during the measurements.

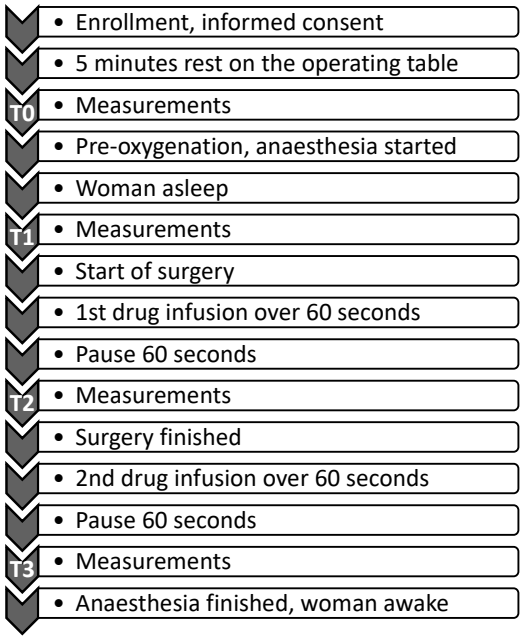


Figure 13. Time sequence of measurements and interventions.

Method for paper III

Study population and setting

This was a prospective randomized double-blind study, performed in the operation theatre at the Department of Gynecology and Obstetrics, Skåne University Hospital. Inclusion criteria were healthy singleton pregnant women scheduled for elective CS. Patients eligible for the study were asked to participate consecutively as they had their pre-anesthetic consultation.

Specific method description

Spinal anesthesia, phenylephrine, caesarean section, oxytocin, and carbetocin are thoroughly described in the introduction. Digital photoplethysmographic pulse wave analysis is described at the beginning of this chapter. A numerical rating scale (NRS) of 0–10 was used to evaluate pain and uterine tonus. The oxytocin dose was 8,3 μg IV (1 mL), and the carbetocin dose was 100 μg IV (also 1 mL). Randomization to either oxytocin or carbetocin was made by a web-based

randomization table (www.random.org) in blocks of 10. Sealed opaque envelopes containing the name of the study drug were prepared and stored in a locked room in the operation ward. The sort of drug administered was blinded to the patient, the anesthesiologist, the surgeon, the operating staff, and the DPA measurement operators (SR, EB, and HJ). The anesthesiology nurse opened the envelope and prepared the injection, but was not involved in DPA measurements or the recording of study data. The randomization key was not revealed until after the study's conclusion. Two-way repeated measures analysis of variance (ANOVA) was used to compare the differences between the groups over time. Delta-values were computed to avoid bias from preexisting differences between the groups.

Study protocol

All evaluations were made with the patient in the supine position, with a slight left lateral tilt on the operating table. Each evaluation involved the manual notes of the NIBP, ECG ST index, and SaO_2 from the anesthesia surveillance system, as well as the automatic readings from the Meridian DPA apparatus. In addition, the rate and infused amount of phenylephrine and intravenous Ringer acetate were noted at each time point. Notes were also taken on any other medication given, any side effects, and the estimated accumulated amount of bleeding. The cesarean section was performed under spinal anesthesia. T0 was the baseline measurement, made just after the delivery of the baby but just before the intervention, i. e the study drug injection. Both drugs were injected during 60s. T1 was made 1 minute after oxytocin administration. T5 5 minutes, T20 20 minutes, and T60 60 minutes after the injection.

Method for paper IV

Study population and setting

The experiments were performed in a calm and quiet room, with a temperature of 21° C, at the maternity unit, Skåne University Hospital, Malmö, Sweden. All of the participating women signed up voluntarily after receiving informed oral and written consent. Oral and written Swedish were understood to all women. Healthy third-trimester pregnant women and healthy non-pregnant women between the ages of 18 and 40 met the inclusion criteria. Diabetes, gestational hypertension, preeclampsia, connective tissue disease, cardiovascular or lung disease, suspicion of intrauterine growth restriction, or other fetal issues were exclusion criteria. In addition to approaching expectant hospital workers and posting a notice in an online Swedish family forum, recruiting pregnant ladies took place mostly at the standard ultrasound check in gestational week 32. Employees at Lund University and volunteer hospital staff made up the control group. In each group, 25 women were recruited.

Study protocol

Participants were asked to abstain from food, caffeine, and nicotine for at least 2 h before the experiment. Their height and weight, age, smoking status and pregnancy status were noted in the CRF. After a 5-minute period of rest in a supine 15° left-tilted position, NIBP, HR, ECG 5-lead ST-index, and SaO_2 were recorded with a Dash 4000 Pro monitoring system. The BP cuff was placed on the left arm and the pulse oximeter on the right third finger. The Meridian™ digital photoplethysmography DPA probe was placed on the right index finger. After the completion of the basal recordings (TB), inhalation of 100% O_2 was started and continued for 5 minutes. A tight-fitting mask connected to a rebreathing system was used (VENTYO Avo, AGA, Lidingö, Sweden). Repeated Dash and Meridian recordings were performed after 1 (time T1), 3 (T3), and 5 minutes (T5). Each Meridian recording takes about 70 s. The Dash recordings were performed immediately after the Meridian recordings. The O_2 inhalation was stopped after the T5 recordings, and the final recordings were performed 5 minutes later (T10).

In pregnant women the FHR was recorded by cardiotocography (CTG) (Avalon FM30, Philips, Stockholm) during the experiment and was classified according to Swedish national guidelines. [177]

Method for paper V

Study population and setting

This study had the same study population and setting as study IV and was performed right after its completion.

Study protocol

The study protocol was similar to that of study IV. After a 10-minute washout period of rest from the O_2 inhalations (study IV), new basal recordings and measurements were made. After the completion of the basal recordings (TB), a tight-fitting mask connected to a rebreathing system was used (VENTYO Avo, AGA, Lidingö, Sweden), and inhalation of 30% N_2O in 70% O_2 was started and continued for 5 minutes. Repeated Dash and Meridian recordings were performed after 1 (time T1), 3 (T3), and 5 minutes (T5). The N_2O inhalation was stopped after the T5 recordings, and the final recordings were performed 5 minutes later (T10). After another 5 minutes of rest, the same procedure was repeated but with an increased N_2O/O_2 ratio of 50/50%.

In pregnant women, the FHR was recorded by cardiotocography (CTG) (Avalon FM30, Philips, Stockholm) during the experiment and was classified according to Swedish national guidelines. [177]

Statistical methods

For statistical computations, Statview version 5.0.1 (SAS Institute, Cary, NC) and SigmaPlot 15 computer software (Alfasoft A/S, Norway) were used. In case of skewed distributions or small sample sizes, non-parametric statistics were used. For comparisons within groups, Wilcoxons' signed-rank matched pairs test was used. For repeated measurements, Friedmans' test (ANOVA on ranks) was used and Holm-Bonferroni adjusted *P* values were used to correct for familywise errors. In studies III-V, Dunn's post-hoc test was used for the baseline comparisons. For comparisons between groups, two-way repeated measures ANOVA with Holm-Sidak post-hoc tests was used. Mann-Whitney-U test was used for comparisons when variables were not normally distributed. Parametric tests were only used when computer software found a normal distribution with the Shapiro-Wilks test and equal variance with Brown-Forsythe's test. All analyses were 2-sided, and a *P* value of <0,05 was considered statistically significant. To avoid bias from possible differences in baseline values (T0) between the groups, we also compared the changes from baseline (set to null) to each time point. This was expressed as Δ-values; For example, the change from T0 to T1, calculated as T1 minus T0, was expressed as ΔT1. Categorical data were compared with Chi-2 test or Fisher's exact probability test.[178]

Ethical considerations

The hemodynamic assessments were non-invasive, pain-free, and did not pose any risks for the mother or the fetus. All study participants were able to understand the given information and give their informed consent. All studies were approved by the Regional Research Ethics Committee in Lund (Dnr 2012/649, 2012/732, 2011/384) and were performed in accordance with The Code of Ethics of the Declaration of Helsinki. In the second study, the study protocol motivated an inversed sequence of injections in the patients randomized to receive the placebo injection first. This did not alter the outcome or risk for the patient. In the third study, a comparison was made between two established pharmacological treatment options. This study was double-blinded for the patient and the staff evaluating the treatment effects. There was no reason to believe that one of the treatments was more harmful than the other. The study was pre-registered with the Swedish Medical Products Agency (EudraCT number: 2013-004224-10, Dnr 5.1- 2013-95167). In the fourth study, pregnant and nonpregnant volunteers received oxygen treatment for five minutes. There were no previous data suggesting any substantially increased health risks from hyperoxygenation of such short duration in healthy pregnant or nonpregnant women, nor for the fetus. The fetal heart rate was monitored in pregnant subjects to ensure fetal well-being. In the fifth study, pregnant and

nonpregnant volunteers received nitrous oxide treatment for five minutes. This was then repeated again after another 5 minutes. There were no previous data suggesting any substantially increased health risk from nitrous oxide inhalations of such short duration in healthy pregnant or nonpregnant women, without any contraindications, nor for the fetus. The fetal heart rate was monitored in the pregnant subjects to ensure fetal well-being.

Results and comments

Study I

Results

Spinal anesthesia resulted in a decrease in BP, increases in PH, DDI/DI, and ETc but not in HR, EEI, *b/a*, *d/a*, and AI. Delivery of the baby resulted in a HR increase, *b/a*, EEI, and AI indicative of vasoconstriction. No change in PH, ETc, and *d/a*. Oxytocin resulted in decreased HR and DBP. PH and EEI increased, other did not change

Conclusion

Spinal anesthesia caused vasodilation and a fall in BP, that was not compensated for by increased chronotropy. All vascular parameters were not affected, possibly due to vasopressor treatment. The delivery of the baby was associated with large artery vasoconstriction and increase in BP and HR. Oxytocin resulted in a decreased BP and HR and some, but not all, of the DPA indices indicated vasodilation. The combined effects of spinal anesthesia, surgery, delivery of the baby, relief of aorto-caval compression, maternal emotions and possible autotransfusion of blood from the contracting uterus all contribute to the noted circulatory changes

Comments

The findings of increased vascular tone immediately after delivery and decreased HR from oxytocin were interesting. HR had increased just before injection, and this value was used as the baseline value for the evaluation of oxytocin effects. Interpretation was difficult due to concomitant surgical activities, relief of aorto-caval compression, possible autotransfusion from the contracting uterus, emotional stress, and phenylephrine treatment. Phenylephrine was used in boluses at the discretion of the anesthetist, which might have influenced the results. The study group was small, and the DPA parameters were not completely unanimous, with quite a few missing values due to finger movements or cold fingers. CS patients are very emotionally affected during the procedure and may not always comply with the given instructions. It is very important that the patient does not move their

fingers during the measurements (70 seconds). Nonparametric statistics, Holm-Bonferroni correction for possible Type I errors, and HR correction were used in order to increase validity.

Study II

Results

51 patients were randomized. Oxytocin had a positive chronotropic effect on the heart, a vasodilatory effect on small and peripheral arteries, and increased the left cardiac ventricular ejection time (ETc). Anesthesia was followed by a significant fall in blood pressure, heart rate, and vascular tone in small and peripheral arteries.

Conclusion

Oxytocin causes mainly vasodilation of small arteries, while large arteries seem less affected. Oxytocin likely increases myocardial workload and oxygen demand. These effects might have been enhanced by the vasodilating effects of anesthesia.

Comments

Here, a more typical pattern with a rise in HR was seen from oxytocin but not from placebo. However, an increase in MAP was seen after both placebo and oxytocin. The start of surgery may have affected the MAP. In total, the results were not completely unanimous, as *b/a*, *d/a*, and AI from the APG did not change. Also here, very transient effects on MAP or DPA-parameters might have occurred just before or after our assessments. The short wash-out time between the injections in the OP-group made placebo comparisons difficult. The changes in ST-index were statistically significant but probably clinically irrelevant. Still, the results have bearing on the effects of oxytocin versus placebo in a hemodynamically more stable setting than during CS.

Study III

Results

85 patients were assessed, 61 randomized and 29 patients in the oxytocin group and 30 in the carbetocin group were analyzed. Also here, Oxytocin was associated with an immediate short-lasting decline in HR. This was not seen in the carbetocin group.

In both groups, the DPA variables indicated both small (peripheral) and large artery dilatation, paired with a lowered MAP. When comparing the changes from baseline (Δ-values) between the groups, only ETc differed, being lower in the oxytocin group at 1, 5, and 20 minutes. After 20 minutes, accumulated phenylephrine consumption had become larger in the carbetocin group. Other secondary outcomes did not differ significantly between groups.

Conclusion

Both carbetocin and oxytocin produce similar cardiovascular adverse effects, with global vasodilation, decreased BP but no increase in HR. The vasodilating effects of carbetocin could be slightly longer-lasting, as reflected by the accumulated phenylephrine consumption. However, the possible negative inotropic and transient negative chronotropic effects of oxytocin might be unfavorable in certain clinical situations.

Comments

The number of women finally randomized was slightly lower than what we aimed for. A reorganization of the elective cesarean section process at the hospital made further recruitment difficult at the time. Nevertheless, power was acceptable. 79%. The negative chronotropic effect of oxytocin that was seen in paper I was also seen here. A lower ΔETc for oxytocin may indicate a negative inotropy as well, which is an unfavorable combination. A study by Langesaeter et al. showed a short increase in CO starting about 40 seconds after the injection and lasting up to 120 seconds.[50] As explained in the introduction, preclinical data have suggested that a decreased SVR is the primary reason for a compensatory increase in CO. In the Langesaeter study, however, it looks like the decreased SVR and the increased CO came almost simultaneously. A study by Rosseland et al. also compared the hemodynamic responses of placebo, oxytocin, and carbetocin during CS.[63] They used an arterial line device (LiDCO) for hemodynamic evaluation. Their study randomized 25 women in each group and focused only on the first 8 minutes after the injection. In general, this paper comes to the same conclusions. However, there are some minor but interesting differences, such as the decrease in HR in our study, and the lower ETc, that must be commented upon.

Small differences in study protocol are probably responsible for the small differences in outcome. In the Rosseland study, the study drug was given already at the presentation of the head and shoulders, while we started after cord clamping, approximately one minute after delivery. This might have implications; we saw in paper I that HR increased immediately after delivery, *before* oxytocin was given. Interestingly, however, this was not seen in the Rosseland placebo group. Another protocol difference is that ephedrine was allowed. Ephedrine causes significant

increase in both HR and CO, while phenylephrine has the inverse effect. The number of patients that received ephedrine was not stated. Had both our studies been larger, surely minor protocol differences would have evened out.

A slightly different timing of measurements can be another explanation. We clocked the injection for 60 seconds, waited 60 s and then started the DPA measurement sequence, which takes approximately 70 s. In 2008, Moertl et al. did a similar comparative study with similar conclusions.[51] If you take a close look at their graphs, a biphasic effect on the HR is seen, with a very short-lived increase followed by a HR *lower* than baseline from about 2-3 minutes up until 5 minutes. The Moertl study gave their injections statim, while we gave ours during 60 s. Statim boluses had become unadvised at the time of our study due to their relatively larger hemodynamic impact compared to slow injections. Because of the relative slowness of the injections, it is possible that a transient peak increase in HR and CO may have been missed by our protocol. Our DPA method has the disadvantage of not making continuous measurements. On the other hand, this would require the patient to remain perfectly still with their hands during the whole operation, which would not have been tolerated.

The protocol was designed to compare only 5 IU of oxytocin with 100 µg carbetocin. Patients receiving additional uterotonics were not further analyzed with the DPA. Thus, we do not know whether they were more hemodynamically affected by the extra uterotonics. Had the study been larger, this group could have been subject to a subgroup analysis.

Study IV

Results

25 nonpregnant and 24 pregnant women completed the experiment. Pregnant women had significantly lower DI, higher HR, PH, EEI and ETc at baseline. In nonpregnant women, oxygen inhalations caused significant decreases in *d/a*, HR, and MAP. In pregnant women, O_2 inhalations caused significant decreases in *d/a*, EEI and HR, together with increases in *b/a*, DI, and AI. When comparing the differences of Δ-values between the groups, AI, *b/a*, DI, EEI, and HR reactions were more pronounced in the pregnant group. ETc was not changed in any comparison. All values except HR return to baseline 5 minutes after the inhalation is finished.

Conclusion

Baseline differences were in accordance with known changes in the circulatory physiology of pregnancy. The reactions of oxygen were very clear-cut

vasoconstrictive in pregnant women. DPA variables were unanimous, indicating both large and small artery vasoconstriction paired with a decrease in HR. Nonpregnant women reacted similarly, but their response was not as pronounced. Pregnant women clearly are more sensitive to vasoconstrictive effects from hyperoxygenation.

Comments

This study demonstrates both the ability of the DPA to detect the well-known physiologic hemodynamic changes in late pregnancy, as well as a clear-cut and prompt vasoconstrictive response from oxygen, that is reversed 5 minutes after finishing the inhalations. This confirms the results from a similar study by McHugh et al.[86] One limitation is the lack of a control series with the subjects breathing room air, in case the fact of just breathing through a tight-fitting mask could have had any impact on hemodynamics, possibly by altering pCO_2 or from emotional factors. ABGs were avoided since we wanted to be non-invasive and pain-free. Pregnant women, especially those with hypertensive or vasoconstricted states, may be at risk of serious adverse effects from hyperoxygenation.

Study V

Results

24 women in each group completed the first part of the experiment, breathing 30% N_2O. In the second session, inhaling 50% N_2O, only 13 pregnant subjects completed the experiments due to considerable side effects. Among the non-pregnant, however, 22 subjects completed this session. From both 30 and 50% N_2O, decreased HR, EEI and *d/a*, with increased *b/a* and AI, were seen in the pregnant group, indicating both large and small artery vasoconstriction. However, the pulse height (PH) had a slower response increasing after inhaling for 5 minutes. A similar pattern was seen in the nonpregnant, albeit a little less pronounced. When comparing the Δ-values between groups, differences were small. ETc rose in the nonpregnant but decreased in the pregnant group at 50%, making the difference significant between the groups, even though it was not significant *within* each group. ΔDI and ΔPH rose and ΔHR decreased more in the pregnant group from 30%, while ΔDI rose more of 50%.

Conclusion

Pregnant women were more sensitive to N_2O than nonpregnant women, both in terms of subjective side effects and hemodynamic changes. N_2O resulted in

vasoconstriction in both the big and small arteries, with a pattern of change that could correspond to a negative inotropic effect. In contrast to non-pregnant women, pregnant women had a drop in HR and MAP. Our findings have implications for those who treat pregnant women with cardiac disease or vasoconstrictive conditions like hypovolemia and preeclampsia. Other methods for labor analgesia might be better suited for parturients at risk.

Comments

Some of the effects seen throughout the experiment were actually larger at 30% N_2O than at 50%. Paired with our results from the oxygenation study (Study IV) and the data from previous studies, we hypothesized that oxygen might cause some of the effects seen from the N_2O inhalations. The effects are indeed quite similar. On the other hand, emotional and central effects from N_2O may both enhance or attenuate vasoconstriction. As the mode of action of N_2O is quite complex with a multitude of receptors involved, it is hard to discern the clear N_2O effects from the effects of oxygenation. The high drop-out rate in the pregnant 50% group was both an important finding and a limitation to the statistical power. Another limitation is the lack of a control series with the subjects breathing room air, and another series breathing N2O 30 % in room air, to avoid bias of the 70% oxygen component. ABGs were avoided since we wanted to be non-invasive and pain-free. Despite the fact that this is a small study, the results were quite unanimous and point to potential problematic circulatory effects of both O_2 and N_2O. Nevertheless, the long experience with N_2O in labor is indicative of its safety in the majority of cases.

Overall conclusions and future perspectives

The medical interventions studied in this thesis all have cardiovascular effects that are sometimes quite profound. These effects can be shown and monitored with a simple and pain-free methodology. Carbetocin seems to have similar cardiovascular adverse effects compared to Oxytocin, namely vasodilation and possible cardiac repercussions. Prudence should be taken when administering these drugs to compromised mothers. Both nitrous oxide and oxygen have vasoconstrictive and possible negative inotropic effects that were more prominent in pregnant women than in nonpregnant controls. Some of the effects seen from nitrous oxide might be due to the oxygen fraction in the gas mixture.

Awareness of cardiovascular effects is important when considering treatment of the mother with oxytocin receptor agonists as well as with nitrous oxide and oxygen. Patients with established or suspected cardiovascular disease may be more sensitive to oxygen, especially patients with preeclampsia. Oxygen treatment should not be used carelessly without a precise indication. Future studies should aim at better describing the effects of oxygen and nitrous oxide on both healthy and preeclamptic parturients, as well as fetal effects, preferably in well-powered RCTs.

Methodological considerations

Considerations of the DPA method

The PPG and APG DPA methods are still rather uncommon for the study of short-term cardiovascular effects. The International Working Group on Maternal Hemodynamics recommendations concerning the studies on maternal hemodynamics state that non-invasive DPA can be used for short-term clinical trend monitoring.[179] The Meridian DPA is validated in pregnancy using applanation tonometry.[164] Minor differences in our results versus the results from other studies may be due to small differences between study protocols or treatment traditions rather than due to the method itself.

Although the studies in this thesis show effects that are logical and confirm many of the results from studies using similar methods, the relative lack of other studies using this technology is a limitation. Unfamiliar terminology and complicated interpretations of variables are other limitations. Much of the preliminary data and basic research on this technology originate from Japan and Korea, making language barriers problematic. For this reason, personal communications with the Korean manufacturer have been necessary to clarify some issues regarding the interpretation of the indices. We did not pay attention to absolute values, as they vary from person to person, instead, we studied individual changes in curve shape derived indices.

Another problem with PPG concerns missing values. Low recognition due to cold fingers, peripheral vasoconstriction, and movement artifacts can be problematic, especially when dealing with fast-acting medications. At some measuring points, the study protocol did not allow time for an extra measurement in case of bad pulse recognition, as surgery was halted and had to be continued. This reduced the power of some of the studies. For future studies of fast-acting interventions, I would recommend the DPA method due to its simplicity and non-invasiveness, but consider a device that has the possibility of continuous measurements and, in addition to the APG indices, employs a more commonly used output terminology. Much promising research in recent years on the methodology is aimed at wearable devices for the estimation of blood pressure, vascular ageing, cardiac arrythmias, and the like,[180,181] as well as novel monitoring techniques in anesthesia and intensive care.[153,162,165]

HR correction

The manufacturer does not recommend HR correction, except for the cardiac ejection time, and this is done within the device resulting in the ejection time compensated (ETc). However, von Wowern et al. found significant but weak correlations between most DPA variables and the HR. Of the variables proposed for future use, DI and EEI had the highest Spearman's rho, of -0.64 and 0.44, respectively, while *b/a* had -0.39, *d/a* 0.28, and AI -0.22. However, in her work, subjects were more diversified in age, gender and concomitant illnesses. In Studies I and II, if a significant linear correlation to HR was found, HR correction to 75 bpm was carried out on that variable. The HR-corrected variable was referred to as "DPA@75" and the correction was made by establishing the slope constant C for the variables that had a significant correlation to the HR. Then the HR-corrected variable was obtained using the equation

$$DPA@75 = DPA + C\,(75 - HR).$$

In a later published systematic review on the subject, PPG correlations with HR were reported as not present or weak in general, except for RI.[182] Correlations with APG indices were not found. However, this was not a meta-analysis of data but a review of studies. It is possible that regression analysis of large amounts of pooled data could come to other conclusions. As HR correlations in Study III were found to be very weak (slope coefficients for DI, EEI, b/a, d/a, and AI were all <0.005) we chose to omit HR correction in Study III-V.

Statistical considerations

The relatively small sample sizes were still large enough to yield robust, statistically significant results.[183] Due to insufficient knowledge of what changes to expect from the DPA, sample size calculations were not performed for studies I, II, IV, and V. However, in study III, we performed a sample size calculation based on our observations from study I, conducted in a similar setting. In study IV, a post-hoc power analysis was carried out using the global DPA assessment variable AI, since further research suggested that this variable sums up many of the DPA changes, albeit not all. When choosing the repeated measures two-way ANOVA, this was in order to get more robust statistics, given the multiple recording points. Given the possibility of post-hoc tests, this was an attractive statistical approach. One possible problem with this method is that the observations are assumed to be independent of each other.[184] Other statistical possibilities for the comparison of multiple observations over time could be using the area under the curve, the peak value and/or the time to peak.[185] When comparing the Δ-values in studies IV and V, the

peak values at 3 minutes seem most appropriate to use for the comparison between groups. Considering the post-hoc correction for family-wise error in the non-parametric Friedmans ANOVA, we used the Holm modification of the Bonferroni method (also referred to as the sequential Bonferroni),[186] as the Bonferroni method is considered unnecessarily strict, yielding a lack of power.[184] In studies III-V, Statview statistical software was abandoned and another statistical software was used (Sigmaplot, Alfasoft, Norway) where Dunn's post-hoc testing was available, making pairwise comparisons versus baseline measurements easily accomplished. For the parametric tests, Holm-Sidak post-hoc test was chosen for the same reason.

Populärvetenskaplig sammanfattning på svenska

I det här projektet ville vi undersöka effekterna på den gravida kvinnans cirkulation av några läkemedel som ofta ges i samband med förlossningsvård: Oxytocin (Syntocinon©), carbetocin (Pabal©), syrgas och lustgas. Varje år föds över 100000 barn i Sverige. Det innebär ca 300 förlossningar per dag. En förlossning är en potentiellt riskfylld händelse både för modern och barnet. Ändå är både barna- och mödradödligheten extremt låg i Sverige. År 2013 var barnadödligheten var 3,8 per 1000 födda (inom 27 dagar från förlossning), och för mammorna handlar det om några enstaka per år.

Man ska dock inte glömma att situationen ser helt annorlunda ut i de länder som inte har så välutvecklad sjukvård. Den farligaste och mest akuta händelsen är utan tvekan störtblödning efter förlossningen. Den vanligaste och mest svårbehandlade orsaken till störtblödning är att livmodern inte drar ihop sig som den ska efter förlossningen, s k *atoni*. Risken anses något högre vid kejsarsnitt. En annan farlig komplikation till graviditet är så kallad havandeskapsförgiftning (preeklampsi), som ger sig till känna med högt blodtryck men som även innebär en påverkan, ibland mycket allvarlig, på flera av kroppens organ.

Under årens lopp har det visat sig att man drastiskt kan minska risken för förlossningsrelaterade blödningar genom att ge läkemedel som får livmodern att dra ihop sig. Dessa ges i förebyggande syfte, omedelbart efter att barnet är fött. Ett par olika läkemedel kan användas, men som standard används idag oxytocin.

Oxytocin är ett hormon som normalt frisätts av hypofysen, och stimulerar livmodern till att dra ihop sig, men det har också andra effekter. En av dessa är att det påverkar blodkärlen, och därmed blodtrycket. Även hjärtat kan påverkas. Om oxytocin ges som snabb injektion direkt i blodbanan brukar dessa effekter bli starka och tydligt mätbara. De är kanske inte farliga för en frisk mamma, men om hon har en hjärtsjukdom sedan tidigare, eller har en pågående stor blödning, så kan följderna bli allvarliga.

Eftersom oxytocin har en ganska kortvarig effekt, får man ofta får upprepa doserna eller ge det som kontinuerligt dropp under flera timmar. Därför har man framställt ett läkemedel som heter Carbetocin. Det är nära besläktat med oxytocin, men effekten sitter i betydligt längre. Man tror att effekterna på hjärta och kärl är

likvärdiga med oxytocin. Carbetocin har inte använts så mycket i Sverige, men rekommenderas numera i många andra länder.

Ett annat läkemedel som ofta används i samband med förlossning är lustgas. Det används som smärtstillande framför allt under värkarbetet i öppningsfasen. En stor fördel med denna gas är dess nästan omedelbara effekt, samtidigt som den också går ur kroppen lika snabbt. Lustgas måste blandas med minst 30 % syrgas, för att inte ge upphov till syrebrist. Effekterna av lustgas på mammans kärl är ofullständigt kända.

Syrgas används i många sammanhang, framför allt inom akutsjukvård. Till gravida kvinnor ges också syrgas, antingen blandat med lustgas, eller ensamt för att behandla eller förebygga misstänkt syrebrist hos foster eller mamma. Man har på senare år alltmer börjat uppmärksamma ogynnsamma effekter av höga syrgasnivåer.

I det här projektet ville vi undersöka hur läkemedel som de ovan nämnda skulle kunna påverka den gravida kvinnans cirkulationssystem. Detta gjordes med hjälp av fem delarbeten. Till vår hjälp hade vi ett mätinstrument som analyserade pulsvågen i kvinnans finger med hjälp av infrarött ljus, en helt smärtfri och ofarlig metod. Utifrån pulsvågens utseende kan man dra slutsatser om hur sammandragna blodkärlen är, och vilka delar av kärlträdet som är mest påverkade. Vi mätte också blodtryck och följde hjärtat med EKG.

I det första delarbetet studerades effekterna av både ryggbedövning och oxytocin på mammans cirkulation i samband med planerat kejsarsnitt. Både bedövningen och oxytocin hade kärlvidgande effekter på mamman.

I det andra delarbetet studerades dels effekterna av narkos, dels jämfördes effekterna av oxytocin med placebo på kvinnor i tidig graviditet i samband med en planerad skrapningsoperation. Här framträdde de kärlvidgande effekterna av oxytocin jämfört med placebo. Även narkos hade kärlvidgande effekter.

Det tredje delarbetet jämförde effekterna av oxytocin och carbetocin. Detta gjordes också under kejsarsnitt. Kvinnorna lottades i två grupper och fick varsitt läkemedel, utan att veta vilket. Carbetocin visade sig ha liknande biverkningar på hjärta, blodtryck och blodkärl som oxytocin.

I det fjärde delarbetet studerade vi effekterna av syrgasandning på kvinnor i sen graviditet och jämförde effekterna med dem hos unga icke-gravida kvinnor. Syrgas hade sammandragande effekter på blodkärlen och en negativ effekt på hjärtats pumpförmåga. Dessa effekter var starkare i den gravida gruppen jämfört med den icke-gravida.

I det sista delarbetet studerade vi lustgasens effekter på både gravida och icke-gravida. Vi jämförde dessutom två olika styrkor av inandad lustgas. Även här var kärleffekterna starkare hos gravida, och de gravida fick även fler övriga biverkningar.

Sammanfattat så har oxytocin och carbetocin liknande kärlvidgande effekter, som i vissa situationer kan vara olämpliga. Man bör använda lägsta möjliga dos och ge läkemedlen långsamt. Lustgas har en viss kärlsammandragande effekt. Den är inte så uttalad att den nämnvärt påverkar friska mammor, och nyttan med den smärtlindrande effekten är så pass stor att den överväger de ganska milda hjärtkärleffekterna. En del av de uppmätta effekterna från lustgasandningen kan i själva verket komma från den andel syrgas som inandas samtidigt. Tack vare den långa erfarenhet och det stora antalet studier som gjorts på lustgasanvändning vid förlossning vet man, att med dagens rutiner och andningssystem är riskerna för både barn, mamma och personal mycket små. Andra smärtlindrande metoder har för övrigt antingen sämre effekt, såsom akupunktur, meditation etc, eller har fler kända risker och biverkningar såsom morfin, petidin m fl, eller är mer komplicerade, såsom epiduralbedövning. Vad gäller syrgas bör man däremot vara mer noggrann än man är idag med hur och när man ska använda sig av det, eftersom nyttan är omtvistad och riskerna inte försumbara.

Acknowledgements

To Per Olofsson, my co-supervisor and former supervisor, for all the encouragement, know-how, and for not giving up on me during all these years.

To Mikael Bodelsson, my supervisor and former co-supervisor, for believing in me (even if I'm not sure you did) and for giving me the position as a teaching assistant for the medical students.

To Ull Hjort, Sofia Schönbeck, Hanna Jonsson, Emilie Bro, Sofia Ovenholm, Annelie Pettersson, and Roba Said for all your work with patient recruiting and data collection.

To Emma von Wowern, for paving the way with your work on the pulse wave analysis, as well as for further support on the way.

To Nana Wiberg, for initially being my co-supervisor

Per-Erik Isberg for help with the statistical considerations.

To Pia Andersson, Emanuel Smeds, and Johan Törnebrant at the BMC B14.

To Jonas Åkesson and Andreas Herbst for all the valuable input at my half-time control.

To Katarina Levin, my role model and mentor at OB/gyn anesthesia.

To Viveka Björck for your encouragement and support at work and as my co-teacher.

To Karin Thorlacius for your work and support at the OB/gyn anesthesia dept.

To all the staff at the OB/gyn anesthesia dept in Lund, with special mention to Katarina Bokelid, Åsa Marsal, Birgitta Andersson and Sabina Wessman for all your supportive work during all these years.

To Camilla Edvinsson for your stubbornness.

To, in no particular order, past and present colleagues and researchers at the anesthesia department in Lund: Bengt Roth, P-O Grände, Hans Friberg, Ulf Schött. Martin Annborn, Svajunas Statkevicus, Peter Bentzer, Thomas Kander, Fredrik Boris-Möller, Lars Algotsson, Johannes Magnusson, Per Flisberg, Gunilla Islander, Johan Lundberg, Peter Reinstrup, Görel Nergelius, Andreas Hvarfner, Louise Walther, Maris Dubniks, Attila Frigyesi, Peter Bansch, Björn Bark, Ingrid

Berkestedt, Bruno Enekvist, and many many others, for your inspiration on both research and clinical skills.

To Johan Persson and Johan Bonnevier, my bosses, for your inspiration and for pushing me forward.

To all colleagues at the OB/gyn (KK) in Lund, with special mention to Dag Wide-Swensson, Stefan Hansson, Christer Borgfeldt, Jan Persson, Thomas Bossmar, Helena Strevens, Celine Lönnerfors, Zuzana Kolkova, Bengt Lindahl, Annie Lantto and Paivi Kannisto, in no particular order.

To my colleagues at OB/gyn anesthesia in Malmö, especially Micke Wallin and Agusta Waage.

To all colleagues and staff at the dept. for anesthesia and intensive care in Helsingborg. Special note to Ola, Florian, Jesper, Anne-Sophie, and Henrik E.

To Marcus Broman, my office roommate, for all interesting discussions.

To Mika Rockholt for your positive thinking.

To Jan Marsal for all your support!

To Andreas and Charlotta Lindkvist Dornonville de la Cour for your supportive discussions.

To Katarina Rehn, my sister, for proof-reading and English-helping.

To all my colleagues and staff at the IPV Lund – you are the greatest!

To all women who participated in the studies.

To my mother and my late father, of course, for your encouragement and mentorship in general knowledge and critical thinking, and for not giving up on me either.

To Hampus, Susanna, and Max for your intellectual inspiration and academic skills.

And last but not least: To my beloved family, Anna, Malte, Ture, and Eskil for all your support. You are the best!

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Paper I

THE JOURNAL OF MATERNAL-FETAL & NEONATAL MEDICINE

http://informahealthcare.com/jmf
ISSN: 1476-7058 (print), 1476-4954 (electronic)

J Matern Fetal Neonatal Med, 2017; 30(7): 759–766

DOI: 10.1080/14767058.2016.1186162

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ORIGINAL ARTICLE

Pulse wave analysis by digital photoplethysmography to record maternal hemodynamic effects of spinal anesthesia, delivery of the baby, and intravenous oxytocin during cesarean section

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Abstract

Objective: To investigate changes in maternal ECG ST index, blood pressure (BP), cardiac left ventricular (LV) ejection function and vascular tone/stiffness in large and small arteries occurring during elective cesarean section (CS) in spinal anesthesia.
Material and methods: Twenty-six women were monitored with photoplethysmographic digital pulse wave (PW) analysis (DPA) before and after spinal anesthesia, after delivery of the baby, after 5 IU oxytocin bolus IV, and 5 min later. Statistics with Wilcoxon matched-pairs signed-rank and Friedman tests at a $p < 0.05$ were performed.
Results: Spinal anesthesia resulted in significantly decreased BP, increased ST index and LV ejection time, and small-artery vasodilation. Delivery of the baby resulted in global vasoconstriction and increases in systolic BP and heart rate (HR). Oxytocin lowered BP, HR and ST index, increased LV ejection power and caused both large- and small-artery vasodilation. ST index and BP recovered after 5 min, but low HR and low vascular tone persisted.
Conclusions: Spinal anesthesia and oxytocin caused arterial vasodilation and cardiac affection. Oxytocin caused a decrease in HR despite a fall in BP, indicating a direct negative chronotropic effect. Delivery of the baby caused momentous cardiovascular changes, possibly due to maternal emotions and auto-transfusion of blood from the uterus.

Keywords

Arterial elasticity, arterial stiffness, oxytocin, pregnancy, pulse wave analysis, spinal anesthesia

History

Received 30 April 2016
Accepted 1 May 2016
Published online 25 May 2016

Introduction

Oxytocin is routinely administered at cesarean section (CS) to contract the uterus and prevent hemorrhage. However, many women then experience discomfort, nausea and chest pain. These symptoms have been attributed to the significant circulatory dose-dependent effects of oxytocin [1] including ECG ST-depression, increase in heart rate (HR), stroke volume and cardiac output (CO), and decrease in systemic vascular resistance and arterial blood pressure (BP) [2–8]. Detailed studies of the immediate hemodynamic response show an increase in HR and decreases in systemic vascular resistance and BP within 30–40 s after a 5 IU oxytocin bolus, with a concomitant increase of CO, followed by a rebound decrease in HR and a slow restitution of the BP [5,9].

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Pharmacological vascular effects can be studied by analyzing pulse wave (PW) curve contour characteristics, determined by propagation of the forward percussion PW along the vascular tree and the reflection of the tidal PW from distal arteries. PW characteristics can be determined by digital PW analysis (DPA), which is a rapid, noninvasive and operator-independent photoplethysmographic (PPG) method. The DPA has been validated against invasive aortic measurement and correlates well with radial pulse applanation tonometry [10,11]. The DPA method can assess cardiac ejection time and distinguish between vascular tone/stiffness in large and small arteries [11].

The primary objective of the study was to investigate the effects of oxytocin during elective CS on cardiac left ventricular (LV) ejection function and systemic arterial stiffness. We hypothesized that oxytocin decreases arterial vascular tone, but there is no knowledge yet whether oxytocin affects both large and small arteries.

Spinal anesthesia is frequently associated with maternal hypotension despite precautions with plasma volume expansion and vasopressor substances [12]. The secondary objectives of the study were to investigate the cardiovascular effects of spinal anesthesia and delivery of the baby; due to adjunctive effects of fluid co-load and vasopressors, and to

a lack of previous studies with the DPA method, we could not settle any hypotheses for these aims.

Material and methods

Study design

The study was prospective, with no interventions added to the routine management, carried out at the Skåne University Hospital in Lund, Sweden. Women who met the inclusion criteria were recruited consecutively and gave their informed consent to be monitored by a Meridian DPA during elective CS in spinal anesthesia. The study recordings were all performed by one of the authors (S.R.). The study was approved by the Regional Research Ethics Committee in Lund (Dnr 2012/649).

The inclusion criteria were healthy women at $\geq$34 gestational weeks scheduled for elective CS in spinal anesthesia with singleton pregnancy and informed consent. The exclusion criteria were hypertension, preeclampsia, abnormal pregnancy with expected surgical problems, coagulopathy, cardiovascular disease, American Society of Anesthesiologists physical status classification system (ASA-class) III or more, disease of upper extremities impeding measurements, or women unwilling to participate.

The pre-defined drop-out factors were blood loss greater than 1000 mL within the time frame of DPA measurements, initial dose of oxytocin other than 5 IU (8.35 μg), insufficient anesthesia, conversion to general anesthesia, administration of other vasoactive or uterotonic drugs than in the protocol, other deviations from the study protocol, technical errors, or patient unwilling to participate further.

Study protocol

All recordings were performed during maternal quiescence in the supine position, with the operation table tilted approximately 15 degrees to the left. Two liters per minute of oxygen was delivered through the nasal route throughout the procedure. All women were connected to a Philips Intellivue MP70 (Philips Healthcare, Stockholm, Sweden) surveillance device and continuously monitored with an oxygen saturation probe, an automatic BP cuff and a 3-lead ECG. From this was derived the ST index, a summation of the absolute values from ECG leads V2, V5 and aVF [13]. For the DPA measurements, the PPG probe (Meridian DPA, Meridian Co., Ltd. Korea, and Salcor AB, Uppsala, Sweden), connected to a laptop (HP 625, Hewlett Packard, Solna, Sweden), was placed on the right second or third finger.

The baseline measurement (T0) was made after 5 min of rest before spinal anesthesia. The next recording (T1) was made 15 min after spinal anesthesia, i.e. just before the start of surgery. Measurement T2 was made immediately after delivery of the baby, but before oxytocin administration and further surgery. Immediately after the T2 recording was finished and the umbilical cord was clamped, a 5 IU (8.35 μg) bolus of oxytocin (Syntocinon, Swedish Orphan AB, Stockholm, Sweden) was given IV during 60 s. When the bolus was finished, a stopwatch was started and 60 s later the next DPA recording was started (T3). The DPA recordings were then continued with measurements 5 min after the bolus was finished (T4).

The BP was measured intermittently every 2 min as well as immediately after at each T recording point. The measurements were performed in the contralateral arm to avoid interference with the DPA measurements. Recordings of ST index, HR and systolic and diastolic BPs (SBP, DBP) were noted manually in a case report form at each T point. The volumes of blood loss and IV fluid given, vasopressor treatment, as well as any other specific treatment were also noted in the case report form at each specific T point.

Spinal anesthesia was administered with the patient sitting. The standard dose was bupivacaine hyperbaric solution 5 mg/mL (Marcain Tung, AstraZeneca, Södertälje, Sweden) 2 mL (10 mg) mixed with 1 mL sufentanil 5 μg/mL (Sufenta, Janssen-Cilag, Sollentuna, Sweden). Short women (<160 cm) received 9 mg of bupivacaine ($n = 3$) and tall women (>179 cm) received 12 mg ($n = 1$). After approximately 15 min preoperative preparation time, spinal anesthesia depth and spread was tested with pinprick and cold, and then surgery was allowed to start.

The protocol for plasma volume expansion implicated co-loading with Ringer-acetat (Fresenius Kabi, Uppsala, Sweden), approximately 20 mL/kg in the first 20 min, starting after the baseline measurement (T0), followed by 5–10 mL/kg during the rest of the procedure. In case the blood loss was >500 mL, or if clinical signs of hypovolemia occurred (low BP, tachycardia, poor capillary perfusion), 500 mL of Venofundin (B. Braun Medical, Danderyd, Sweden) could be given. Greater blood loss than 1000 mL was an exclusion criterion.

The protocol for vasoactive drugs implicated the use of phenylephrine 50–100 μg IV if mean arterial pressure (MAP) fell below 20% of baseline, or below 60 mmHg, or if clinical signs of low BP occurred, such as nausea or pallor. Atropine or ephedrine was administered in case of bradycardia. This standard protocol was used also after the delivery of the baby.

Digital photoplethysmography

The physiological background to the DPA method has been described previously [10,14]. The Meridian DPA™ reports 17 different parameters, but for this study we selected parameters with the best repeatability and best correlation to gold standard applanation tonometry: pulse height (PH), aging index (AI), ejection time compensated (ETc), cardiac ejection elasticity index (EEI), dicrotic index (DI), dicrotic dilation index (DDI), and the ratios *b/a* and *d/a* [11]. Descriptions of the parameters are shown in Table 1.

The DPA method cannot distinguish between decreased arterial wall elasticity due to structural remodeling of the arterial wall (aging, vascular disease), low compliance due to vascular volume expansion, or vasoconstriction; in the literature and in this paper, the terms ''vascular tone'' and ''stiffness'' are used interchangeably.

Statistical analyses

Some of the DPA variables are HR dependent [11] and the statistical analyses were accordingly performed with both crude and HR-adjusted DPA values. If simple linear regression analyses between HR and a DPA variable at T0 yielded a statistically significant correlation ($p < 0.05$), and the intervention (spinal anesthesia, delivery of baby, oxytocin

Table 1. Description of the digital pulse wave analysis parameters used in the study (for detailed description, see [11]).

Parameter	Physiological background	Conditions with high values	Conditions with low values	Interpretation of increase	Interpretation of decrease
Pulse height (PH)	Circulation in small finger arteries, perfusion of finger tips	High BP, hyperthyroidism, fever, anemia, excessive blood volume, exercise, well-tuned athlete	Peripheral vaso-constriction, low BP, hypovolemia/dehydration, hypothyroidism, increased peripheral resistance	Peripheral vasodilatation	Peripheral vasoconstriction
Left ventricular ejection time compensated (ETc)	Represents systole, i.e. time from onset of the systolic upstroke limb to the closure of the aortic valve	Aortic valve stenosis, heart insufficiency, impaired CO, decreased large artery compliance (high vascular tone)	Hyperthyroidism, diastolic hypertension, small LV, decreased preload	Increase in LV ejection time, decrease in CO, increase in large artery vascular tone	Decrease in LV ejection time, increase in CO, decrease in large artery vascular tone
Cardiac ejection elasticity index (EEI)	Index for LV ejection capacity and compliance/elasticity of large arteries	Large-artery vasodilatation, anemia, increased LV ejection power, hyperthyroidism, congested heart failure	Large-artery vasoconstriction, arteriosclerosis, LV ejection insufficiency	Increase in LV ejection power, large-artery vasodilatation	Decrease in LV ejection power, large-artery vasoconstriction
Dicrotic index (DI)	Represents the peripheral circulation, indicates peripheral resistance	Small-artery vasoconstriction	Small-artery vasodilatation	Peripheral vasoconstriction	Peripheral vasodilatation
Dicrotic dilatation index (DDI)	DDI = 1 – DI. Index for elasticity in small arteries	Small-artery vasodilatation	Small-artery vasoconstriction, atherosclerosis	Small-artery vasodilatation	Small-artery vasoconstriction
b/*a*	Early systolic PW peaks identified by second derivatives of the crude PW curve contour; indicates LV ejection capacity and large-artery compliance/elasticity	Low large-artery elasticity, increased cardiovascular risk, vasoconstriction, atherosclerosis, increases by age	Young persons, athletes	Large-artery vasoconstriction, decreased LV ejection	Large-artery vasodilatation, increased LV ejection
d/*a*	*d* is a late systolic PW peak identified by derivative of the crude PW curve contour; mainly reflects the intensity of the tidal PW from small peripheral arteries	High small-artery elasticity, young persons	A longer negative *d* peak develops by advancing age, indicating arterial stiffness, atherosclerosis	Small-artery vasodilatation	Small-artery vasoconstriction
Ageing index (AI)	AI = (*b*-*c*-*d*-*e*)/*a*, representing the global vascular stiffness, i.e. ''vascular age''	Atherosclerosis, increases by age	Young persons, athletes	Global arterial vasoconstriction	Global arterial vasodilatation

BP: blood pressure; CO: cardiac output; LV: left heart ventricle; PW: pulse wave.

Table 2. Hemodynamic effects of spinal anesthesia and delivery of the baby at cesarean section.

	Effects of spinal anesthesia		Effects of delivery	
Parameter	Wilcoxon test* T0–T1†	Interpretation	Wilcoxon test* T1–T2†	Interpretation
Systolic BP	↓ <0.0002	SBP decrease	↑ 0.025	SBP increase
Diastolic BP	↓ 0.0004	DBP decrease	0.70	No change
MAP	↓ 0.0003	MAP decrease	0.20	No change
Heart rate (HR)	0.53	No change	↑ 0.031	HR increase
ST index	↑ 0.028	ST increase	0.74	No change
PH	↑ 0.0057	Fingertip hyperemia as a sign of peripheral vasodilatation	0.20	No change
ETc	↑ 0.028	Increase in LV ejection time, decrease in CO, and/or large-artery vasoconstriction	0.94	No change
EEI	0.73	No change	0.12	No change
EEI@75‡	–	Not calculated because HR was unchanged	↓ 0.041	Large-artery constriction, decrease in LV ejection power
DI	↓ 0.0066	Small-artery vasodilation	(↑) 0.062	Marginal small-artery vasoconstriction
DDI	↑ 0.0066	Small-artery vasodilation	0.31	No change
DDI@75‡	–	Not calculated because HR was unchanged	↓ 0.16	No change
b/a	0.22	No change	↑ 0.045	Large-artery vasoconstriction decrease in LV ejection
d/a	0.38	No change	0.50	No change
AI	0.14	No change	↑ 0.003	Global arterial vasoconstriction

Figures are p values and arrows indicate a significant increase or decrease of parameter values; arrows within brackets denote a p values ≥ 0.05 but <0.1. BP: blood pressure; MAP: mean arterial blood pressure; ST index: changes of the ECG ST segment; LV: left heart ventricle; CO: cardiac output.

*Wilcoxon signed-rank matched-pairs test.

†For explanation of measurement points T0, T1 and T2, see text.

‡EEI and DDI, but no other parameters, were correlated with HR at T0; HR-adjustments to HR 75 bpm are denoted EEI@75 and DDI@75.

administration) resulted in a significant change in HR, the DPA variable in question was adjusted to a HR of 75 bpm, denoted DPA@75, with the equation DPA@75 = DPA+C (75-HR). C denotes the slope constant.

The cardiovascular effects of spinal anesthesia were analyzed with recordings from point T0 to T1, the effects of the start of surgery and the delivery of the baby between T1 and T2, and the effects of oxytocin were analyzed with recordings T2–T3–T4. The longitudinal changes in single T–T steps were analyzed with the Wilcoxon matched-pairs signed-rank test with a two-sided p values < 0.05 considered significant. To evaluate the risk of type I errors the Friedman non-parametric one-way ANOVA for repeated measurements T2–T3–T4, and Holm-Bonferroni adjustments of the p values achieved at the Wilcoxon tests, were also calculated: in the three T2–T3, T3–T4 and T2–T4 comparisons the Holm–Bonferroni significance level is $<0.05/3$ equal to <0.0167 for the Wilcoxon test with the lowest p values, $<0.05/2$ equal to <0.025 for the second lowest, and $<0.05/1$ equal to <0.05 for the third.

Results

Among the 26 recruited women, three women were excluded from DPA analyses from T3 and onwards because they were given a bolus of 10 IU (16.70 µg) oxytocin instead of 5 IU. In five women the measurements T0–T1 (spinal anesthesia) could not be analyzed due to technical recording errors at T0, but they were included in the measurements T1–T4. Six women had missing ETc, EEI, or DDI values at T2 and/or T3.

At T0 significant correlations were only found between HR and EEI ($p = 0.037$, $R^2 = 0.22$) and DDI ($p = 0.048$, $R^2 = 0.20$).

Effects of spinal anesthesia (T0–T1)

From measurement point T0 to point T1 the HR was not affected and hence no HR-adjustments of DPA parameters were made. Spinal anesthesia resulted in significant decreases in SBP and DBP and an increase in ECG ST index (Table 2, Figure 1). The DPA parameters PH, DI and DDI showed peripheral/small-artery vasodilation; ETc indicated increased LV ejection time suggesting decreased CO and/or large-artery vasoconstriction, while EEI (large-artery stiffness, LV ejection capacity), *b/a* (large-artery stiffness, LV ejection capacity), *d/a* (small-artery stiffness) and AI (global vascular stiffness) were unchanged.

Effects of surgery and delivery of the baby (T1–T2)

The HR increased significantly from T1 to T2 and the DPA parameters EEI and DDI were accordingly adjusted to EEI@75 and DDI@75, respectively. After the start of surgery and delivery of the baby (point T2), the SBP increased significantly but the DBP and MAP as well as the ST index remained unchanged (Table 2, Figure 1). A large-artery vasoconstriction and/or decreased LV ejection power were indicated by significant changes of *b/a* and EEI@75, a marginally significant small-artery vasoconstriction by DI ($p = 0.062$), and a global arterial vasoconstriction by AI. No significant changes were found for PH, ETc and *d/a*.

Effects of oxytocin (T2–T4)

The hemodynamic effects of oxytocin are shown in Table 3 and Figure 1. The HR decreased significantly at T2–T3, and EEI and DDI were accordingly HR-adjusted. From T2 to T3, the oxytocin injection resulted in significant decreases in DBP

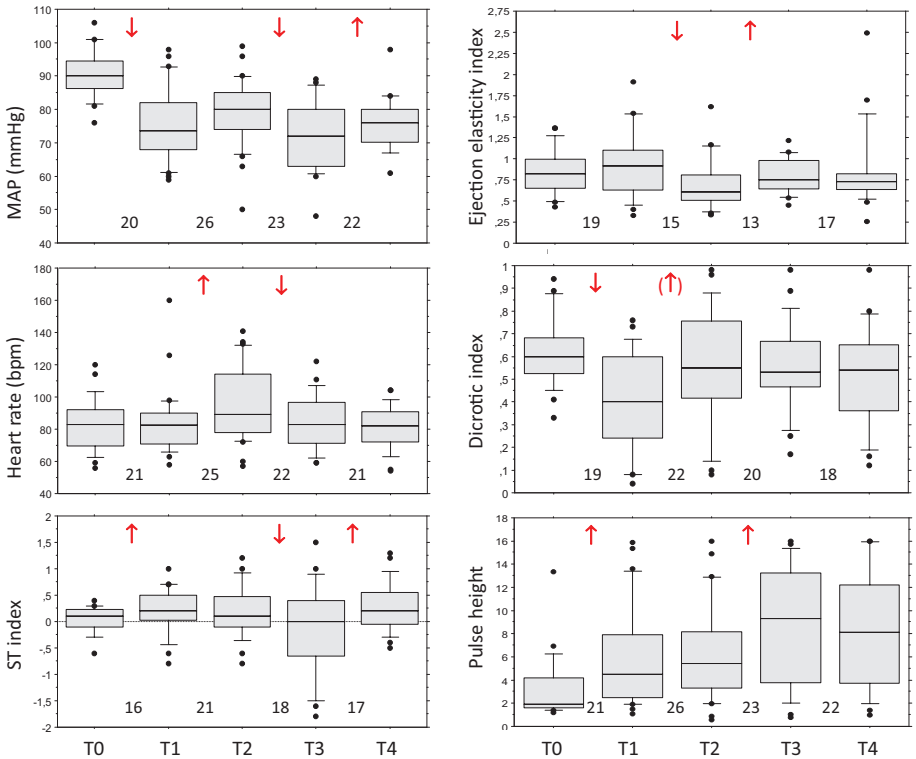

Figure 1. Box plots showing sequential changes in maternal mean arterial blood pressure (MAP), heart rate, ECG ST index, ejection elasticity index, dicrotic index and pulse height from before spinal anesthesia (point T0), after spinal anesthesia but before surgery (T1), after delivery of the baby but before oxytocin injection (T2), 1 min after IV oxytocin (T3), and 5 min after oxytocin (T4). Arrows denote significant changes (Wilcoxon matched-pairs signed-rank test, $p < 0.05$; within brackets $p < 0.10$ but ≥ 0.05) and direction of change. Figures denote number of women in paired comparisons.

and MAP as well as in ST index, but the SBP remained unchanged (Table 3, Figure 1). A large-artery vasodilation and/or increased LV ejection power were indicated by a significant change of EEI@75, and a small-artery vasodilation by PH. No significant changes were found for ETc, DI, DDI@75, *b/a*, *d/a* and AI.

Restitution to T2 values of the DBP, MAP and ST index had occurred at point T4, 5 min after the oxytocin bolus. The initial T2–T3 changes in HR and PH were still significant at T4. In addition, from T3 to T4 changes in *d/a* and AI indicated small-artery and global vasodilation. Throughout T2–T3–T4, oxytocin had no significant effects on SBP, ETc, DI, DDI@75 and *b/a*.

Discussion

The procedures with spinal anesthesia, intravenous fluids, vasoactive drugs and delivery of the baby and placenta make it problematic to interpret the hemodynamic effects of oxytocin at CS. In addition, relief of aorto-caval compression when emptying the uterus, bleeding and maternal emotions may interfere [15]. At the start of the serial post-oxytocin recordings, significant circulatory changes had already occurred. Spinal anesthesia, and the concomitant procedures, resulted in a vasodilation of small arteries and peripheral hyperemia, accompanied by a fall in both SBP and DBP and an increase in the ECG ST index. Even so, the DPA parameter ETc increased, indicating a prolongation of the LV ejection time [11], i.e. large-artery vasoconstriction and/or a decrease in CO. The ETc elevation could be an effect of phenylephrine, a vasoconstricting alpha-1-adrenergic receptor agonist with well-known side effects of decreased HR and CO [16].

Start of surgery and delivery of the baby resulted in increases of HR and SBP and a global vasoconstriction. A further deepening of the spinal anesthesia during this time interval is not unlikely, but would have a further vasodilatory effect. We found no previous studies addressing the hemodynamic effects of the cesarean delivery procedure *per se*, but it seems clear that surgery and delivery of the baby had profound effects on the maternal circulation. During surgery and delivery of the baby the mother is exposed to both positive and negative mental stress and, in addition, the circulatory effects could be due to a catecholamine surge or auto-transfusion of blood from the empty and shrunk uterus.

Table 3. Hemodynamic effects of oxytocin administration (T2 to T4) during cesarean section.

	Effects of oxytocin				
	Wilcoxon signed-rank test				Friedman test
Parameter	T2–T3	T3–T4	T2–T4	Interpretation	T2–T3–T4
Systolic BP	0.38			No change	0.35
		0.31		No change	
			0.74	No change	
Diastolic BP	↓ 0.0162*			Diastolic BP decrease	0.019
		↑ 0.024*		Diastolic BP increase, restitution	
			0.45	Back to T2 level at T4	
Mean arterial pressure (MAP)	↓ 0.018			MAP decrease	0.050
		↑ 0.030	0.20	MAP increase, restitution Back to T2 level at T4	
Heart rate	↓ 0.012*			Heart rate decrease	0.003
		0.10		No change	
			↓ 0.002*	Heart rate decrease, occurred T2–T3	
ST index	↓ 0.026			ST decrease	0.016
		↑ 0.002*		ST increase, restitution	
			0.31	Back to T2 level at T4	
PH	↑ <0.001*			Fingertip hyperemia	0.0001
		0.31		No change	
			↑ 0.020*	Hyperemia, occurred T2–T3	
ETc	0.33			No change	0.45
		0.18		No change	
			0.68	No change	
EEI	(↑) 0.059			(Large-artery dilatation, ↑ LV ejection power)	0.20
		0.99		No change	
			0.30	No change	
EEI@75†	↑ 0.028*			Large-artery dilatation, ↑ LV ejection power	0.058
		0.70		No change	
			0.12	No change	
DI	0.85			No change	0.92
		0.99		No change	
			0.80	No change	
DDI	0.64			No change	0.93
		0.39		No change	
			0.55	No change	
DDI@75†	0.20			No change	0.15
		0.37		No change	
			0.64	No change	
b/a	0.25			No change	0.70
		0.52		No change	
			0.73	No change	
d/a	0.86			No change	0.053
		↑ 0.033		Small-artery vasodilation	
			↑ 0.018	Small-artery vasodilation, occurred T3–T4	
AI	0.98			No change	0.16
		↓ 0.039		Global arterial vasodilation	
			↓ 0.030	Global arterial vasodilation	

Figures are *p* values and arrows denote a significant increase or decrease of the parameter; arrows within brackets denote a *p* values ≥0.05 but <0.1.
**p* values significant after Holm-Bonferroni adjustments (see text).
†EEI and DDI were the only parameters that significantly correlated with HR and were adjusted to a HR of 75 bpm.

Negative stress triggers increases in oxygen consumption, respiration, BP, CO and peripheral vascular resistance, whereas relaxation responses are mostly the opposite [17]. Sinha et al. [18] found that in healthy young males happiness induces increases in HR and SBP, decreases in LV ejection time, stroke volume and peripheral vascular resistance, whereas DBP and CO remain unaffected. In accordance, watching a comedy induces a rise in BP and vasodilation [19].

Regarding auto-transfusion of blood, the effects of acute blood volume expansion have been investigated in experiments on healthy animals and humans. Jandhyala and Hom [20] showed in dogs that blood transfusion significantly increased BP and central venous pressure and reduced HR. The decrease in HR was explained by a reflex compensation to the elevated BP. Increases in systemic BP and central venous pressure have been shown in several animal and human studies, with linear relations between the magnitudes of volume expansion and increase in pressure [21–23]. Most of the transfused blood is pooled in the low-pressure vasculature, acting as a distensible reservoir [21–23].

To study the isolated effect of blood volume expansion on vascular smooth muscles, Jandhyala and Hom [20] denervated the vasculature in a hind limb of dogs. By volume expansion, the vascular resistance increased. However, in other vascular beds a volume expansion may result in a decrease in vascular resistance, as demonstrated in the pulmonary vasculature in dogs [22]. Thus, the findings in our study could point to a combined hemodynamic effect of maternal emotions and

blood volume expansion: the increase in HR being a result of positive emotions, the increase in SBP being a result of positive emotions and auto-transfusion of blood, and the increase in vascular tone being a result of auto-transfusion.

A 5 IU IV oxytocin bolus given during 60 s resulted within 1–5 min in a vasodilation of both large and small arteries, accompanied by a fall in HR, DBP and ST index. Since the normal response to a decline in BP due to vasodilation would be an increase in HR, the findings indicate a direct negative chronotropic effect of oxytocin. Although none of the women in the present series experienced chest pain or discomfort, the findings point to a transient cardiac ischemia caused by oxytocin. The coronary arteries are perfused mainly during diastole, but since oxytocin tended to slow down the HR rather than to increase it, and the LV ejection time was not significantly affected, a shortening of diastole was not etiological of ischemia. An alternative mechanism to cardiac ischemia caused by oxytocin is coronary vasoconstriction, which has been demonstrated in dogs [24].

Five minutes after the oxytocin administration, a global vasodilation and fall in HR persisted, but the DBP and ST index had returned to levels recorded before the oxytocin administration. Hence, the vasodilation and negative chronotropic effects were not just transient.

Previous studies on IV oxytocin bolus effects during CS have shown a decrease in peripheral vascular resistance and a positive chronotropic effect resulting in an increase in CO [5,7]. In contrast, we found a negative chronotropic effect lasting for at least 6 min and a possible positive inotropic effect as indicated by a rapid increase in EEI (increased LV ejection power). Also, animal studies have shown a negative chronotropic effect [2,25], but the inotropic effect is not clear, since studies have shown a decrease in LV contraction force [2] as well as an increase [25]. Cardiac synthesis of oxytocin and oxytocin receptors have been found in rats and dogs [2,26], suggesting not only a systemic vascular effect of oxytocin but also direct cardiac effects by autocrine and/or paracrine pathways.

The divergent results can possibly be explained by the fact that oxytocin has a biphasic vascular effect, as demonstrated by Thomas et al. [5] and Moertl et al. [9]: within the first post-oxytocin minute the HR increases and the SBP decreases, after which the HR decreases and the SBP increases with a slight rebound bradycardia occurring with a nadir at 3–4 min post oxytocin. Thomas et al. [5] injected a 5 IU IV bolus as quick as possible and Moertl et al. [9] during 10 s, which might maximize the cardiovascular effects.

The maternal hemodynamic effects apparently depend on the oxytocin injection time: when given as a *statim* bolus of 5 IU oxytocin the peak effects on BP and HR occur within 30–60 s [1,5,9], but when the same dose is given as an infusion over 5 min the effects are blunted with no biphasic effect curve [5]. It is also clear that the hemodynamic effects depend on the oxytocin dose: Sartain et al. [15] found less hemodynamic effects of a 2 IU oxytocin bolus compared with a 5 IU bolus when injected over 5–10 s, and Jonsson et al. [8] made the same experience when comparing 5 and 10 IU doses injected during one minute, with peak hemodynamic effects after 2 min.

The different doses of oxytocin used and the different injections times explain the inconsistency in the literature concerning the half-life as well as the peak effect of IV oxytocin. The pharmacokinetics of oxytocin in pregnant baboons has been explained by Kowalski et al. [27] using a two-compartment model, with a redistribution phase half-life of 1.1–1.7 min and an elimination phase half-life of 8.0–9.6 min. To add to the complexity, the two-compartment model seems to be valid only with high doses (>0.5 μg/kg), but at lower doses the pharmacokinetics is described with a one-compartment model [28].

Given these pharmacokinetic data, and adding the results from the studies by Thomas et al. [5] and Jonsson et al. [8] and considering patient safety, we gave the oxytocin bolus during 60 s, assuming a delayed and blunted peak effect. The DPA recording at time point T3 began 60 s after the last drop of oxytocin and lasted for a good minute; thus, it is possible that our T3 measurement covered parts of both the initial and the rebound phases.

It is well known that the chest discomfort experienced by some women during a CS is related to the dose and speed of oxytocin injection [5,15]. The adverse hemodynamic effects of oxytocin are added to the already present extensive adverse effects of spinal anesthesia, with global vasodilation, fall in BP and cardiac affection, as demonstrated in the present study (Figure 1). In the perspective of our findings, we believe it is wise to administer even a small bolus like 5 IU over a longer time than the minute used in this study, particularly in women showing circulatory instability. Furthermore, efforts should be made to enhance the spinal anesthesia procedure in order to reduce the adverse circulatory effects. Spinal anesthesia with concomitant procedures carries a risk also for the fetus [29].

Apart from a decline in HR after oxytocin, our results generally support the findings in previous studies. However, our study is the first to use the DPA technology and to show that oxytocin causes vasodilation in large as well as in small and peripheral arteries. Since the DPA is noninvasive, simple to use and the recording time is only about one minute, it is well suited for pharmacological research and for screening. A disadvantage is that the method is sensitive to body movements and cold fingers [14,30,31]. Other methods for PW analysis, like applanation tonometry and oscillometry, are too slow to catch the rapid hemodynamic responses to vasoactive drugs like oxytocin.

Weaknesses and strengths

The complex interaction of hemodynamic events makes it difficult to selectively analyze the effects of the individual procedures during a CS. A weakness is that the study series was relatively small, comprising less than 20 paired observations for some of the statistical analyzes. Small series is a common problem in clinical experimental research, though our sample sizes were in only two paired comparisons below the recommended threshold for using the Wilcoxon matched-pairs signed-rank test [32]. This is a non-parametric statistical tests, which then is more robust than its parametric equivalent, the paired *t*-test. Furthermore, to evaluate the risk of type I errors we also tested with the Friedman non-parametric one-way ANOVA for repeated measurements and performed Holm–Bonferroni adjustments of p values. The strengths of the study are the novelty of digital photoplethysmography for

PW analysis, a hitherto not explored method to study arterial stiffness in obstetrics, and the longitudinal analyses of circulatory events occurring during the different steps of the CS procedure.

Summary

Both spinal anesthesia and oxytocin 5 IU IV bolus gave rise to profound maternal circulatory effects, mainly arterial vasodilation and cardiac affection with ST index changes. Contrary to previous studies, oxytocin resulted in a decrease in HR, suggesting a direct negative chronotropic effect. The DPA parameters implied that oxytocin within minutes results in vasodilation in both large and small arteries and increased LV ejection power. Cesarean surgery and delivery of the baby resulted in a global increase in vascular tone and increases in SBP and HR, suggesting momentous circulatory effects by these procedures. We believe these seemingly contradictory changes can be a combined effect of maternal emotions and auto-transfusion of blood from the empty and reduced uterus.

Declaration of interest

The authors declare no conflicts of interest. This study was supported by grants from the Lund University Medical Faculty (ALF) and Region Skåne.

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Paper II

Rabow et al. BMC Pregnancy and Childbirth
https://doi.org/10.1186/s12884-018-2029-1

BMC Pregnancy and Childbirth

RESEARCH ARTICLE Open Access

Effects of oxytocin and anaesthesia on vascular tone in pregnant women: a randomised double-blind placebo-controlled study using non-invasive pulse wave analysis

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Abstract

Background: Oxytocin is an uterotonic drug with profound cardiovascular effects, which in compromised patients could lead to serious events. The objective was to investigate whether oxytocin affects cardiac function and vascular tone in large and small arteries. We hypothesized that oxytocin decreases arterial vascular tone and elevates cardiac output.

Methods: 51 pregnant women were randomised to treatment with 8.3 μg (5 U) oxytocin or placebo injection during first trimester surgical evacuation of the gravid uterus under general anaesthesia. Oxytocin or placebo was administered once either early or late in the procedure, in a double-blind fashion. Digital photoplethysmography pulse wave analysis variables, heart rate, mean arterial blood pressure and electrocardiographic ST index were recorded before and after anaesthesia and after each injection. Non-parametric statistics were used with a two-sided P value < 0.05 considered significant.

Results: Anaesthesia induced a significant fall in blood pressure, heart rate and vascular tone in small and peripheral arteries. Oxytocin had a vasodilatory effect on small and peripheral arteries and increased the left cardiac ventricular ejection time. The ST index decreased.

Conclusions: Pulse wave analysis indicated peripheral vasodilation and increased cardiac output after oxytocin, implying increased myocardial oxygen demand. These effects might have been enhanced by the vasodilating effects of anaesthesia. Previous studies have demonstrated myocardial ischaemia after oxytocin, as reflected by a decrease in ST index in the present study.

Trial registration: Trial registration number ISRCTN17860978, 2018/03/14, Retrospectively registered.

Keywords: Anaesthesia, Arterial stiffness, Oxytocin, Photoplethysmography, Placebo, Pregnancy, Pulse wave analysis, RCT, Vascular tone

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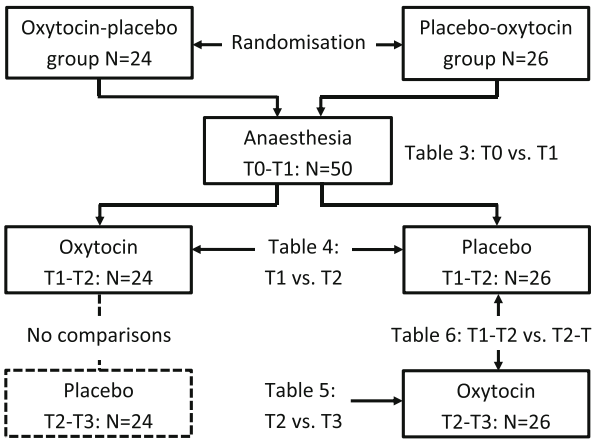

Fig. 1 Flow chart showing the steps of the experiment. The first drugs were administered between the T1 and T2 measurement points, and the second drugs between T2 and T3

Table 1 Description of the digital pulse wave analysis variables used in the study, revised from von Wowern et al. [5]

Variable	Physiological background	Conditions with high values	Conditions with low values	Interpretation of increase	Interpretation of decrease
Pulse height (PH)	Circulation in small finger arteries, perfusion of finger tips	High BP, hyperthyroidism, fever, anemia, excessive blood volume, exercise, well-tuned athlete	Peripheral vaso-constriction, low BP, hypovolemia/ dehydration, hypothyroidism, increased peripheral resistance	Peripheral vasodilatation	Peripheral vasoconstriction
Left ventricular ejection time compensated (ETc)	Represents systole, i.e. time from onset of the systolic upstroke limb to the closure of the aortic valve	Aortic valve stenosis, increased large artery compliance (low vascular tone)[a]	LV failure, decreased preload, hypovolemia, decreased large artery compliance (high vascular tone) [a]	Increase in LV ejection time, Decreased afterload, decreased SVR, increased preload [a]	Decrease in LV ejection time, Increased afterload, increased SVR, decreased preload [a]
Cardiac ejection elasticity index (EEI)	Index for LV ejection capacity and compliance/elasticity of large arteries	Large artery vasodilatation, anemia, increased LV ejection power, hyperthyroidism, congested heart failure	Large artery vasoconstriction, arteriosclerosis, LV ejection insufficiency	Increase in LV ejection power, large artery vasodilatation	Decrease in LV ejection power, large artery vasoconstriction
Dicrotic index (DI)	Represents the peripheral circulation, indicates peripheral resistance	Small artery vasoconstriction	Small artery vasodilatation	Peripheral vasoconstriction	Peripheral vasodilatation
b/a	Early systolic PW peaks identified by second derivatives of the crude PW curve contour; indicates LV ejection capacity and large artery compliance/ elasticity	Low large artery elasticity, increased cardiovascular risk, vasoconstriction, atherosclerosis, increases by age	Young persons, athletes	Large artery vasoconstriction, decreased LV ejection	Large artery vasodilatation, increased LV ejection
d/a	*d* is a late systolic PW peak identified by second derivative of the crude PW curve contour; mainly reflects the intensity of the tidal PW from small peripheral arteries	High small artery elasticity, young persons	A longer negative *d* peak develops by advancing age, indicating arterial stiffness, atherosclerosis	Small artery vasodilatation	Small artery vasoconstriction
Ageing index (AI)	AI = (*b-c-d-e*)/*a*, representing the global vascular stiffness, i.e. "vascular age"	Atherosclerosis, increases by age	Young persons, athletes	Global arterial vasoconstriction	Global arterial vasodilatation

BP blood pressure, *SVR* systemic vascular resistance, *LV* left heart ventricle, *PW* pulse wave
[a]) See Discussion for interpretation

Background

Oxytocin is used to contract the uterus for prevention and treatment of post-partum haemorrhage after both vaginal delivery and Caesarean section (CS) [1]. It is also used after curettage to prevent post-operative uterine atony and bleeding [2]. Oxytocin has cardiovascular side effects such as tachycardia, vasodilation, hypotension and chest pain. This may lead to serious cardiovascular events in an already compromised patient [3].

We have previously studied the cardiovascular effects of oxytocin using digital photoplethysmographic pulse wave analysis (DPA) during elective CS [4]. We found that oxytocin causes arterial vasodilation of both small and large arteries and has a direct negative chronotropic effect with increased left ventricular (LV) ejection power accompanied by electrocardiographic (ECG) ST changes. However, the combination of CS, spinal anaesthesia, intravenous fluids, vasoactive drugs and delivery of the baby and placenta, made it problematic to study the haemodynamic effects of oxytocin exclusively. Therefore, we wanted to conduct a study in a more stable clinical setting. For this purpose, we chose to study the circulatory effects in first trimester pregnant women undergoing uterine evacuation after miscarriage or for surgical termination of pregnancy.

The DPA method can assess cardiac LV ejection time (LVET) and distinguish between tonus changes in large and small arteries [5]. Using DPA in combination with ECG ST index and mean arterial blood pressure (MAP) measurements adds information whether there are direct cardiac effects of oxytocin [5, 6]. The method has been validated against invasive aortic pressure measurements during vasoconstrictory and vasodilatory manipulations [7][Takazawa 1998], the physiological background to the digital photoplethysmographic volume pulse wave contour characteristics has been thoroughly described [8, 9] and the method correlates well with the gold standard applanation tonometry method [5, 8]. The DPA has the advantage of being rapid, non-invasive, pain-free, and user independent.

Methods

The primary objective of the study was to investigate whether oxytocin affects both large and small arteries, and cardiac LV ejection function, using the DPA method. Based on our own observations [4] and observations by Weis et al. [10], we hypothesised that oxytocin decreases arterial vascular tone and elevates cardiac output (CO). The regional research ethics committee in Lund approved the study (dnr 2012/649) and all enrolled women gave their informed oral and written consent. The study was performed in accordance with The Code of Ethics of the Declaration of Helsinki. The women were recruited consecutively at the Department of Obstetrics and Gynaecology at Skåne University Hospital, Malmö, during the spring 2013, as part of the Master's degree projects by U. H. and S. S. All women scheduled for termination of pregnancy in the first trimester by vacuum aspiration or curettage, who met the inclusion criteria, were asked to participate. Inclusion criteria were healthy women assessed as American Society of Anesthesiologists physical status classes I-II, with a gestational age below 12 weeks, age above 18 years, and understanding oral and written Swedish. In all, 54 women were asked to participate, of whom 3 declined, and the recruitment stopped after 51 included patients. A sample size based on power calculation could not be performed, because in comparison with placebo, the oxytocin effects on DPA variables were unknown.

The women were randomised by P.O. using a web-based random number generator [11] to first treatment with either intravenous (IV) oxytocin or placebo. Before the start of anaesthesia, the nurse anaesthetist opened a sealed opaque envelope containing the treatment allocation. The nature of the injection was blinded to the woman, to the researchers, and to the surgeon. Women given oxytocin as the first injection were given placebo as the second injection (oxytocin-placebo sequence, OP group) and vice versa (placebo-oxytocin sequence, PO group) (Fig. 1). The oxytocin injection comprised 1 mL of Oxytocin Pilum 8.3 μg/mL (5 U) (Orifarm Generics, Stockholm, Sweden) and the placebo injection comprised 1 mL of NaCl 9 mg/mL.

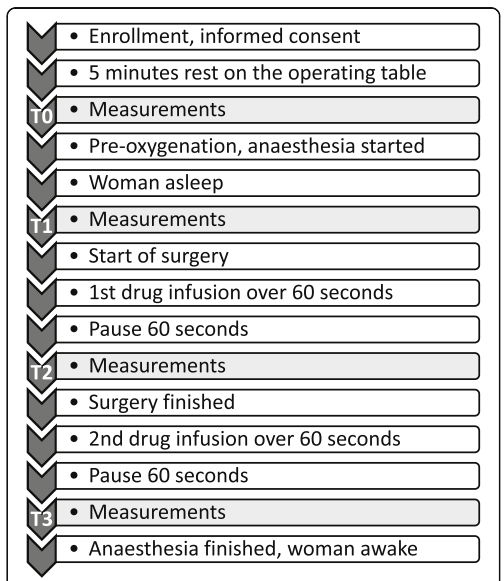

Fig. 2 Study protocol with time sequences of monitoring, anaesthesia and intravenous drug injections

The physiological background to the DPA method has been described previously [6, 8]. The Meridian DPA™ reports 17 different variables, but for this study we selected those variables with the best repeatability and best correlation to gold standard applanation tonometry: pulse height (PH), ageing index (AI), cardiac LV ejection time (LVET) compensated (ETc), cardiac ejection elasticity index (EEI), dicrotic index (DI), and the ratios b/a and d/a [5]. The variables are described in Table 1.

The sequences of monitoring and treatments are shown in Fig. 2. Three hours prior to scheduled surgery, the women were pre-medicated with two intravaginal misoprostol 0.2 mg tablets (Cytotec®, Pfizer AB, Sollentuna, Sweden) and two oral paracetamol 500 mg tablets (Alvedon®, GlaxoSmithKline Consumer Healthcare, Bröndby, Denmark). Upon arrival at the operating room, a peripheral IV catheter was introduced. A 5-lead ECG, a blood pressure (BP) cuff and a peripheral oxygen saturation (SaO_2) probe were connected to the surveillance monitor (DASH 4000, GE Medical Systems Information Technologies, Danderyd, Sweden). The ECG ST index was automatically derived from the ECG lead II. Readings of BP, SaO_2, and ST index were manually noted in a case report form.

For the DPA measurements, a customized pulse oximetry probe was placed on the right second or third finger, and then connected to the Meridian DPA™ (Meridian Co. Ltd., Korea, and Salcor AB, Uppsala, Sweden). The Meridian DPA was connected to a laptop (HP 625, Hewlett Packard, Solna, Sweden). Each DPA measurement takes 70 s to perform, during which surgery was halted.

Since the surgery was performed with the woman in the lithotomy position and the DPA measurements are sensitive to body position, the woman was placed in this position on the operating table already before initialising anaesthesia. After 5 min of rest in this position, the baseline measurements (time point T0) were performed (Fig. 2). The woman was then pre-oxygenated with 100% oxygen through a breathing mask. General anaesthesia was commenced with an injection of fentanyl 100 μg (Fentanyl® B. Braun 50 μg/mL) followed by a bolus dose of propofol (Propofol®-Lipuro B. Braun 10 mg/mL), individually titrated to loss of consciousness and eyelid reflex, after which anaesthesia was maintained with propofol only. The women were kept on mask airway during anaesthesia.

At each time point, the measurements were started with a DPA recording (lasting 70 s) paralleled by the ECG ST index reading, followed by a BP measurement. The second measurements were performed after the induction of anaesthesia, but before the start of surgery (time point T1, see Fig. 2). The first drug injection was given when the cervical dilatation was completed and uterine evacuation began. The injection time was one minute. A stopwatch was started and the point T2 DPA recording started 60 s after finishing the injection.

The second drug injection was given at the end of surgery but before end of anaesthesia and the point T3

Table 2 Demographic characteristics

	Oxytocin-placebo group N=24	Placebo-oxytocin group N=26	Total number	Significance of difference (*P*)
Age (years)	32.4 ± 6.0 33 (20, 43)	28.4 ± 6.4 28.5 (18, 41)	50	0.032
Body mass index (kg/m^2)	26.0 ± 4.6 25.4 (19.1, 37,5)	23.0 ± 3.6 22.5 (17.8, 31.2)	50	0.018
Propofol (mg)	303 ± 89 290 (200, 560)	313 ± 65 300 (220, 460)	50	0.36
Surgical abortion	2	6	8/50	0.19
Unsuccessful medical abortion	5	8	13/50	
Missed/incomplete abortion	17	12	29/50	

Figures are mean ± standard deviation and median (range)
Statistics were performed with the Mann-Whitney *U* test or Fisher's exact probability test

Table 3 Haemodynamic effects of general anaesthesia in first trimester pregnant women. For explanation of measurement points T0 and T1, see text and Fig. 2

Variable	Number of cases	Cardiovascular effect of anaesthesia measured T0-T1			
		T0 value Mean ± SD Median (range)	T1 value Mean ± SD Median (range)	Significance of difference (*P*)	Cardiovascular effect
MAP (mmHg)	49	85 ± 12 84 (65, 112)	65 ± 9 64 (49, 89)	0.0001	Blood pressure drop
HR (bpm)	33	73 ± 14 70 (44, 96)	65 ± 9 63 (48, 84)	0.002	Heart rate drop
ECG ST index	48	0.15 ± 0.28 0.20 (− 0.70, 0.90)	0.20 ± 0.22 0.20 (− 0.30, 0.60)	0.13	
PH	33	2.0 ± 1.9 1.3 (0.6, 10.5)	5.3 ± 2.9 4.9 (0.8, 14.9)	0.0001	Peripheral vasodilation
ETc (ms)	33	374 ± 30 372 (313, 442)	361 ± 45 368 (165, 437)	0.56	
EEI	27	0.69 ± 0.28 0.59 (0.27, 1.32)	0.60 ± 0.18 0.58 (0.18, 1.00)	0.19	
EEI@75	27	0.71 ± 0.26 0.74 (0.19, 1.21)	0.68 ± 0.19 0.69 (0.28, 1.14)	0.61	
DI	33	0.66 ± 0.14 0.65 (0.37, 0.93)	0.66 ± 0.14 0.66 (0.36, 0.94)	0.31	
DI@75	33	0.65 ± 0.08 0.65 (0.50, 0.83)	0.56 ± 0.14 0.58 (0.25, 0.80)	0.0009	Small-artery vasodilation
b/a	33	−0.63 ± 0.14 − 0.64 (−1.05, − 0.39)	− 0.60 ± 0.15 − 0.56 (− 1.02, − 0.26)	0.46	
d/a	33	− 0.20 ± 0.10 − 0.17 (− 0.49, − 0.07)	− 0.18 ± 0.14 − 0.15 (− 0.54, − 0.01)	0.24	
AI	33	− 0.48 ± 0.30 − 0.53 (− 1.03, 0.24)	−0.32 ± 0.28 − 0.38 (− 0.77, 0.42)	0.010	Global vasoconstriction

MAP, mean arterial blood pressure, *HR* heart rate *ECG*, electrocardiogram, *PH* pulse height, *ETc* cardiac left ventricular ejection time compensated, *EEI*, cardiac ejection elasticity index, *EEI@75*, EEI adjusted to a HR of 75 bpm, *DI* dicrotic index; DI@75, DI adjusted to a HR of 75 bpm; *b/a*, ratio between second derivatives of crude pulse wave contour; *d/a*, ratio between second derivatives of crude pulse wave contour; AI, ageing index
Statistics performed with Wilcoxon matched-pairs signed-rank test

measurements were performed in the same way as for the T2 measurements (Fig. 2).

Since the plasma half-time elimination of oxytocin is 3–20 min [12], the comparison of oxytocin vs. placebo could not be performed in the OP group after the second injection due to a too short wash-out time of oxytocin after the first injection. Thus, the oxytocin effect was in comparison with placebo studied cross-sectionally in the OP group at T1-T2 and longitudinally in the PO group for T1-T2 vs. T2-T3 (Fig. 1). For each studied variable, the difference from before until after administration was calculated, denoted Δ value. A positive Δ value denotes an increase and a negative value a decrease.

The DPA data were automatically exported to an Excel file in the laptop and later converted to a statistics software document (StatView version 5.0.1, SAS Institute, Cary, NC, USA). The Meridian manufacturer recommends that at least 80% of the pulse waves should be recorded to ensure good quality of the mathematical analyses of the pulse wave contour, so recordings with < 80% recognition were excluded from statistical analyses.

The Mann-Whitney U test was used to compare continuous variables between groups. For longitudinal comparisons within groups the Wilcoxon signed-ranks matched-pairs test was used. Categorical data were compared with Chi-2 test or Fisher's exact probability test. Fisher's exact test in 2×3 tables was performed with software available on the web [13]. Two-sided P values < 0.05 were considered statistically significant.

Some of the DPA variables are heart rate (HR) dependent [5] and the statistical analyses were accordingly performed with both crude and HR-adjusted DPA values. If simple linear regression analyses yielded a statistically significant correlation ($P < 0.05$) between HR and a DPA variables at T0, and the intervention (anaesthesia, oxytocin or placebo administration) also resulted in a significant change in HR, the DPA variables in question was adjusted to a HR of 75 bpm, denoted DPA@75, with the equation DPA@75 = DPA ± C(75-HR). C denotes the slope constant. The DPA

Table 4 Haemodynamic effects of 5 U (8.3 μg) oxytocin and placebo (NaCl) given intravenously to first trimester pregnant women undergoing surgical evacuation of the uterus. For explanation of time points T1 and T2, see text and Figs. 1 and 2

Variable	Effect of drug injection measured T1-T2								Δ value[a] *P*
	Oxytocin (OP group) N = 24				Placebo (PO group) *N* = 26				
	T1 value Mean ± SD Median (range)	T2 value Mean ± SD Median (range)	*P*[b]	Effect	T1 value Mean ± SD Median (range)	T2 value Mean ± SD Median (range)	*P*[b]	Effect	
MAP (mmHg)	67 ± 10 65 (49, 89)	76 ± 12 76 (57, 97)	0.001	BP increase	64 ± 9 62 (52, 88)	73 ± 8 74 (57, 87)	0.0001	BP increase	0.61
HR (bpm)	64 ± 8 63 (48, 82)	68 ± 9 71 (53, 84)	0.011	HR increase	66 ± 9 65 (51, 84)	66 ± 8 65 (53, 82)	0.90	No change	0.020
ECG ST index	0.21 ± 0.24 0.30 (−0.20, 0.60)	0.15 ± 0.19 0.10 (− 0.40, 0.60)	0.30	No change	0.19 ± 0.21 0.10 (− 0.30, 0.60)	0.33 ± 0.21 0.30 (0.00, 0.80)	0.0005	ST increase	0.0008
PH	5.3 ± 2.9 4.8 (0.8, 13.3)	9.6 ± 2.5 8.8 (6.1, 15.0)	< 0.0001	Peripheral vasodilation	5.3 ± 3.0 4.9 (1.8, 14.9)	9.9 ± 3.3 9.5 (4.9, 16,0)	< 0.0001	Peripheral vasodilation	0.45
ETc (ms)	360 ± 39 366 (245, 418)	381 ± 41 383 (267, 444)	0.021	Decreased afterload, decreased SVR, increased preload	362 ± 51 369 (165, 437)	356 ± 55 371 (156, 404)	0.70	No change	0.069
EEI	0.58 ± 0.19 0.58 (0.18, 0.93)	0.59 ± 0.16 0.60 (0.26, 0.77)	0.65	No change	0.61 ± 0.18 0.60 (0.31, 1.00)	0.53 ± 0.13 0.51 (0.36, 0.83)	0.12	No change	0.17
EEI@75	0.67 ± 0.18 0.66 (0.28, 0.98)	0.65 ± 0.16 0.67 (0.32, 0.95)	0.95	No change	0.69 ± 0.20 0.72 (0.32, 1.14)	0.61 ± 0.15 0.57 (0.41, 0.96)	0.23	No change	0.43
DI	0.65 ± 0.15 0.67 (0.36, 0.94)	0.55 ± 0.11 0.55 (0.33, 0.77)	0.001	Small-artery vasodilation	0.66 ± 0.13 0.66 (0.41, 0.92)	0.67 ± 0.14 0.66 (0.41, 0.99)	0.84	No change	0.015
DI@75	0.55 ± 0.14 0.57 (0.25, 0.77)	0.49 ± 0.11 0.50 (0.32, 0.65)	0.023	Small-artery vasodilation	0.58 ± 0.14 0.58 (0.28, 0.80)	0.59 ± 0.15 0.61 (0.22, 0.88)	0.97	No change	0.10
b/a	− 0.59 ± 0.16 − 0.54 (− 0.95, − 0.26)	−0.57 ± 0.13 − 0.57 (− 0.85, − 0.25)	0.74	No change	−0.62 ± 0.14 − 0.61 (− 1.02, − 0.40)	−0.56 ± 0.08 − 0.55 (− 0.78, − 0.39)	0.094	No change	0.19
d/a	−0.17 ± 0.14 − 0.14 (− 0.54, − 0.01)	− 0.20 ± 0.09 − 0.20 (− 0.39, − 0.08)	0.38	No change	−0.18 ± 0.14 − 0.18 (− 0.50, − 0.01)	− 0.23 ± 0.13 − 0.20 (− 0.76, − 0.08)	0.084	No change	0.84
AI	− 0.31 ± 0.29 − 0.38 (− 0.77, 0.21)	−0.27 ± 0.24 − 0.27 (− 0.63, 0.24)	0.99	No change	−0.32 ± 0.29 − 0.37 (− 0.70, 0.42)	−0.25 ± 0.20 − 0.30 (− 0.50, 0.25)	0.086	No change	0.27

OP group, women given oxytocin at first injection and placebo at second injection; PO group, women given placebo at first injection and oxytocin at second injection

[a)] The Δ values are not shown, but represent the T2 value minus T1 value. *P* denotes significance of difference in Δ value between oxytocin and placebo injections, performed with the Mann-Whitney *U* test

[b)] *P* denotes significance of difference between T1 and T2 values, performed with the Wilcoxon matched-pairs signed-ranks test

variable ETc and the ECG variable ST index are automatically adjusted for HR when reported by the respective apparatus.

Results

One patient in the OP group did not receive the allocated intervention due to a surgical complication with perforation of the uterus. Thus, 24 women allocated to the OP group and 26 to the PO group were included in the study. Their demographic characteristics are shown in Table 2.

At time point T0, in 17/50 (34%) women the PH was below the 80% threshold for receiving adequate signals for pulse wave contour analysis, thus disabling reliable calculations of DPA variables. This excluded the longitudinal comparisons T0-T1 (effects of anaesthesia) in 34–46% of cases. For recordings T1-T3, the recording error rate was 4–8%.

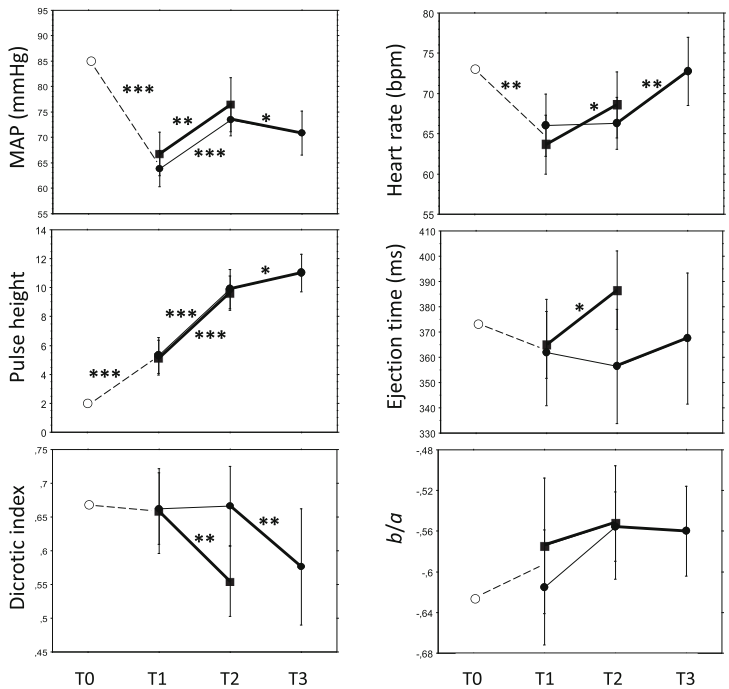

Fig. 3 Sequential changes of mean arterial blood pressure (MAP), heart rate, pulse height, left ventricular ejection time, dicrotic index and *b*/*a* from time point T0 through T3 (for details, see text). Dashed lines represent the effect of general anaesthesia. Oxytocin/placebo were administered between T1 and T2 and vice versa between T2 and T3, where filled squares represent the oxytocin-placebo group and filled circles the placebo-oxytocin group. The oxytocin-placebo group were not analysed at T2-T3, as explained in the text. Bold lines represent oxytocin effects and thin lines placebo effects. Values are mean with 95% confidence interval. The asterisk * denotes a *P* value < 0.05, ** denotes *P* < 0.01 and *** *P* < 0.001, calculated with the Wilcoxon signed-ranks matched-pairs test.

At point T0, a significant relationship was found between HR and DI ($P < 0.0001$, r^2 0.67) and EEI ($P = 0.017$, r^2 0.17) and these variables were accordingly adjusted in the statistical analyses (called DI@75 and EEI@75). AI, *b*/*a* and *d*/*a* were not significantly related to HR ($P \geq 0.50$).

Anaesthesia caused a decrease in MAP and HR and a small-artery and peripheral vasodilation, as indicated by PH and DI@75, and a global vasoconstriction was indicated by AI (Table 3).

The surgery started after point T1 (Fig. 2), and oxytocin and placebo showed from T1 to T2 the following effects (Table 4, Fig. 3):

- MAP increased by equal magnitudes in the OP and PO groups, i.e. no matter the sort of injection.
- An increase in HR was seen only after oxytocin, and the difference to placebo was confirmed by comparison of ΔHR values.
- The ECG ST index changed only after placebo, confirmed by a difference in Δ values.
- PH increased (peripheral vasodilation) by equal magnitudes after oxytocin and placebo, confirmed by the absence of difference in ΔPH values.
- ETc increased (increase in LVET, increased preload, and/or decreased afterload) only after oxytocin, but the difference in ΔETc values did not reach significance ($P = 0.069$).
- EEI and EEI@75 were not affected by oxytocin or placebo.
- Changes of DI and DI@75 after oxytocin indicated small-artery vasodilation, and the difference was confirmed by a difference in ΔDI values.
- *b*/*a*, *d*/*a* and AI did not change significantly in any group.

Due to a probable insufficient wash-out effect of oxytocin given as the first injection in the OP group,

Table 5 Haemodynamic effects of 5 U (8.3 μg) oxytocin given as the second injection at T2-T3 in women given placebo as the first injection

Variable	Oxytocin (PO group) $N = 26$			
	T2 value Mean ± SD Median (range)	T3 value Mean ± SD Median (range)	P^{a}	Effect
MAP (mmHg)	73 ± 8 74 (57, 87)	71 ± 11 71 (51, 90)	0.046	BP decrease
HR (bpm)	66 ± 8 65 (53, 82)	73 ± 10 72 (53, 88)	0.001	HR increase
ECG ST index	0.33 ± 0.21 0.30 (0.00, 0.80)	0.18 ± 0.29 0.20 (− 0.40, 0.70)	0.014	ST decrease
PH	9.9 ± 3.3 9.5 (4.9, 16,0)	11.0 ± 3.0 11.5 (5.5, 16.0)	0.019	Peripheral vasodilation
ETc (ms)	356 ± 55 371 (156, 404)	367 ± 60 381 (179, 430)	0.39	No change
EEI	0.53 ± 0.13 0.51 (0.36, 0.83)	0.50 ± 0.13 0.48 (0.33, 0.80)	0.33	No change
EEI@75	0.61 ± 0.15 0.57 (0.41, 0.96)	0.52 ± 0.15 0.52 (0.31, 0.84)	0.33	No change
DI	0.67 ± 0.14 0.66 (0.41, 0.99)	0.58 ± 0.20 0.53 (0.26, 0.99)	0.006	Small-artery vasodilation
DI@75	0.59 ± 0.15 0.61 (0.22, 0.88)	0.56 ± 0.20 0.55 (0.12, 1.06)	0.013	Small-artery vasodilation
b/a	−0.56 ± 0.08 − 0.55 (− 0.78, − 0.39)	− 0.56 ± 0.10 − 0.57 (− 0.74, − 0.35)	0.056	No change
d/a	−0.23 ± 0.13 − 0.20 (− 0.76, − 0.08)	− 0.22 ± 0.09 − 0.21 (− 0.40, − 0.04)	0.42	No change
AI	−0.25 ± 0.20 − 0.30 (− 0.50, 0.25)	−0.20 ± 0.19 − 0.20 (− 0.68, 0.05)	0.15	No change

[a] *P* denotes significance of difference between T2 and T3, performed with the Wilcoxon matched-pairs signed-ranks test

the effects of placebo given as the second injection T2-T3 were not analysed (Fig. 1). Table 5 shows the effects of oxytocin when comparing T2 and T3 values. Effects were found on MAP, HR, ST index, PH, DI and DI@75, whereas no effects were found on ETc, EEI, EEI@75, *d*/*a* and AI. A decrease in *b*/*a* did not reach statistical significance ($P = 0.056$, which would indicate large-artery vasodilation and increase in LV ejection if significant).

At point T3 surgery had finished, but the women were still under anaesthesia (Fig. 2). In longitudinal comparisons in the PO group, the effects of oxytocin measured T2-T3 were compared with the effects of placebo measured T1-T2 (Table 6, Fig. 1). EEI and EEI@75 statistics could not be performed due to too few cases in comparisons ($N = 10$). The results in Table 6 are interpreted in Table 7, together with an overall interpretation of oxytocin effects displayed in Tables 4-6.

Figure 3 shows the sequential variable changes throughout the experiment from T0 to T3, and Table 7 shows a comprehensive interpretation of oxytocin effects, where some interpretations need further explanations. The MAP increased at T1-T2 in both the oxytocin and placebo groups with no significant difference in magnitude (Table 4), whereas the difference to placebo in the comparison T1-T2 vs. T2-T3 was significant (Table 6); as oxytocin at T2-T3 caused a decrease (Tables 5 and 6) and placebo at T1-T2 an increase (Table 4), the comprehensive interpretation is that MAP decreased after oxytocin (Table 7).

The ECG ST index was unchanged after oxytocin, whereas it increased after placebo at T1-T2 comparisons (Table 4). The difference to placebo in the comparison T1-T2 vs. T2-T3 was significant, where oxytocin showed a decrease and placebo an increase (Tables 4-6). The interpretation is that ECG ST index decreased after oxytocin (Table 7).

The ETc increased at T1-T2 after oxytocin whereas placebo had no effect (Table 4). In the longitudinal comparison with placebo at T1-T2 vs. T2-T3 (Table 6) there was no difference to placebo, and at T2-T3 oxytocin had no effect on ETc (Table 5). The findings were then not unanimous.

Table 6 Haemodynamic effects of oxytocin (administered during sequence T2-T3) relative to placebo (sequence T1-T2) in first trimester pregnant women in the placebo-oxytocin group ($N = 26$). For interpretation and comparisons of oxytocin effects, see Table 7

Variable	Placebo Δ value T1-T2[a] Mean ± SD Median (range)	Oxytocin Δ value T2-T3[b] Mean ± SD Median (range)	Significance of difference[c] (*P*)
MAP (mmHg)	10 ± 9 10 (− 13, 23)	− 3 ± 7 − 2 (− 16, 12)	0.0002
HR (bpm)	0 ± 5 0 (− 13, 9)	6 ± 7 4 (− 4, 22)	0.020
ECG ST index	0.14 ± 0.16 0.10 (− 0.10, 0.50)	− 0.15 ± 0.28 − 0.10 (− 0.90, 0.30)	0.001
PH	4.7 ± 2.9 4.1 (− 0.8, 10.1)	1.0 ± 1.8 0.9 (− 2.8, 3.4)	0.005
ETc (ms)	−3 ± 48 5 (− 200, 55)	2 ± 48 6 (− 160, 107)	0.70
DI	0.00 ± 0.18 − 0.02 (− 0.41, 0.46)	− 0.11 ± 0.16 − 0.14 (− 0.34, 0.30)	0.016
DI@75	0.00 ± 0.18 0.00 (− 0.39, 0.49)	−0.06 ± 0.17 − 0.01 (− 0.25, 0.50)	0.11
b/a	0.06 ± 0.15 0.02 (− 0.19, 0.53)	−0.02 ± 0.08 − 0.05 (− 0.14, 0.21)	0.024
d/a	−0.04 ± 0.13 − 0.03 (− 0.39, 0.27)	−0.02 ± 0.09 − 0.00 (− 0.18, 0.16)	0.78
AI	0.07 ± 0.23 0.08 (− 0.55, 0.62)	0.06 ± 0.20 0.04 (− 0.26. 0.47)	0.94

[a] Δ value calculations *T2* value minus T1 value
[b] Δ value calculations: T3 value minus T2 value
[c] Statistics performed with Wilcoxon matched-pairs signed-ranks test, comparing the changes (Δ value) obtained by oxytocin and placebo

No harmful side effects were noted during the study and no woman complained of chest discomfort.

Discussion

This study supports the hypothesis that oxytocin decreases vascular tone. The changes in DPA variables after an oxytocin bolus suggest vasodilation and decreased vascular tone of small and peripheral arteries. This was established at both cross-sectional and longitudinal comparisons with placebo. The PH, an indicator of the peripheral circulation, increased after anaesthesia and then further after the first drug injection, of equal magnitude after oxytocin and placebo. PH has previously been found to increase with increasing depth of anaesthesia due to reduced sympathetic activity [14]. Then, a continuously increasing PH with increasing depth of anaesthesia might explain the placebo effect of the first injection.

The second injection was given when surgery was finished and the depth of anaesthesia was at steady state or ceasing. Then, oxytocin caused small-artery and peripheral vasodilation, fall of MAP and increase in HR, which further supports the conclusion that oxytocin causes a small-artery and peripheral vasodilation.

The increase in MAP in both groups at the start of surgery might be the result of an increase in sympathetic activity due to painful stimuli. It is, however, possible that a fall in MAP of a very short duration failed to be captured in our study protocol, as MAP was measured after the one-minute DPA recording was completed. The BP measurement takes up to 30 s, meaning that MAP was measured 2–3 min after the end of the oxytocin injection. It has been demonstrated in previous studies that the MAP reduction reaches its nadir already within 1–2 min, and returns to normal after another minute [15, 16]. The ECG changes also occur within 1–2 min [17]. Furthermore, oxytocin has a biphasic effect, with a rapid initial HR increase and decrease in systolic BP followed by a fall in HR and increase in BP [3, 18]. We might then not have captured the rapid initial effect of oxytocin in our study. Also the duration of the bolus injection has been attributed to the nadir lag time. Some researchers used *statim* bolus and others, like us, used a 60 s injection time. A short injection time might maximise the initial effects. Since the BP measurements could interfere with the DPA measurements, we had no choice but to await finishing the DPA measurement before we could record the BP.

The ETc increased after oxytocin at T1-T2 whereas placebo had no effect. Considering the whole experiment, the effect of oxytocin on ETc was not unanimous, but as the T1-T2 comparison was the only one performed during equal conditions in the OP and PO groups, our overall interpretation is that oxytocin caused an increase in ETc. According to our previous communications with the South Korean manufacturer of the Meridian DPA, an increase in ETc could mean aortic valve stenosis or LV failure, as previously described [4, 5]. It might be true concerning aortic valve disease, but is more complex concerning LV failure [19]. Both ETc and the similar measure Flow Time Corrected, derived from oesophageal Doppler velocimetry of aortic blood flow, correlate strongly with the LVET [5, 20]. Lewis et al. pointed out already in 1977 that LV muscle failure and diminished preload is associated with a shortened LVET, and that a marked increase in SV would lengthen the LVET [19].

Later on, Singer et al. [21, 22] using oesophageal Doppler velocimetry, demonstrated that the LVET was increased when preload was increased from a hypovolemic state, but also when preload was decreased from an overload state. Thus, LVET is reaching its maximum at optimal filling pressures. As preload diminishes, compensatory peripheral vasoconstriction causing increased systemic vascular resistance (SVR) usually occur. In effect, vasodilating agents alone also produce an increase in LVET, leaving preload unaffected. Taken together, in

Table 7 Summary of observations based on haemodynamic effects of oxytocin administered at first injection T1-T2 (Table 4) and second injection T2-T3 (Tables 5 and 6). For further explanation of comparisons, see Fig. 1, and for explanation of interpretations, see text

Variable	Table 4 T1-T2 in OP group *N* = 24	Table 5 T2-T3 in PO group *N* = 26	Table 6 T1-T2 vs. T2-T3 in PO group *N* = 26	Summary of observations
MAP (mmHg)	No change[a]	Decrease	Decrease	Decrease
HR (bpm)	Increase	Increase	Increase	Increase
ECG ST index	No change	Decrease	Decrease	Decrease
PH	No change[b]	Increase ➔ peripheral vasodilation	Increase ➔peripheral vasodilation	Increase ➔ peripheral vasodilation
ETc (ms)	Increase ➔ large-artery vasodilation, decreased afterload, decreased SVR, increased preload	No change	No change	Increase ➔ large-artery vasodilation, decreased afterload, decreased SVR, increased preload
EEI	No change	No change	N/A[c]	No change
EEI@75	No change	No change	N/A[c]	No change
DI	Decrease ➔ small-artery vasodilation	Decrease ➔ small-artery vasodilation	Decrease ➔ small-artery vasodilation	Decrease ➔ small artery vasodilation
DI@75	Decrease ➔ small-artery vasodilation	Decrease ➔ small-artery vasodilation	No change	Decrease ➔ small artery vasodilation
b/a	No change	No change	No change/decrease ➔ large-artery vasodilation, increase in LV ejection	No change
d/a	No change	No change	No change	No change
AI	No change	No change	No change	No change

[a] *MAP* increased after both oxytocin and placebo
[b] *PH* increased after both oxytocin and placebo, indicating peripheral vasodilation
[c] *EEI* and *EEI@75* statistics could not be performed due to too few cases in comparisons (N = 10)

healthy patients without fluid overload, LVET increases not only by increased preload but also by decreased afterload, i.e. from decreased SVR [23].

From this argumentation, we believe that the rise in ETc after the first oxytocin injection indicates a reduction in SVR, since preload is assumed unaffected. As HR increased without a fall in MAP, an increase in CO is assumed. An increase in CO leads to an increase in myocardial oxygen demand. Signs of myocardial ischemia have previously been noted after oxytocin injection [17], and that observation could explain the different responses in ECG ST index after oxytocin and placebo.

Thirty-four percent of DPA values were missing at T0 due to cold fingers, probably caused by pre-operative stress-induced peripheral vasoconstriction [14]. Among confounding factors, sympathetic activity induced by noxious stimuli from the surgical procedure might explain changes seen in the placebo group between T1 and T2. Although there were no differences between the groups in the total doses of propofol given, variations in anaesthetic depth is another possible confounding factor.

The cardiovascular effects of anaesthesia included decreases in BP and HR and dilatation of small and peripheral arteries. However, the global index AI indicated vasoconstriction. AI is a composite index of four indices reflecting different phases of the pulse wave from early systole to early diastole, i.e. *b*/*a*, *c*/*a*, *d*/*a* and *e*/*a* [5]. The two indices reported separately in the present study, i.e. *b*/*a* and *d*/*a*, did not change significantly, and the variable reflecting large arteries, EEI, did not change either. Then, the significant change of AI can be interpreted as the amalgamated result of non-significant changes of the subset of indices, or it was a result of a type 1 error. Oxytocin has both vasodilatory and vasoconstrictory properties via the same receptor, V1aR [24], and various vascular beds and organs display different distributions and receptor sensitivity [25]. Although not possible to demonstrate in the present study, vasoconstriction in medium-sized arteries could be a physiological response to peripheral vasodilation and falls in BP and HR.

DPA with digital photoplethysmography is a non-invasive, operator-friendly and rapid method to study vascular tone and pharmacological hemodynamic effects in a clinical setting where the effects come swift. As illustrated by the DPA measurements before initializing anaesthesia, cold fingers must be avoided as they distort the results. That applies to finger movements as well.

A strength of the study is the randomised double-blinded placebo-controlled design in a normal clinical setting. In comparison with our previous study on oxytocin during CS, where the procedures with spinal anaesthesia, IV fluids, vasoactive drugs and delivery of the baby made it problematic to interpret the hemodynamic effects of oxytocin [4], the present study was less compromised by confounding factors. Another strength is the DPA method's ability to investigate effects on large and small arteries separately, by using derivative mathematics to analyse the systolic and diastolic segments of the pulse wave contour. It is a limitation that the study protocol could not be adapted to capture short biphasic courses of events. As surgery needed to be stopped during DPA and BP measurements, for the safety of the women we could not perform double measurements, as would have been experimentally preferred. Variations in anaesthetic depth and sympathetic activity are possible confounders that could not be controlled for.

Misoprostol 0.4 mg was administered vaginally 3 h prior to scheduled surgery. The drug has a plasma half-time of about 30 min, but due to slow absorption by the vaginal route the bioactivity could remain for a few hours [26]. It is therefore possible that remainders of misoprostol persisted at the time of the experiments. However, the lasting bioactivity has been shown on the myometrium [26], whereas no cardiovascular effects of misoprostol have been demonstrated [27, 28]. We therefore believe possible remainders of misoprostol did not confound the results. The placebo-controlled design of the study could ensure it was not misoprostol effects that we measured, and the longitudinal measurements were performed during a short time-span when steady-state concentrations of misoprostol would not bias the results.

Conclusions

This study confirmed the hypothesis that oxytocin decreases vascular tone in small and peripheral arteries, resulting in a lower BP and a compensatory increase in HR. These effects might have been enhanced by the vasodilating effects of anaesthesia. We could not confirm any effect on vascular tone in large arteries. The net oxytocin effect on the heart is likely to be an increased CO, implying increased myocardial oxygen demand. The demonstrated multiple effects of oxytocin on the cardiovascular system suggest a cautious use of oxytocin in pregnant women.

Abbreviations

AI: Ageing index; b/a: Second derivative quotient of the acceleration phase the percussion pulse wave; BP: Blood pressure; CO: Cardiac output; CS: Caesarean section; d/a: Second derivative quotient of percussion wave clashing the reflected tidal wave; DI: Dicrotic index; DI@75: DI adjusted to a heart rate of 75 bpm; DPA: Digital pulse wave analysis; ECG: Electrocardiogram; EEI: Ejection elasticity index; EEI@75: EEI adjusted to a heart rate of 75 bpm; ETc: Left ventricular ejection time compensated (for heart rate); Ftc: Flow time corrected; HR: Heart rate; IV: Intravenous; LV: Left ventricle of the heart; LVET: Left ventricular ejection time; MAP: Mean arterial blood pressure; OP: Oxytocin-placebo sequence; PH: Pulse height; PO: Placebo-oxytocin sequence; ST index: Difference in ECG ST segment from the isoelectric baseline; SVR: Systemic vascular resistance; **Δ** value: Difference between measurement at time point T_n minus measurement at point T_{n-1}

Funding

The study was funded by grants from the Medical Faculty at Lund University (ALF) and from Region Skåne. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Availability of data and materials

The datasets used are available from the corresponding author on reasonable request.

Authors' contributions

PO conception and design of the study, PO and SR planning and carrying out the study, analysing data and writing the article, UH and SS carrying out the study, analysing data, reviewing the manuscript. All authors have read and approved the manuscript.

Ethics approval and consent to participate

The regional research ethics committee in Lund approved the study (dnr 2012/649) and all enrolled women gave their informed oral and written consent.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Publisher's Note

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Received: 25 June 2018 Accepted: 25 September 2018
Published online: 22 November 2018

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Paper III

THE JOURNAL OF MATERNAL-FETAL & NEONATAL MEDICINE
2023, VOL. 36, NO. 1, 2208252
https://doi.org/10.1080/14767058.2023.2208252

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ORIGINAL ARTICLE

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Cardiovascular effects of oxytocin and carbetocin at cesarean section. A prospective double-blind randomized study using noninvasive pulse wave analysis

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ABSTRACT

Background: Oxytocin is routinely administered after delivery for prophylaxis and treatment of postpartum hemorrhage, but it is associated with considerable cardiovascular side-effects. Carbetocin, a synthetic oxytocin analogue, has a myometrial contraction effect of 60 min when given IV, compared with 16 min for oxytocin.

Objective: To investigate whether there are differences in cardiovascular effects between oxytocin and carbetocin up to 1 h after treatment.

Methods: Sixty-one healthy pregnant women undergoing elective cesarean section in spinal anesthesia were randomized to receive an IV bolus of either five units (8.3 μg) of oxytocin or 100 μg of carbetocin after delivery of the baby. Heart rate (HR), mean arterial blood pressure, ECG ST index, oxygen saturation (SaO_2), and photoplethysmographic digital pulse wave analysis variables were recorded before and at 1, 5, 20, and 60 min after drug administration. Vasopressor use, uterine tonus, total bleeding, and need for additional uterotonics were also assessed. Repeated measurement ANOVA was used for statistical analyses.

Results: The drugs had equal vasodilatory and hypotensive effects. Oxytocin, but not carbetocin, caused a decrease in HR at 1 min and a sustained decrease in cardiac left ventricular ejection time. Aggregate vasopressor use was higher in the carbetocin group. Neither drug caused any change in ST index, SaO_2, or subjective cardiac symptoms. Uterine tonus, need for additional uterotonics, or total bleeding did not differ significantly between the groups.

Conclusion: Single doses of oxytocin and carbetocin had similar dilatory effects on vascular tonus, where the difference in aggregate vasopressor use can be attributed to a more persistent hypotensive effect of carbetocin. A transient negative chronotropic and sustained negative inotropic effect occurred after oxytocin. Neither drug showed any alarmingly adverse effects. Differences in drug effects may be attributed to differences in oxytocin and vasopressin receptor signaling pathways.

ARTICLE HISTORY
Received 4 February 2023
Revised 15 April 2023
Accepted 24 April 2023

KEYWORDS
Carbetocin; cardiovascular effects; cesarean section; oxytocin; pharmacologic effects; pulse wave analysis

Introduction

Oxytocin is routinely administered at cesarean section (CS) to contract the uterus and prevent postpartum hemorrhage. However, many women then experience discomfort, nausea, and chest pain. These symptoms have been attributed to the significant circulatory dose-dependent effects of oxytocin [1] including ECG ST-depression, increases in heart rate (HR), stroke volume and cardiac output (CO), and decreases in systemic vascular resistance and arterial blood pressure (BP) [2–8]. Detailed studies of the immediate hemodynamic response show an increase in HR and decreases in systemic vascular resistance and BP within 30–40 s after a 5 U oxytocin *statim* bolus, with a concomitant increase of CO, followed by a rebound decrease in HR and a slow restitution of the BP [7,9].

Oxytocin has a half-life of only 1–6 min, and more recently, the longer acting oxytocin analogue carbetocin was registered for PPH prevention. Carbetocin is an octapeptide that works along the same molecular pathways as oxytocin, but with a half-life of about 40 min [10,11]. A single IV dose of carbetocin 100 μg

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results in uterine contraction within 2 min, with a duration of around 60 min, in comparison with 16 min for oxytocin [12–14]. In contrast to oxytocin, carbetocin is heat-stable with no need of cold storage [15].

Due to its short duration, oxytocin is often given repeatedly at CS [12], potentially causing receptor desensitization and deteriorating uterotonic effect, with an increased risk of hypotension and cardiovascular side-effects. Prophylactic carbetocin has in a number of meta-analyses proved superior to oxytocin in effectiveness to prevent PPH, need of additional uterotonics, blood transfusion, etc., but with a similar safety profile [12,14,16,17].

Oxytocin and carbetocin have similar physical side-effects, such as nausea, flushing, vomiting, headache, tremor, chest pain, etc., though in a large meta-analysis carbetocin was found to induce a lower rate of vomiting [18]. Regarding cardiovascular side-effects, we found only three randomized controlled studies comparing hemodynamic differences as the primary endpoint [9,19,20]. In two of these studies patients were monitored for no more than 8 min after drug administration, despite an effect time of carbetocin of 1 h [9,19]. In the third study, there was no clear basal measurement for drug effect comparisons [20]. The longer effect time of carbetocin raises a question about more sustained cardiovascular side-effects of carbetocin in comparison with oxytocin.

Pharmacological cardiovascular effects can be studied in detail by analyzing pulse wave (PW) curve contour characteristics, determined by propagation of the forward percussion PW along the arterial vascular tree and the following reflection of the tidal PW from distal arteries. PW characteristics can be determined by digital PW analysis (DPA), which is a rapid, noninvasive, and operator-independent photoplethysmographic method. The DPA method has been validated against invasive aortic measurements and correlates well with radial pulse applanation tonometry [21,22]. The DPA method can assess cardiac ejection time and distinguish between tonus changes in large and small arteries [22].

During elective CS we found that oxytocin causes a global arterial vasodilation and has a direct negative chronotropic effect with increased left ventricular (LV) ejection power accompanied by electrocardiographic (ECG) ST changes [23]. A similar pattern with peripheral vasodilation and increased CO was seen using DPA after oxytocin during elective first trimester uterine surgery, accompanied by minor ST changes [24].

Previous studies comparing hemodynamic effects of carbetocin and oxytocin have not shown any significant differences [9,10,19,20,25]. In the present study, we aimed to further elucidate and compare the effects of carbetocin and oxytocin on arterial elasticity (stiffness) and hemodynamic parameters using noninvasive DPA, with a follow-up time of 1 h. We hypothesized that the cardiovascular effects of the drugs will be similar, but that the effect of carbetocin will last longer.

Material and methods

The Regional Research Ethics Committee in Lund (Dnr 2012/732) granted ethical approval. The study was pre-registered with the Swedish Medical Products Agency (EudraCT number: 2013-004224-10, Dnr 5.1-2013-95167). The study was performed at the Skåne University Hospital maternity units in Lund and Malmö, Sweden.

The inclusion criteria were healthy women 18–40 years old, scoring 1–2 according to the American Society of Anesthesiologists (ASA) physical status classification [26], with singleton pregnancy planned for elective CS under spinal anesthesia at gestational week 35 or more. Exclusion criteria were significant cardiovascular disease, lung disease, hypertension, pre-eclampsia, non-gestational diabetes mellitus, medications influencing the cardiovascular system, and general anesthesia for CS. Women were invited to participate in the study at the scheduled pre-operative assessment. The women should be able to understand oral and written Swedish, giving their oral and written consent.

Randomization to either oxytocin or carbetocin was made by a web-based randomization table (www.random.org) in blocks of 10 and sealed opaque envelopes containing the name of the study drug were prepared and stored in the pharmacy storage and preparation room in the operation ward. The sort of drug administered was blinded to the patient, the anesthesiologist, the surgeon, the operating staff and the DPA measurement operators (SR, EB, HJ). The anesthesiology nurse opened the envelope and prepared the injection, but she was not involved in DPA measurements or recording of study data. The randomization key was not revealed until after the study was closed.

The physiological background to the DPA method has been described previously [21,27]. The DPA measurements were performed with a customized pulse oximetry probe placed on the right second or third finger and connected to a Meridian DPA™ (Meridian Co. Ltd., Korea, and Salcor AB, Uppsala, Sweden) and a laptop (HP625, Hewlett Packard, Solna, Sweden).

The Meridian apparatus uses both crude and second derivative photoplethysmography, known as acceleration plethysmography [28], and generates several different variables reflecting cardiac performance and arterial vascular tonus. For the present study, we selected those variables that have shown best repeatability and best correlation to gold standard arterial applanation tonometry [22]: pulse height (PH), cardiac LV ejection time compensated (ETc), dicrotic index (DI), cardiac ejection elasticity index (EEI), aging index (AI), and the ratios *b/a* and *d/a* (representing second derivates of the crude PW curve contour). These variables are described in Table 1. For detailed descriptions of the mathematical and physiological details of DPA, see article by von Wowern et al. [22].

Upon arrival to the operating room, an IV-line access was established and a 1000 ml Ringer's acetate solution (Fresenius-Kabi, Uppsala, Sweden) was started. A surveillance monitor (DASH 400, GE Medical Systems Information Technologies, Danderyd, Sweden, or Philips Intellivue MP70, Philips Healthcare, Stockholm Sweden) with a five-lead ECG, a BP cuff, and a SaO_2 probe was connected. The ECG ST index was automatically derived from the ECG lead II. The BP cuff was placed on the left arm. Readings of BP, SaO_2, and ST index were manually noted in a case report form (CRF).

All women received spinal anesthesia in the sitting position with 2 ml hyperbaric bupivacaine (Marcain Tung 5 mg/mL, AstraZeneca, Södertälje, Sweden) and 1 ml sufentanil (Sufenta 5 μg/mL, Janssen-Cilag, Sollentuna, Sweden). A continuous IV infusion with phenylephrine (Fenylefrin Abcur 0.1 mg/mL, Abcur AB, Helsingborg, Sweden) was given to stabilize BP. After given spinal anesthesia, the women were placed on the operation table in a supine, slightly left-tilted position. Block height was determined by pinprick and loss of cold sensation before surgery.

After delivery of the baby and clamping and cutting the umbilical cord, the first (baseline) measurements were performed, denoted time 0 (T0). Then a bolus dose of the study drug was administered IV, i.e., either 1 ml oxytocin ($8.3\ \mu g = 5$ IU) or 1 ml carbetocin (100 μg) according to the randomization. The injection time was 1 min. A stopwatch was started and new measurements were made 1, 5, and 20 min (T1, T5, and T20) after completed bolus injection. A final measurement was performed in the recovery room, 60 min after the bolus injection (T60). Each DPA measurement takes 70 s to perform, during which surgery was halted. Additional data from the operation (CS indication, gestational week, estimated blood loss, additional uterotonics and other drugs) were registered in the CRF by the research technicians performing the measurements. Uterine tonus was assessed by the surgeon after 20 min (T20) using a Numerical Rating Scale (NRS) of 0–10, where 0 was uterine inertia and 10 was maximal contraction. Chest pain or pressure as assessed by the patient was noted at T1 and T60, also using the NRS 0–10.

Atropine 0.5 mg (Atropin 0.5 mg/mL, Mylan AB, Stockholm Sweden) or additional phenylephrine (0.1 mg/mL) was given when indicated, at the discretion of the anesthetist. The speed of the infusion pump, the amount of infused phenylephrine and the amount of infused IV fluid were noted at given times in the CRF. Decisions regarding the need of additional drugs were left at the discretion of the obstetrician or the anesthetist, but this was considered a deviation from the study protocol (dropout) and subsequent recordings were not included in the statistical analyses. A blood loss >1000 ml was considered a dropout factor and subsequent recordings were excluded.

Sample size calculation

Using a single DPA variable for sample size calculation was not relevant since the pattern of change is more important than a change of a single variable. Two previous studies comparing hemodynamic effects of carbetocin and oxytocin during CS, but with other methodologies, used HR or BP to estimate sample size [9,19]. We considered MAP clinically most appropriate for sample size calculation. In our previous study monitoring the hemodynamic effects of oxytocin during CS, a mean MAP of 79.3 mmHg decreased to 72.0 mmHg after oxytocin with a standard deviation (SD) of 10 mmHg [23]. Using these data, sample size calculation yielded that, with a type I risk of 5% and a type II risk of 20%, 29 participants would be necessary for each group (https://clincalc.com/Stats/SampleSize.aspx). In our earlier studies using DPA, we experienced a dropout rate of 10 to 25% from erroneous measurements and missing values, often due to movements or cold fingers. Therefore, we planned to randomize 40 + 40 women, but after asking 85 women for participation, the routines for planned CSs were re-organized and planned CSs were outreached from our university hospital to smaller hospitals in the region. Among the 85 women, 61 women gave their oral and written consent to participate (see Figure 1).

Table 1. Description of the digital pulse wave analysis (DPA) parameters used in the study, revised from von Wowern et al. [22].

Parameter	Physiological background	Conditions with high values	Conditions with low values	Interpretation of increase	Interpretation of decrease
Pulse height (PH)	Circulation in small finger arteries, perfusion of finger tips	High BP, hyperthyroidism, fever, anemia, excessive blood volume, exercise, well-tuned athlete	Peripheral vaso-constriction, low BP, hypovolemia/ dehydration, hypothyroidism, increased peripheral resistance	Peripheral vasodilatation	Peripheral vasoconstriction
Left ventricular ejection time compensated (ETc)	Represents systole, i.e. time from onset of the systolic upstroke limb to the closure of the aortic valve	Aortic valve stenosis, increased large artery compliance (low vascular tone)	LV failure, decreased preload, hypovolemia, decreased large artery compliance (high vascular tone)	Increase in LV ejection time, decreased afterload, decreased SVR, increased preload	Decrease in LV ejection time, increased afterload, increased SVR, decreased preload
Cardiac ejection elasticity index (EEI)	Index for LV ejection capacity and compliance/elasticity of large arteries	Large artery vasodilatation, anemia, increased LV ejection power, hyperthyroidism, congested heart failure	Large artery vasoconstriction, arteriosclerosis, LV ejection insufficiency	Increase in LV ejection power, large artery vasodilatation	Decrease in LV ejection power, large artery vasoconstriction
Dicrotic index (DI)	Represents the peripheral circulation, indicates peripheral resistance	Small artery vasoconstriction	Small artery vasodilatation	Peripheral vasoconstriction	Peripheral vasodilatation
b/*a*	Early systolic PW peaks identified by second derivatives of the crude PW curve contour; indicates LV ejection capacity and large artery compliance/elasticity	Low large artery elasticity, increased cardiovascular risk, vasoconstriction, atherosclerosis, increases by age	Young persons, athletes	Large artery vasoconstriction, decreased LV ejection	Large artery vasodilatation, increased LV ejection
d/*a*	*d* is a late systolic PW peak identified by second derivative of the crude PW curve contour; mainly reflects the intensity of the tidal PW from small peripheral arteries	High small artery elasticity, young persons	A longer negative *d* peak develops by advancing age, indicating arterial stiffness, atherosclerosis	Small artery vasodilatation	Small artery vasoconstriction
Aging index (AI)	AI = (*b*-*c*-*d*-*e*)/*a*, representing the global vascular stiffness, i.e. "vascular age"	Atherosclerosis, increases by age	Young persons, athletes	Global arterial vasoconstriction	Global arterial vasodilatation

Note: BP: blood pressure; SVR: systemic vascular resistance; LV: left heart ventricle; PW: pulse wave.

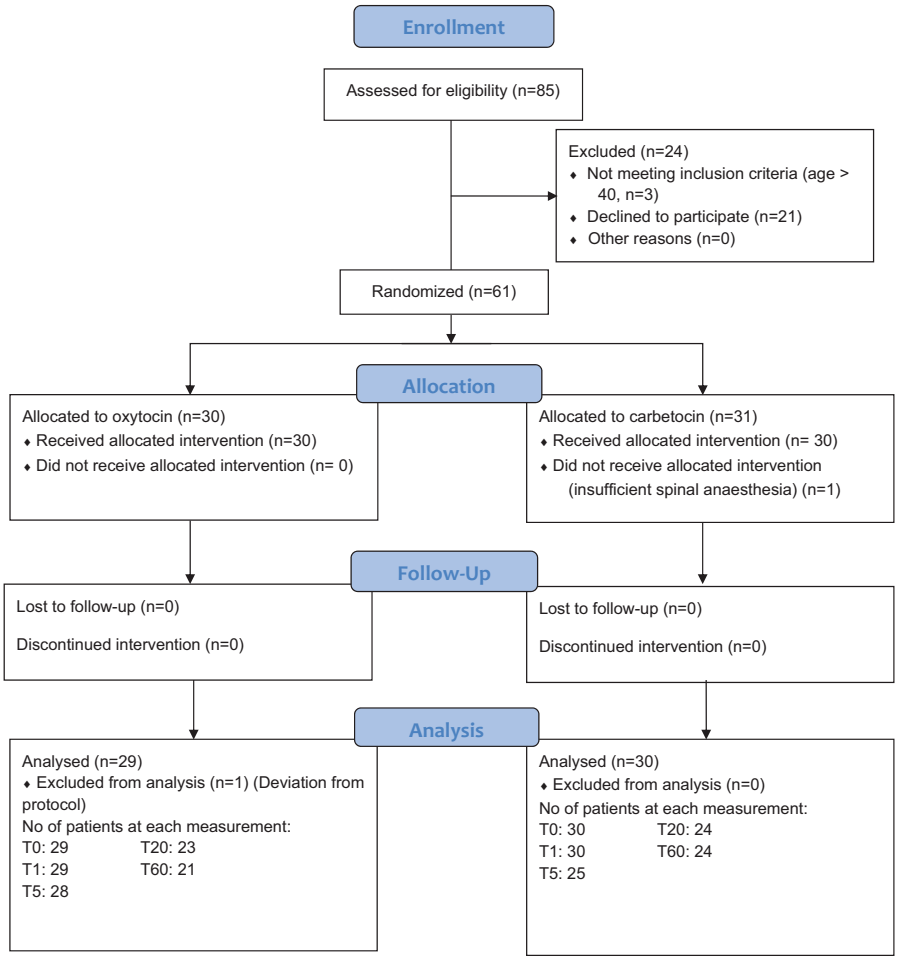

Figure 1. CONSORT 2010 flow diagram.

Statistical analyses

Statistical analyses were performed with SigmaPlot 15 computer software (Alfasoft A/S, Norway). For longitudinal drug effect changes (T0–T1–T5–T20–T60), a one-way ANOVA for repeated measurements (RM) was performed. In case of significant changes over time (two-sided $p < .05$), post-hoc comparisons were made using Holm-Sidak method for comparisons versus T0. In case the Shapiro–Wilk normality test failed ($p < .05$), Friedman's non-parametric RM ANOVA was carried out and if significant, Dunn's post-hoc analysis for comparisons versus T0 was used. Comparisons between the carbetocin and oxytocin groups were made by two-way RM ANOVA, using post-hoc analysis with Holm-Sidak method for comparisons at each time point. The study was randomized, but to avoid bias from possible differences in baseline values (T0) between the groups, we also compared the changes from baseline (set to null) to each time point expressed as Δ-values; For example, the change from T0 to T1, calculated as T1 minus T0, was expressed as ΔT1. Categorical data were compared with Fisher's exact test. Grubbs outlier test (https://www.graphpad.com/quickcalcs/Grubbs1.cfm) was used to identify outliers and exclude cases (variables) with apparently erroneous values.

Table 2. Patient characteristics.

	Oxytocin $N = 30$ Mean (SD) Median (range)	Carbetocin $N = 31$ Mean (SD) Median (range)	Significance of difference (p)
Maternal age (years)	32.0 (3.8) 31.5 (26–39)	33.4 (4.0) 34.5 (22–40)	.09
Gestational age (weeks)	38.4 (1.00) 38 (36–41)	38.4 (0.96) 38 (36–41)	.7
Body mass index (kg/m^2)	29.1 (3.2) 29.0 (24.6–34.3)	29.5 (4.3) 29.9 (20.4–41.1)	.8

Note: Statistics by the Mann–Whitney *U* test.

Table 3. Longitudinal effects of intravenous oxytocin (5 IU) given immediately after T0 (baseline).

		Post-hoc analyses				
Variable	RM ANOVA T0–T1–T5–T20–T60 p Value	T0–T1 p Value Mean difference	T0–T5 p Value Mean difference	T0–T20 p Value Mean difference	T0–T60 p Value Mean difference	Interpretation
HR	<.001[a]	.002 −8.7 bpm	.2	.047 −6.2 bpm	<.001 −13.1 bpm	Pulse decrease
MAP	<.001[a]	<.001 −11.8 mmHg	<.001 −11.0 mmHg	<.001 −10.5 mmHg	<.001 −10.3 mmHg	Blood pressure decrease
ST index	.2[a]	N/A	N/A	N/A	N/A	–
SaO_2	.09[a]	N/A	N/A	N/A	N/A	–
PH	<.001[a]	.005 +2.10	.003 +2.36	<.001 +4.06	.4 +0.62	Peripheral vasodilation
ETc	<.001[a]	.6	.006 −56.3 ms	<.001 −74.7 ms	.02 −52.9 ms	Shortened LV ejection time
DI	.7[a]	N/A	N/A	N/A	N/A	–
EEI	<.001[a]	.6	.6	.01 +0.168	<.001 +0.398	Increased LV ejection power, large artery vasodilation
AI	<.001[b]	1.00	.3	.028 Decrease	<.001 Decrease	Global arterial vasodilation
b/a	<.001[a]	.2	.2	.008 −0.089	<.001 −0.177	Large artery vasodilatation, increased LV ejection
d/a	<.001[b]	.4	.14	.001 Increase	<.001 Increase	Small artery vasodilatation

Notes: T0: baseline measurement at time 0; T1: measurement after 1 min; T5: after 5 min; T20: after 20 min; T60: after 60 min; HR: heart rate in beats per minute (bpm); MAP: mean arterial blood pressure; SaO_2: oxygen saturation. For explanation of other variables, see Table 1. RM ANOVA: repeated measurements analysis of variance; N/A: not applicable when ANOVA was not significant; LV: left cardiac ventricle.
[a]One-way RM ANOVA used when the Shapiro–Wilk normality test indicated a normal distribution. *Post-hoc* comparisons with the Holm-Sidak method.
[b]When the Shapiro–Wilk test failed ($p < .05$), Friedman's non-parametric RM ANOVA was used, and if significant, Dunn's *post-hoc* analysis for comparisons versus T0 was used and direction of change indicated.

Results

Patient characteristics and baseline measurements at T0 (before drug administration) were statistically not different (Table 2). The CONSORT flow-chart of women invited to the study is shown in Figure 1. There was one dropout in the carbetocin group because of inadequate spinal anesthesia. There was one dropout in the oxytocin group due to glyceryl nitrate administration before delivery. A few additional cases were excluded from analyses from T5 and on because of estimated blood loss >1000 ml, additional uterotonics given, or other apparent protocol violation (Figure 1).

The longitudinal effects of carbetocin and oxytocin, respectively, are shown in Tables 3 and 4, and presented graphically in Figures 2 and 3. For both drugs, significant changes over time were seen for all variables except for ST index, SaO_2, and DI.

At T1 the HR was not affected by carbetocin (Table 4), whereas a significant decrease of about 9 bpm in mean was seen in the oxytocin group (Table 3, Figure 2). After 5 min the HR had rebounded to the same level as for carbetocin. After 60 min the HR had decreased in both groups to a level of 10–13 bpm below baseline.

The MAP decreased significantly with about 12 mmHg after 1 min in both groups and stayed significantly lower than baseline throughout the experiment (Figure 2).

The global index of arterial vascular compliance/elasticity, AI, decreased onward after drug injections, indicating vasodilation, with no significant differences between the drugs. DPA variables representing large artery vascular tonus (EEI, *b/a*) and small artery vascular tonus (PH, *d/a*), also changed significantly over time, indicating vasodilation, with no significant difference

Table 4. Longitudinal effects of intravenous carbetocin (100 μg) given immediately after T0 (baseline).

		Post-hoc analyses				
Variable	RM ANOVA T0–T1–T5–T20–T60 *p* Value	T0–T1 *p* Value Mean difference	T0–T5 *p* Value Mean difference	T0–T20 *p* Value Mean difference	T0–T60 *p* Value Mean difference	Interpretation
HR	.002[b]	1.0	1.0	1.0	.002 Decrease	Pulse decrease at 60 min
MAP	<.001[a]	<.001 −12.5 mmHg	<.001 −11.6 mmHg	<.001 −15.3 mmHg	<.001 −9.5 mmHg	Blood pressure decrease
ST index	.09[b]	N/A	N/A	N/A	N/A	–
SaO_2	.15[b]	N/A	N/A	N/A	N/A	–
PH	<.001[a]	.09	.09	.002 +2.91	.09 +1.75	Peripheral vasodilatation
ETc	<.001[a]	.5	.9	.9	0.9	Biphasic curve, no differences from T0 value
DI	.4[a]	N/A	N/A	N/A	N/A	–
EEI	<.001[a]	.4	.3	<.001 +0.213	<.001 +0.544	Increase in LV ejection power, large artery vasodilatation
AI	<.001[b]	1.00	.2	.01 decrease	<.001 decrease	Global arterial vasodilatation
b/a	<.001[a]	.3	.02 −0.064	<.001 −0.152	<.001 −0.256	Large artery vasodilation, increased LV ejection
d/a	<.001[a]	<.001 +0.074	<.001 +0.099	<.001 +0.109	<.001 +0.188	Small artery vasodilation

Notes: T0: baseline measurement at time 0; T1: measurement after 1 min; T5: after 5 min; T20: after 20 min; T60: after 60 min.
[a]One-way RM ANOVA used when the Shapiro–Wilk normality test indicated a normal distribution. *Post-hoc* comparisons with the Holm-Sidak method.
[b]When the Shapiro–Wilk test failed ($p < .05$), Friedman's non-parametric RM ANOVA was used, and if significant, Dunn's *post-hoc* analysis for comparisons versus T0 was used and direction of change indicated.

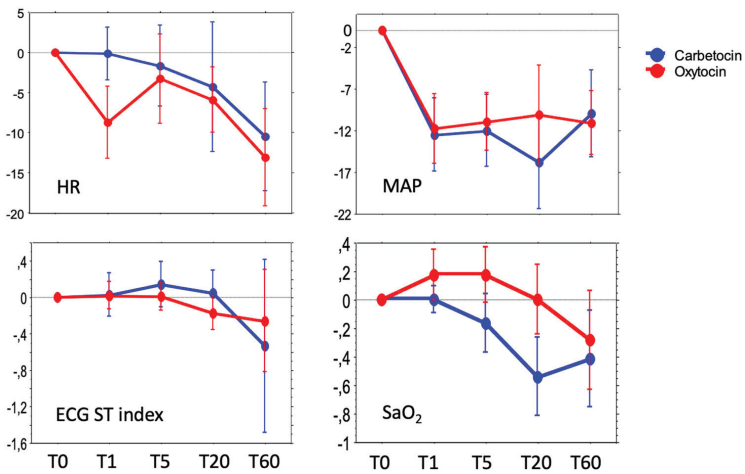

Figure 2. Longitudinal effects of intravenous carbetocin (100 μg) and oxytocin (8.3 μg = 5 IU), given at cesarean section at time T0 (baseline), on heart rate (HR, bpm), mean arterial blood pressure (MAP, mmHg), electrocardiogram (ECG) ST index (mm), and oxygen saturation (SaO_2, %). Repeated measurements were performed after 1 min (T1), 5 min (T5), 20 min (T20), and 60 min (T60). Values denote the mean changes from baseline (set to null) to each time point expressed as Δ-values, with 95% confidence interval. Two-way repeated measurements ANOVA showed no significant differences between the drugs ($p \geq .11$).

between the drugs. DI, indicating peripheral resistance, did not change significantly over time in any group.

Considering the whole series of measurements T0–T1–T5–T20–T60, the two-way RM ANOVA showed no significant effect differences between oxytocin and carbetocin for any variable ($p \geq .14$, table not shown).

A two-way RM ANOVA of ΔT-values (ΔT1–ΔT5–ΔT20–ΔT60) showed a significant difference between the drugs only for ETc, where ETc was lower in the oxytocin group from T1 to T20, but not at T60 (table not shown).

Secondary outcomes

The aggregate amount of phenylephrine infused was significantly larger in the carbetocin group. This difference was significant from 20 min onward. The total

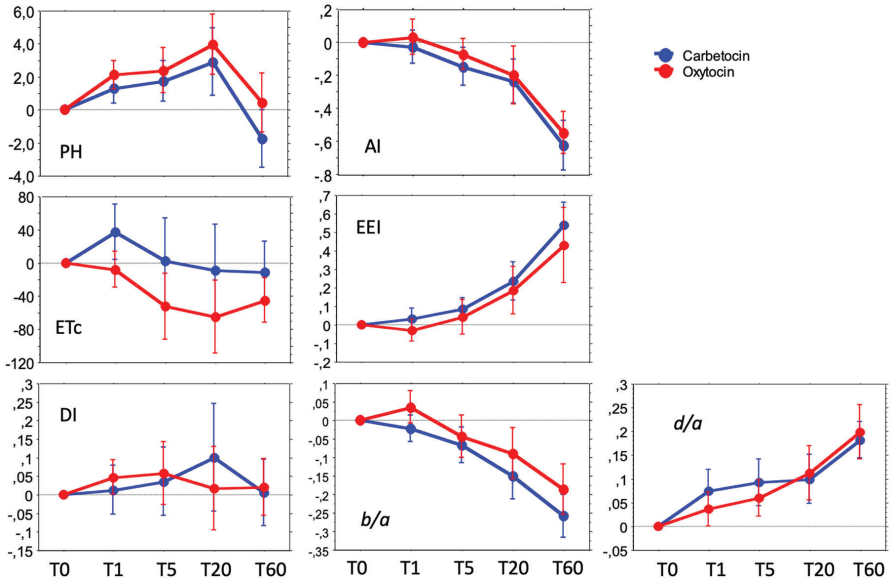

Figure 3. Longitudinal effects of intravenous carbetocin (100 μg) and oxytocin (8.3 μg = 5 IU) given at cesarean section at time T0 (baseline) on variables derived from the digital pulse wave analysis: pulse height (PH), aging index (AI), left ventricular ejection time compensated (ETc, ms), cardiac ejection elasticity index (EEI), dicrotic index (DI), and the second derivates *b/a* and *d/a* of the crude digital pulse wave curve contour. Repeated measurements were performed after 1 min (T1), 5 min (T5), 20 min (T20), and 60 min (T60). Values denote the mean changes from baseline (set to null) to each time point expressed as Δ-values, with 95% confidence interval. Two-way repeated measurements ANOVA showed a significant difference of ETc from T1 to T20.

amount of Ringer's acetate infused did not differ significantly between the groups at any time. The total estimated blood loss, uterine inertia, and extra use of uterotonics were not significantly different between the groups. Five women had an estimated blood loss >1000 ml, all in the carbetocin group. In four of them, bleeding was due to surgical complications (Table 5).

There were no significant differences between carbetocin and oxytocin in the maternal experience of chest pressure or discomfort (five and seven women, respectively), and no associations with changes of BP, ST index, or HR were found. One woman in the carbetocin group had ST index changes of 2.3–2.9 mm from T1 onwards, but no symptoms of chest pain or discomfort. When scrutinizing her CRF, we found a decrease in BP that had not been treated properly.

Discussion

This study showed similar cardiovascular effects of carbetocin and oxytocin during the whole 1h measurement period. Both drugs caused a global vasodilation with lowering of vascular tonus in both large and small arteries, accompanied by a slight drop in BP but without any compensatory increment in HR. In contrast to carbetocin, oxytocin had a prompt but short-lived mild negative chronotropic effect and a shortening effect on LV ejection time (ETc) that lasted up to 20 min, but was equalized at 60 min.

The cardiovascular effects of uterotonics in time and magnitude depend on whether they are given *statim*, slowly, or as an infusion. For both carbetocin and oxytocin, when given *statim* IV the HR peaks after half a minute, paralleled by a nadir in BP and peripheral vascular resistance [7,9]. When given IV over 60 s, the peaks and nadirs seem to occur about 1 min after finishing the injections [19]. This pattern has also been demonstrated for methylergometrine when given IV during 30 s [6]. When oxytocin is given as an infusion over 5 min the cardiovascular effects are considerably weaker [7]. For carbetocin, no difference in maximum HR occurs when given either rapidly or during 10 min IV, but as expected, the HR increase is delayed when given slowly [29].

In our study the uterotonics were given as recommended, during 60 s, then there was a 60 s delay until the DPA recording started at T1, and that recording took 70 s. Transient hemodynamic changes occurring

Table 5. Summary of additional measurements and side-effects.

	Oxytocin $N = 29$ Mean (SD) Median (range)	Carbetocin $N = 30$ Mean (SD) Median (range)	Significance of difference (p)
Additional uterotonics (n of patients)	7	3	.2
Ringer-acetate, total volume infused (mL)	1252 (526)	1248 (340)	>.15
	1100 (700–2900)	1100 (800–2000)	At all times[a]
Phenylephrine, total volume infused (mL)	9.9 (6.7)	12.9 (5.6)	.03
	7.4 (2.6–25.0)	11.7 (4.0–28.3)	At 20 and 60 min[a]
Chest pain	1. (2.1)	0.7 (1.7)	.7
1 min after drug	0 (0–8)	0 (0–6)	
(score 0–10)	7/29 score >1	5/30 score >1	
Chest pain	0.4 (1.5)	0.1 (0.6)	.8
20 min after drug (score 0–10)	0 (0–6)	0 (0–3)	
	2/26 score >1	0/28 score >1	
Uterine contraction	8.3 (1.4)	8.9 (1.3)	.06
20 min after drug (score 0–10)	8 (5–10)	9 (5–10)	
Blood loss >1000 mL	0	5[b]	.052
Total blood loss (mL)	381 (223)	618 (624)	.1
	400 (100–1000)	375 (200–3300)	

Note: Statistics performed with the Mann–Whitney U test or Fisher's exact test with two-tailed p-value, as appropriate.
[a]Aggregate volume measured at 5, 20 and 60 min after drug administration.
[b]Two cases of low anterior placenta (both 1.5 L bleeding), one case of myoma (3.3 L), one difficult ventouse extraction (1.2 L), one unknown reason (1.1 L).

within the first 2 min after injection start could then not be captured in our study. Nevertheless, apart from a drop in HR, we found no substantial discrepancies between our findings and the findings in studies using other methodologies [3,6,7,9,19]. *Nota bene*, a similar pattern with a drop in HR was found in our previous study of oxytocin given at CS [23]. In a study by Moertl et al. comparing the hemodynamic effects of carbetocin and oxytocin [9], the drugs were injected in 10 s, which could explain the slightly different cardiovascular responses compared to our study. Rapid injection of oxytocin or carbetocin is nowadays inadvisable [30].

Among DPA variables indicating cardiac function, the EEI indicated an increase in LV ejection power and large artery vasodilation after 20 min in both groups, suggesting increased CO. The ETc decreased significantly in the oxytocin group but not in the carbetocin group. The differences were statistically significant from 1 to 20 min when calculated with changes from baseline, i.e. with Δ-values.

A decrease in ETc represents a shortening of the LV ejection time, which indicates negative inotropy and/or decreased preload or hypovolemia [31–33]. The relation is not completely linear, since it depends on whether the patient is in a high or low preload state [24]. LV ejection time can actually be shortened from both positive and negative inotropic agents, though mostly it is associated with negative inotropy [34,35]. The decrease of ETc in the oxytocin group is not consistent with our earlier studies on oxytocin, where ETc remained either unchanged or increased [23,24]. In a previous study from our group the ETc variable showed a rather poor reliability, which we believe is due to methodological difficulties in identifying the endpoint of systole [22]. Thus, the findings of shortening of ETc by oxytocin, and a possible difference to carbetocin, are uncertain findings although in favor of carbetocin. The findings call for further investigations to reveal the clinical relevance.

One woman in the carbetocin group showed already after 1 min an ST index increase of 2.3–2.9 mm but had no subjective symptoms. We scrutinized her CRF and found poorly managed hypotension. The importance of proper treatment of hypotension associated with spinal anesthesia, drugs, and hypovolemia must be emphasized. For all other women ST index remained stable during the whole 1-h period. This is important since a growing number of pregnant women have concomitant heart disease [36]. Since oxytocin may cause a dose-dependent ST-depression, troponin release, prolongation of QT-time, and arrhythmia, it is essential to investigate the myocardial effects also of carbetocin [37].

In agreement with previous studies [10,12,25], there was no difference between the groups in blood loss. These studies, as well as meta-analyses [14,38,39], show a reduced need for extra uterotonics when using carbetocin compared to oxytocin, in both elective and non-elective CS, although in our study, this difference did not reach significance. Repeated doses of oxytocin might increase the risk of hypotension and cardiovascular side-effects [3]. Like other studies [9,19], we found no difference in the frequency of chest pain and discomfort.

Oxytocin receptors (OXTR) are present in the uterus, mammary glands, heart, brain, and blood vessels [40].

The biology of OXTR is intricate, with varied, context-dependent cellular processing, similarities to vasopressin receptors, and widespread peripheral and central expression. OXTR belongs to a large family of G protein-coupled cell surface receptors, which are activated by various signaling pathways [40]. Oxytocin and vasopressin differ in only two amino acid sequences, which explains why oxytocin also activates vasopressor receptors V1a (V1aR) and V1b (V1bR). Passoni et al. found that carbetocin activates the OXTR but not V1aR and V1bR, and that carbetocin can even act as a competitive antagonist on vasopressin receptors. [41]. Carbetocin selectively activates only the OXTR/Gq pathway, whereas oxytocin activates OXTR coupling to G-protein subtypes Gq, Gi, and Go. The Passoni study thus indicates important differences in key molecular pharmacological properties between carbetocin and oxytocin, where carbetocin exerts a "weaker" action on OXTR. The unique functional selective OXTR/Gq coupling of carbetocin might explain the small but significant differences in vascular activity between carbetocin and oxytocin in our study.

Strengths and limitations: A few cases were lost to full statistical analyses due to additional uterotonics and blood loss above 1000 ml, and occasional variable analyses were lost due to technical problems or finger movements. The dropouts constrained mainly the T20 and T60 measurements, thus reducing the power of the study. We minimized selection and operator bias by using a double-blinded randomized design. As the main outcome was the effects on large and small artery elasticity, we only included healthy (ASA 1–2) women without cardiovascular and systemic disorders. The photoplethysmographic DPA method is sensitive to movements and cold fingers, but when that is mastered, it is one of very few simple and painless noninvasive methods to measure hemodynamics. When interpreting the results, one must realize that CS is a complex procedure from a hemodynamic viewpoint, with effects caused not only by uterotonics but also by interference of spinal anesthesia, phenylephrine and IV fluid infusions, bleeding, emptying of uterus, relief of aortocaval compression, and maternal emotions.

Conclusion

This double-blinded randomized study showed only minor differences between single doses of oxytocin and carbetocin when comparing cardiac performance and large and small artery elasticity. Neither drug showed any alarmingly adverse effects on the cardiovascular system. For both drugs equally, within the first minutes a peripheral vasodilation occurred with a drop in BP. The higher accumulated vasopressor dose after 20 min can be attributed to a more sustained hypotensive effect of carbetocin, conveniently treated with phenylephrine. Despite vasodilation and a relative hypotension after both carbetocin and oxytocin, the HR did not increase in any group. In fact, oxytocin had a transient negative chronotropic effect. In addition, oxytocin had a sustained negative inotropic effect, as reflected by a shortening of the LV ejection time. Differences in drug effects may be attributed to differences in oxytocin and vasopressin receptor signaling pathways. Bleeding, use of extra uterotonics and other side-effects did not differ between the drugs. It should be noted that our conclusion is valid only for single doses of 5 U oxytocin and 100 μg carbetocin; With those doses given at elective CS additional uterotonics are needed three times as often after oxytocin (9% vs 3%) [12], where repeated oxytocin doses might increase the risk of hypotension and cardiovascular side-effects.

Author contributions

SR: conceptualization, planning, recruiting, performing, statistical analyses, analyzing results, literature search, writing the manuscript. HJ: recruiting, performing, statistical analyses, analyzing results, literature search, reviewing manuscript. EJ: recruiting, performing, statistical analyses, analyzing results, literature search, reviewing manuscript. PO: conceptualization, planning, ethics approval, medical agency approval, statistical analyses, analyzing results, literature search, writing the manuscript.

Disclosure statement

PO was previously Consultant Medical Adviser of Ferring Pharmaceuticals AB, Malmö, Sweden, the manufacturer of carbetocin (Pabal©), but resigned in 2016. The company has not been involved in planning, performance or supporting the study. SR, HJ and EB declare no conflicts of interest.

Funding

The study was funded by grants from the Medical Faculty at Lund University (ALF) and Region Skåne. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

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Paper IV

Hemodynamic effects of hyperoxygenation in nonpregnant and third-trimester pregnant women. An interventional comparative study using non-invasive pulse wave analysis

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Conflict of interest statement

The authors declare no conflicts of interest.

Funding information: The study was funded by grants from the Medical Faculty at Lund University (ALF) and Region Skåne. The funders had no role in study design, data collection and analysis, the decision to publish, or the preparation of the manuscript.

ABSTRACT

Introduction

Oxygen (O_2) therapy is a common medical treatment that can be lifesaving. In obstetrics, maternal hyperoxygenation is used for intrauterine resuscitation in cases of non-reassuring fetal status, during nitrous oxide therapy for labor pain, and during cesarean section under spinal anesthesia. Prolonged hyperoxygenation can cause oxidative cell damage with cerebral, respiratory, and ocular symptoms, but very few studies have investigated possible maternal side effects from short-term hyperoxygenation. In this experimental study, we investigated the vascular and hemodynamic short-term effects of 100% inhaled O_2 in third-trimester pregnant women and in healthy nonpregnant female controls. Our hypothesis was that hyperoxygenation increases arterial tonus in both pregnant and nonpregnant women.

Material and methods

25 healthy third-trimester pregnant women and 25 nonpregnant women of fertile age inhaled 100% O_2 for 5 min. Heart rate (HR), mean arterial blood pressure (MAP), ECG ST index, and photoplethysmographic digital pulse wave analysis (DPA) were assessed before, during, and 5 min after inhalation. One-way ANOVA for repeated measurements with post-hoc analyses was used to assess longitudinal changes within groups, and two-way ANOVA for repeated measurements was used to compare data between groups.

Results

Hyperoxygenation caused global vasoconstriction and decreases in HR and MAP in pregnant women, whereas in nonpregnant women, such changes were more discrete, engaging small arteries only. The effects occurred within 1 min. All effects ceased and returned to baseline values within 5 min after cessation of extra O_2. Cardiac functions were not affected in any group, and no subjective side effects or fetal heart rate anomalies were noted.

Conclusion

Hyperoxygenation has prompt vasoconstrictive effects on both large and small arteries, as well as negative chronotropic effects. Third trimester pregnant women are more affected than nonpregnant controls. It remains to be explored whether maternal hyperoxygenation can aggravate pregnancy conditions associated with hypovolemia and hypertension.

List of abbreviations

AI: Ageing index; **ANOVA**: Analysis of variance; **APG:** Acceleration plethysmogram; ***b/a***: Second derivative quotient of the acceleration phase of the percussion pulse wave; **BMI**: Body mass index; **BP**: Blood pressure; **CO**: Cardiac output; **CTG**: cardiotocogram, cardiotocography; ***d/a***: Second derivative quotient of the percussion wave clashing with the reflected tidal wave; **DI**: Dicrotic index; **DPA**: Digital pulse wave analysis; **ECG**: Electrocardiogram; **EEI**: Ejection elasticity index; **ETc**: Left ventricular ejection time compensated (for heart rate); **FHR**: Fetal heart rate; **FiO_2**: Fraction of inspired oxygen; **HR**: Heart rate; **LV**: Left ventricle of the heart; **MAP**: Mean arterial blood pressure; **MDA**: Malondialdehyde; **NO**: Nitric oxide; **N_2O**: Nitrous oxide; **O_2**: Oxygen; **PH**: Pulse height; **PW**: Pulse wave; **RCT**: Randomized controlled trial; **ROS**: Reactive oxygen species; **SaO_2**: Oxygen saturation; **ST-index**: Difference in ECG ST segment from the isoelectric baseline; **SVR**: Systemic vascular resistance

INTRODUCTION

Oxygen (O_2) therapy is common in medicine and can be lifesaving. However, O_2 toxicity is of concern since hyperoxygenation may cause excessive production of reactive oxygen species (ROS), resulting in vasoconstriction and decreased microcirculation, nitrosative stress and inflammation with broncho-epithelial injury, DNA damage, and uncoupling of mitochondrial respiration. [1,2] A cautious use of hyperoxygenation has thus been proposed.[2–6]

Maternal hyperoxygenation has since long been used for intrauterine resuscitation in labor, as indicated by pathological fetal heart rate (FHR) patterns, and O_2 is routinely used during cesarean section in spinal anesthesia. Concerns have been raised as meta-analyses have failed to show any clinically relevant fetal improvement from maternal hyperoxygenation or any beneficial effects on normoxic mothers.[7–11] Another use of extra O_2 in obstetrics is during nitrous oxide (N_2O) inhalation for labor pain. N_2O is used in about two-thirds of deliveries in Europe.[12] N_2O is always mixed with pure O_2 to avoid hypoxia, with mixtures ranging from 30 to 70% O_2.

Few studies have addressed the short-term maternal effects of inhaled high-fraction O_2. In nonpregnant human volunteers, hyperoxygenation causes impaired cardiac diastolic relaxation and increased left ventricular (LV) filling pressure,[13] as well as a reduction in heart rate (HR) and cardiac index, increased mean arterial blood pressure (MAP), systemic vascular resistance (SVR), and large artery tonus.[14] To our knowledge, only two studies on maternal hemodynamic effects from hyperoxygenation have been published. Polvi et al. found no hemodynamic effects of hyperoxygenation in pregnant women,[15] whereas McHugh et al. found vasoconstriction and decreased cardiac output (CO).[16]

The effects of medications on the heart and arterial vascular tonus can be studied by analyzing arterial pulse wave contour characteristics. The contour of the forwardly propagating percussion pulse wave (PW) merged with the reflected tidal PW from distal arteries can be analyzed by non-invasive digital photoplethysmographic PW analysis (DPA). Detailed analyses of the merged PW contours give information about arterial tonus, or stiffness, in the proximal and distal parts of the vascular tree, as well as an estimation of cardiac LV ejection time.[17,18]

In the present experimental study, we aimed to investigate the hemodynamic short-term effects of 100% inhaled O_2, as estimated with DPA, in third-trimester pregnant women and in healthy female nonpregnant controls of fertile age. Our hypothesis was that O_2 would increase arterial vascular tonus in both pregnant and nonpregnant women.

MATERIAL AND METHODS

The experiments were performed at the maternity unit at the Skåne University Hospital, Malmö, Sweden. The Regional Research Ethics Committee in Lund approved the study (Dnr 2011/384). All participating women were volunteers and enrolled after informed oral and written consent. All women could understand oral and written Swedish.

Inclusion criteria were healthy third-trimester pregnant women and healthy nonpregnant women of age 18-40 years. Exclusion criteria were cardiovascular or lung disease, connective tissue disease, gestational hypertension, preeclampsia, diabetes, suspicion of intrauterine growth restriction, or other fetal problems.

Recruitment of pregnant women was mainly done at the routine ultrasound examination in gestational week 32, but also by asking pregnant hospital staff and by announcement in a Swedish family forum on the internet. The control group consisted of hospital staff and employees at Lund University who volunteered for the study. We recruited 25 women in each group.

The experiments were performed in a calm and quiet room with a temperature of 21°C (69.8°F) at the delivery unit in Malmö, Skåne University Hospital. Participants were asked to refrain from food, caffeine, and nicotine for at least 2 h before the experiment. After a 5-min period of rest in the supine 15° left-tilted position, the blood pressure (BP), HR, ECG, and tissue O_2 saturation (SaO_2 by pulse oximetry) were recorded with a Dash 4000 Pro monitoring system (GE Medical Systems Information Technologies, Danderyd, Sweden). The BP cuff was placed on the left arm and the pulse oximeter on the right third finger. ECG was monitored through 5 channels, and the system was programmed to obtain a continuous ST segment trend.

PWs were recorded with Meridian^{TM} digital photoplethysmography DPA (Salcor AB, Uppsala, Sweden) with an LED pulse oximetry probe placed on the right index finger. Pulsatile blood volume changes in the finger are recorded (plethysmography) because light is absorbed in the tissue relative to the oxyhemoglobin content (red cell density) and only non-absorbed light reaches the photodiode. The contour components of the coalescing percussion-tidal PWs are characterized mathematically. In addition to crude PW curve contour analysis, the Meridian device also calculates the second derivative plethysmogram for the accelerated plethysmogram (APG).[19]

The device generates several different variables, reflecting heart function and arterial vascular tonus. We selected variables with the best repeatability and best correlation to gold standard arterial applanation tonometry:[18] pulse height (PH), cardiac LV ejection time compensated (ETc), dicrotic index (DI), cardiac ejection elasticity index (EEI), ageing index (AI), and the ratios *b*/*a* and *d*/*a* (representing second derivates of the crude PW curve contour). The variables are described in

Table 1. For further mathematical and physiological details of the DPA variables, we refer to the works of von Wowern et al.[18]

After basal recordings (time TB), inhalation of 100% O_2 was started and continued for 5 min. A tight-fitting mask connected to a rebreathing system was used (VENTYO Avo, AGA, Lidingö, Sweden). Repeated Dash and Meridian recordings were performed after 1 min (time T1), 3 min (T3), and 5 min (T5). Each Meridian recording takes about 70 s. The Dash recordings were performed immediately after the Meridian recordings. The O_2 inhalation was stopped after the T5 recordings, and the final recordings were performed 5 min later (T10).

In pregnant women, the FHR was recorded by cardiotocography (CTG) (Avalon FM30, Philips, Stockholm) before and during the experiment to reassure fetal wellbeing. The CTG traces were classified according to Swedish national guidelines. [20]

All manually obtained recordings were noted in an individual case report form, while Meridian recordings were automatically transcribed onto an Excel sheet on a connected laptop.

Statistical analyses

Data collected in CRFs and Excel files were transferred to a statistical software program (SigmaPlot, Alfasoft AS, Norway). Unreasonable outlier DPA values were identified by the Grubbs test (https://www.graphpad.com/quickcalcs/Grubbs1.cfm) and personal assessments. For longitudinal comparisons within each time series (TB-T1-T3-T5), one-way repeated measurements (RM) ANOVA with post-hoc pairwise comparisons versus TB using the Holm-Sidak method was performed. The software automatically tests for normal distribution with Shapiro-Wilk's test and for equal variance with Brown-Forsythe's test. In the case of a skewed distribution, the Friedman non-parametric one-way ANOVA for repeated measurements was performed instead. If Friedman's test showed significant changes over time (two-sided $P<0.05$), post-hoc testing with Dunn's method was made to find where in the time series statistically significant differences versus TB occurred. The TB and T10 values were compared with paired *t*-test or Wilcoxon's signed-ranks matched-pairs test, as appropriate.

Table 1. Description of digital pulse wave analysis parameters used in the study, revised from von Wowern et al.(18)

Parameter	Physiological background	Conditions with high values	Conditions with low values	Interpretation of increase	Interpretation of decrease
Pulse height (PH)	Circulation in small finger arteries, perfusion of finger tips	High BP, hyperthyroidism, fever, anemia, excessive blood volume, exercise, well-tuned athlete	Peripheral vaso-constriction, low BP, hypovolemia/dehydration, hypothyroidism, increased peripheral resistance	Peripheral vasodilatation	Peripheral vasoconstriction
Left ventricular ejection time compensated (ETc)	Represents systole, i.e. time from onset of the systolic upstroke limb to the closure of the aortic valve	Aortic valve stenosis, increased large artery compliance (low vascular tone)[a]	LV failure, decreased preload, hypovolemia, decreased large artery compliance (high vascular tone) [a]	Increase in LV ejection time, decreased afterload, decreased SVR, increased preload [a]	Decrease in LV ejection time, increased afterload, increased SVR, decreased preload
Cardiac ejection elasticity index (EEI)	Index for LV ejection capacity and compliance/elasticity of large arteries	Large artery vasodilatation, anemia, increased LV ejection power, hyperthyroidism, congested heart failure	Large artery vasoconstriction, arteriosclerosis, LV ejection insufficiency	Increase in LV ejection power, large artery vasodilatation	Decrease in LV ejection power, large artery vasoconstriction
Dicrotic index (DI)	Represents the peripheral circulation, indicates peripheral resistance	Small artery vasoconstriction	Small artery vasodilatation	Peripheral vasoconstriction	Peripheral vasodilatation
b*/*a	Early systolic PW peaks identified by second derivatives of the crude PW curve contour; indicates LV ejection capacity and large artery compliance/elasticity	Low large artery elasticity, increased cardiovascular risk, vasoconstriction, atherosclerosis, increases by age	Young persons, athletes	Large artery vasoconstriction, decreased LV ejection	Large artery vasodilatation, increased LV ejection
d*/*a	*d* is a late systolic PW peak identified by second derivative of the crude PW curve contour; mainly reflects the intensity of the tidal PW from small peripheral arteries	High small artery elasticity, young persons	A longer negative *d* peak develops by advancing age, indicating arterial stiffness, atherosclerosis	Small artery vasodilatation	Small artery vasoconstriction
Ageing index (AI)	AI = (*b*-*c*-*d*-*e*)/*a*, representing the global vascular stiffness, i.e. "vascular age"	Atherosclerosis, increases by age	Young persons, athletes	Global arterial vasoconstriction	Global arterial vasodilatation

BP, blood pressure; SVR, systemic vascular resistance; LV, left heart ventricle; PW, pulse wave

To enable comparisons between pregnant and nonpregnant women, where differences were expected at TB, the TB values were set to 0 in both groups and the changes at T1 and onwards were expressed as Δ-values; For example, the change from TB to T3 (T3 minus TB) was expressed as ΔT3. For longitudinal comparisons between the groups, the series ΔT1- ΔT3- ΔT5 were compared with two-way RM ANOVA, using post-hoc analysis with the Holm-Sidak method for comparisons at each time point. Categorical data were compared with Fisher's exact test. A significant difference was defined as a two-sided *P* value <0.05.

Since the magnitude of expected differences was unknown, we could not perform a sample size calculation in advance and instead performed a post-hoc power calculation (https://clincalc.com/Stats/Power.aspx).

RESULTS

Twenty-five women in the nonpregnant group and 24 in the pregnant group completed the experiment. Recordings from one pregnant woman were lost due to technical problems.

Demographic data and basal recordings at TB are shown in Table 2. Pregnant women had a higher age and BMI, and among basal recordings, HR, SaO_2, ST index lead V5, PH, DI, EEI, and ETc were significantly different between the groups.

Table 2. Patient characteristics and baseline measurements before hyperoxygenation. For explanation of digital pulse wave analysis (DPA) variables, see Table 1.

	Pregnant (n=24) **Mean (SD)** **Median (range)**	**Nonpregnant (n=25)** **Mean (SD)** **Median (range)**	**P value**
Age (years)	30.1 (4.2) 30 (19 – 37)	26.5 (2.2) 27 (23 – 33)	<0.001
Smoker	1	2	1.0
Body mass index (kg/m2)	26.9 (3.8) 25.2 (20.0 – 35.0)	22.1 (4.3) 20.9 (18.0 – 39.2)	<0.001
Gestational week	33.5 (2.1) 34 (29 – 38)	-	-
Mean arterial blood pressure (mmHg)	84.4 (8.2) 83.1 (69.3 – 99.6)	82.8 (8.1) 83.7 (69 – 107)	0.5#
Heart rate (bpm)	89.2 (13.7) 85 (65 – 113)	69.0 (14.4) 67.0 (45 – 104)	<0.001#
SaO2 (%)	97.8 (1.3) 98 (95 – 100)	99.2 (1.0) 99 (96 – 100)	<0.001
ST-index I	0.21 (0.17) 0.2 (-0.2 – 0.5)	0.24 (0.26) 0.2 (-0.6 – 0.7)	0.5
ST-index II	0.18 (0.34) 0.2 (-0.5 – 0.8)	0.21 (0.38) 0.2 (-0.6 – 1.2)	0.8#
ST-index V5	0.05 (0.22) 0.0 (-0.3 – 0.5)	0.24 (0.25) 0.2 (-0.3 – 0.7)	0.005
AI	-0.64 (0.27) -0.63 (-1.26 – -0.03)	-0.62 (0.16) -0.62 (-0.93 – -0.30)	0.7#
b/a	-0.67 (0.11) -0.66 (-0.96 – -0.45)	-0.67 (0.08) -0.67 (-0.80 – -0.53)	0.9#
d/a	-0.11 (0.08) -0.11 (-0.27 – 0.02)	-0.17 (0.09) -0.20 (-0.43 – -0.01)	0.02#
DI	0.52 (0.17) 0.53 (0.22 – 0.81)	0.80 (0.14) 0.81 (0.55 – 0.98)	<0.001#
EEI	1.07 (0.41) 1.00 (0.45 – 1.72)	0.70 (0.21) 0.63 (0.41 – 1.24)	<0.001
ETc (ms)	347.7 (20.1) 350 (289.0 – 382.0)	331.0 (22.1) 331 (295 – 385)	0.014#
PH	7.30 (3.54) 7.78 (0.77 – 13.47)	3.06 (2.38) 1.92 (0.19 – 9.27)	<0.001#

Fisher's exact test were used for categorical data; The unpaired *t*-test was used for normally distributed variables (indicated with #) and the Mann-Whitney *U* test for skewed distributions.

No maternal side effects or FHR abnormalities were observed. ETc values at TB from three women and the MAP value at T3 from one woman were erroneous and accordingly excluded from statistical analyses.

The effects of hyperoxygenation on pregnant women are shown in Table 3 and Figure 1. Significant changes (indicating global vasoconstriction) were seen in all investigated variables except the ETc, PH, and ST index. All changes occurred within 1 min and all variables except HR returned to basal levels within 5 min after finishing hyperoxygenation (Table 3: T10 HR value 3.4 bpm, or 3.3% lower than at TB). The mean HR fell by a maximum of 9.3 bpm (10.2%) and the mean MAP by a maximum of 3.3 mmHg (3.8%). In six women, the HR drop was ≥20 bpm, but none of them had a MAP drop of ≥15 mmHg.

The effects of hyperoxygenation in nonpregnant women are shown in Table 4 and Figure 1. Within 1 min, SaO_2 increased, MAP decreased, and *d/a* decreased (indicating small artery vasoconstriction). At 3 min, significant decreases were seen in HR (mean -5.7 bpm, -7.0%) and MAP (mean -5.0 mmHg, -5.8%). In four women, the HR drop was ≥20 bpm, and in two of them, MAP dropped by ≥15 mmHg. Five minutes after stopping hyperoxygenation (T10), all variables had returned to basal levels.

Comparisons of Δ-values between pregnant and nonpregnant women are shown in Table 5 and Figure 2. Significant differences were found for HR, SaO_2, AI, *b/a*, DI, and EEI, and more frequently at T5 than at T3. Overall, DPA parameters indicated larger vasoconstrictions in the pregnant group.

A post-hoc power calculation on the difference between the groups in ΔAI at T5, where the mean value in the pregnant group was 0.152 (standard deviation 0.14) and in non-pregnant women 0.020 (0.20), yielded a power of 76% and an alpha of 0.05.

Table 3. Cardiovascular effects of 100 % O_2 inhalation during 5 min in third-trimester pregnant women. Measurements were performed before inhalation (basal, TB), after 1 min (T1), 3 min (T3), 5 min (T5), and 5 min after stopping inhalation (T10). Figures denote *P* values and arrows (↑↓) direction of change. For explanation of variables, see Table 1. ANOVA was carried out both with and without the T10 control measurements (upper and lower row on each variable). For descriptive statistics, see supplementary table 6

Variable	Before-during-after oxygen	Before-during oxygen	Before-during oxygen			Before-after oxygen	Interpretation
	ANOVA TB-T1-T3-T5-T10	ANOVA TB-T1-T3-T5	TB-T1	TB-T3	TB-T5	TB-T10	
AI	<0.001[b] -	- <0.001[a]	↑ <0.001 ↑ <0.001	↑ 0.004 ↑ <0.001	↑0.002 ↑ <0.001	1.0	Global arterial vasoconstriction
b/a	<0.001[b] -	- <0.001[b]	↑ 0.01 ↑ 0.006	↑ <0.001 ↑ <0.001	0.1 0.2	1.0	Large artery vasoconstriction
d/a	<0.001[a] -	- <0.001[a]	↓ <0.001 ↓ <0.001	↓ 0.011 ↓ 0.003	↓ <0.001 ↓ <0.001	0.08	Small artery vasoconstriction
DI	0.011[b] -	- 0.009[a]	↑ 0.003 ↑ 0.002	0.2 0.2	0.1 0.1	1.0	Peripheral vasoconstriction
EEI	<0.001[b] -	- <0.001[b]	↓ <0.001 ↓ <0.001	↓ 0.01 ↓ <0.001	↓ <0.001 ↓ <0.001	1.0	Decreased left ventricular ejection power, large artery vasoconstriction
ETc	0.7[b] -	- 0.5[b]	- -	- -	- -	-	*No effect*
HR	<0.001[a] -	- <0.001[a]	↓ <0.001 ↓ <0.001	↓ <0.001 ↓ <0.001	↓ <0.001 ↓ <0.001	↓ 0.03	Heart rate decrease
MAP	0.01[b] -	- 0.1[b]	1.0 -	0.3 -	0.4 -	0.8	*No effect*
PH	0.01[a] -	- 0.3[b]	0.8 -	0.5 -	0.4 -	0.2	*No effect*
SaO_2	<0.001[b] -	- <.001[b]	↑ <0.001 ↑ <0.001	↑ <0.001 ↑ <0.001	↑ <0.001 ↑ <0.001	1.0	SaO_2 increase
ST-index I	0.009[b] -	- 0.2[b]	0.4 -	1.0 -	1.0 -	0.5	*No effect*
ST-index II	0.2[b] -	- 0.5[b]	-	-	-	-	*No effect*
ST-index V5	0.5[b] -	- 0.3[b]	-	-	-	-	*No effect*

a) Normal distribution (Shapiro-Wilk test): One-way repeated measurements analysis of variance (ANOVA) with Holm-Sidak post-hoc test was used.
b) Skewed distribution: Friedman's nonparametric repeated measurements ANOVA with Dunn's post hoc test.

Table 4. Cardiovascular effects of 100 % O_2 inhalation during 5 min in nonpregnant women. Measurements were performed before inhalation (basal, TB), after 1 min (T1), 3 min (T3), 5 min (T5), and 5 min after stopping inhalation (T10). Figures denote *P* values and arrows direction of change. For explanation of variables, see Table 1. ANOVA was carried out both with and without the T10 control measurements (upper and lower row on each variable). For descriptive statistics, see supplementary table 7,

Variable	Before-during-after oxygen	Before-during oxygen	Before-during oxygen			Before-after oxygen	Interpretation
	ANOVA TB-T1-T3-T5-T10	ANOVA TB-T1-T3-T5	TB-T1	TB-T3	TB-T5	TB-T10	
AI	0.01[a] -	- 0.7[a]	0.9 -	0.7 -	0.8 -	0.08	*No effect*
b/a	0.07[b] -	- 0.5[b]	- -	- -	- -	-	*No effect*
d/a	0.002[a] -	- 0.001[a]	↓ 0.002 ↓ <0.001	↓ 0.02 ↓ 0.007	↓ 0.04 ↓ 0.01	0.5 0.6	Small artery vasoconstriction
DI	0.02[a] -	 0.03[a]	0.9 0.9	0.9 0.9	0.07 0.054	0.2	*No effect*
EEI	0.02[b] -	- 0.1[b]	1.0 -	0.2 -	1.0 -	0.8 -	*No effect*
ETc	0.07[a] -	- 0.1[b]	- -	- -	- -	-	*No effect*
HR	0.002[b] -	- 0.001[b]	0.4 0.3	↓ <0.001 ↓ <0.001	0.4 0.3	0.5	Heart rate decrease by 7% at 3 min
MAP	<0.001[a] -	- <0.001[a]	↓ 0.001 ↓ 0.001	↓ <0.001 ↓ <0.001	↓ <0.001 ↓ <0.001	0.2	Decrease in MAP by 5-6%
PH	1.0[b] -	- 0.9[b]	- -	- -	- -	- -	*No effect*
SaO_2	0.001[b] -	- <0.001[b]	↑ 0.01 ↑ 0.009	↑ 0.02 ↑ 0.02	↑ 0.02 ↑ 0.02	1.0	SaO_2 increase
ST-index I	0.009[b] -	- 0.055[b]	0.1 -	0.6 -	0.2 -	1.0 -	*No effect*
ST-index II	0.3[b] -	- 0.3[b]	- -	- -	- -	- -	*No effect*
ST-index V5	0.1[b] -	- 0.07[a]	- -	- -	- -	- -	*No effect*

a) Normal distribution (Shapiro-Wilk test): One-way repeated measurements analysis of variance (ANOVA) with Holm-Sidak post-hoc test was used.
b) Skewed distribution: Friedman's nonparametric repeated measurements ANOVA was used with Dunn's post hoc test.

Table 5. Comparison between pregnant and nonpregnant women after breathing 100% O_2 for 3 and 5 min. ΔT3 denotes the difference between T3 and TB values, and ΔT5 between T5 and TB values.

Variable	Time	Pregnant (N=24) Median (range) or mean (SD)	Nonpregnant (N=25) Median (range) or mean (SD)	*P* value	Interpretation
AI	ΔT3	0.144 (0.171)	0.038 (0.187)	0.045	Larger global vasoconstriction in pregnant group
	ΔT5	0.152 (0.144)	0.020 (0.204)	0.01	Larger global vasoconstriction in pregnant group
b/a	ΔT3	0.074 (0.078)	0.024 (0.085)	0.04	Larger large artery vasoconstriction in pregnant group
	ΔT5	0.053 (0.094)	0.00 (0.088)	0.04	Larger large artery vasoconstriction in pregnant group
d/a	ΔT3	-	-	0.6	*No difference*
	ΔT5	-	-	0.16	*No difference*
DI	ΔT3	-	-	0.5	*No difference*
	ΔT5	0.034 (0.097)	-0.054 (0.122)	0.008	Larger peripheral vasoconstriction in pregnant group
EEI	ΔT3	-0.16 (-0.08 – 0.17)	-0.09 (-0.49 – 0.19)	0.07	*No difference*
	ΔT5	-0.229 (0.29)	0.038 (0.24)	<0.001	Larger large artery vasoconstriction in pregnant group
ETc	ΔT3	-	-	0.5	*No difference*
	ΔT5	-	-	0.2	*No difference*
PH	ΔT3	-	-	0.5	*No difference*
	ΔT5	-	-	0.3	*No difference*
HR (bpm)	ΔT3	-	-	0.1	*No difference*
	ΔT5	-6 (-28 – 2)	-1 (-23 – 15)	0.002	HR lower in pregnant group
MAP (mmHg)	ΔT3	-	-	0.2	*No difference*
	ΔT5	-	-	0.6	*No difference*
SaO_2 (%)	ΔT3	2 (-2 – 3)	1 (0 – 3)	0.001	SaO_2 increase larger in pregnant group
	ΔT5	2 (-2 – 2)	1 (0 – 3)	0.003	SaO_2 increase larger in pregnant group
ST-index I	ΔT3	-	-	0.7	*No difference*
	ΔT5	-	-	0.7	*No difference*
ST-index II	ΔT3	-	-	0.8	*No difference*
	ΔT5	-	-	0.2	*No difference*
ST-index V5	ΔT3	-	-	0.3	*No difference*
	ΔT5	-	-	0.8	*No difference*

Normally distributed data are displayed as mean (standard deviation) and compared with unpaired *t*-test, and skewed data are displayed as median (range) and compared with the Mann-Whitney *U* test

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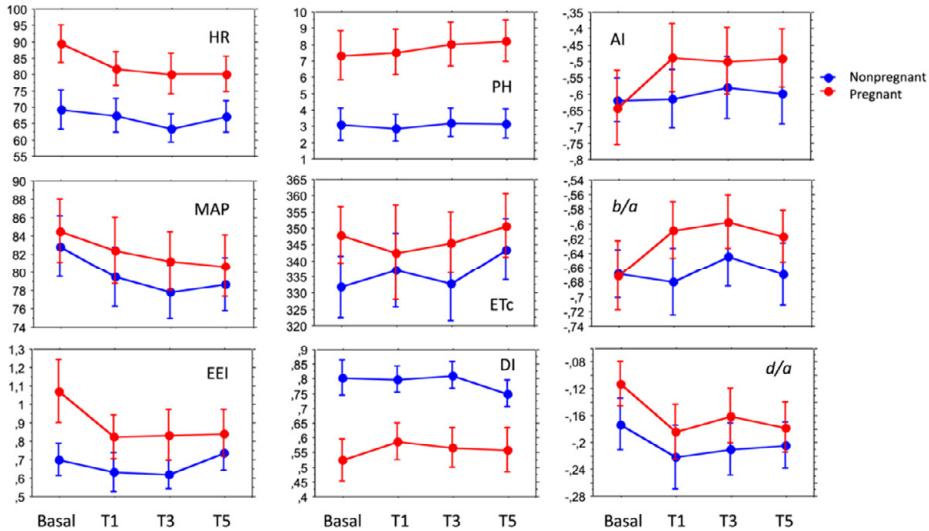

Figure 1. Hemodynamic effects of inhalation of 100% oxygen in 24 healthy third-trimester pregnant women and 25 healthy nonpregnant women of fertile age. Measurements of heart rate (HR, bpm), mean arterial blood pressure (MAP, mmHg), and digital photoplethysmographic (PPG) pulse wave analysis of cardiac ejection elasticity index (EEI), pulse height (PH), left ventricular ejection time compensated (ETc, ms), dicrotic index (DI), and the second derivative (APG) indices ageing index (AI), *b/a*, and *d/a* were performed before hyperoxygenation (Basal), and after 1 (T1), 3 (T3), and 5 minutes (T5). Mean values with 95% confidence interval.

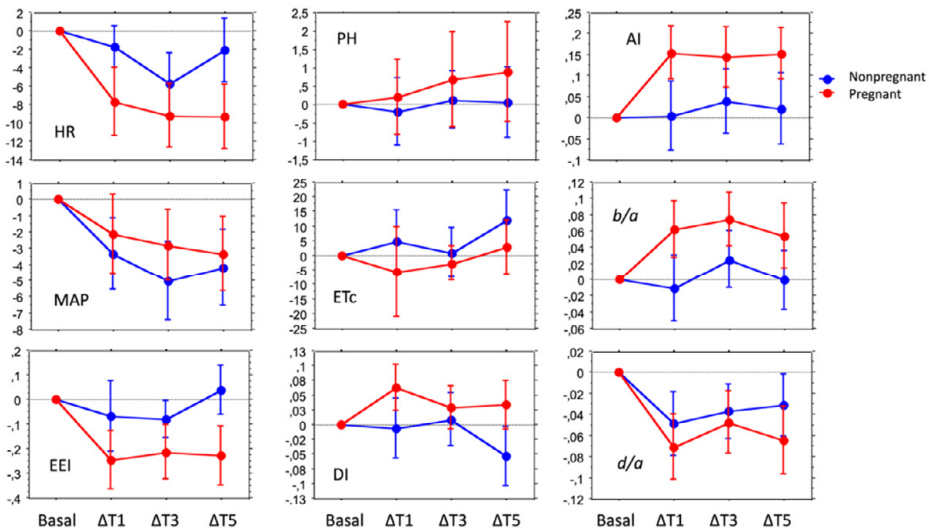

Figure 2. Hemodynamic effects of inhaled 100% oxygen in pregnant and nonpregnant women. The graphs show mean changes from baseline to each measurement time point. Baseline is set to null and changes to each time point are expressed as Δ-values, with 95% confidence interval.

DISCUSSION

This study showed that maternal hyperoxygenation with 100% O_2 caused vasoconstriction in both pregnant and non-pregnant women. Vasoconstriction occurred already after 1 min and was more prominent in the pregnant group. While pregnant women showed global vasoconstriction and higher vascular tonus in general, in non-pregnant women, the DPA variables indicated vasoconstriction only in the small arteries.

The HR and MAP decreased during hyperoxygenation in both groups, with a significantly more pronounced lowering of the HR in pregnant women at 5 min. The decreases were moderate and the difference between groups small, however. The mean decreases were 10% in pregnant women and 7% in nonpregnant women. The corresponding figures for MAP were 4% and 6%. A drop in MAP and HR paired with vasoconstriction indicates a decrease in CO,[21] but no woman experienced any subjective symptoms.

Among other variables reflecting cardiac function, only EEI in pregnant women was significantly affected. ECG ST index and ETc (LV ejection time) were unaffected in both groups. EEI (ejection elasticity index) decreased in pregnant women, indicating a fall in LV ejection capacity and an increase in large artery tonus. The variable cannot discriminate between ejection capacity and vascular tonus, however, and it is an open question whether the decrease in CO is due to a reduction in HR alone or occurs in conjunction with a decreased LV ejection capacity. In any case, our results suggest that hyperoxygenation results in a drop in CO that is more pronounced in pregnant women than in nonpregnant women.

With the exception of BP, our observations are in congruence with a systematic review and meta-analysis on the hemodynamic effects of acute hyperoxia published by Smit et al.[22] In 19 included studies on healthy volunteers of both genders, hyperoxygenation caused a 6.5% decrease in HR, a 3% decrease in stroke volume, a 10.2% decrease in CO, a 2% increase in MAP, and a 12.1% increase in SVR, but no change in O_2 delivery. The authors explain that the reduction in CO is driven by a reduction in HR rather than stroke volume. However, the heterogeneity in the meta-analysis was very high (68-95%) making the generalizability uncertain. Among studies with an O_2 exposure time of ≤10 min (N=9), the heterogeneity was 0%, but no separate sensitivity analyses of studies were presented. We speculate that the BP response among our nonpregnant volunteers (-6% in MAP) differed from that of volunteers in the meta-analysis (+2%) because our patients were all female and younger.

The vasoactive effects of superimposed O_2 in pregnant women have been investigated in a few studies, but most of them focused on fetal and neonatal effects.[7] By Doppler blood flow velocimetry, Polvi and coworkers recorded vascular flow resistance in the maternal uterine artery and the internal carotid artery during

hyperoxygenation and found no changes relative to room air breathing and no changes in BP or HR.[15] McHugh et al. evaluated maternal hemodynamics after hyperoxygenation in late pregnancy and in nonpregnant women.[16] In pregnant women, hyperoxygenation resulted in a rise in SVR and a fall in HR and cardiac index, but no change in BP. The changes in SVR and cardiac index did not return to baseline within 10 min. after cessation of extra O_2. As in our study, nonpregnant women were less affected. Their results agree with ours, though in our study variables returned to basal values within 5 min. after cessation of O_2.

Another difference was the mode of O_2 administration, where the McHugh study used a flow of 12 L/min in a non-rebreather mask. Using an open non-rebreather mask, 12 L of O_2 per minute may result in a FiO_2 of anything between 40 and 80%, depending on the type and fitting of the mask.[23,24] We used 100% O_2 in a tight-fitting mask connected to a rebreathing system, resulting in a higher and more predictable fraction of inspired O_2, expecting to result in a FiO2 of more than 80% within 3 min.[25,26]

Maternal hyperoxygenation is commonly used for intrauterine resuscitation in labor when FHR indicates impending fetal hypoxia. Positive effects on fetal oxygenation have been shown in small invasive and non-invasive human studies.[27–31] In a fetal lamb experiment, hyperoxygenation increased oxygenation of the abdominal organs but not the brain.[32] Hyperoxygenation has recently been questioned in normoxic pregnant women, claiming there is no evidence the fetus will benefit.[33] Studies on non-compromised fetuses are not conclusive for compromised fetuses,[29,30,34,35] and studies on distressed fetuses are non-randomized.[36–39] The latest Cochrane review from 2012 contained no randomized controlled trial (RCT) assessing the distressed fetus.[9] Three later RCTs have addressed the issue,[4041] but all of them had methodological difficulties common in this kind of intricate research: the inclusion of non-reassuring intermediary CTGs rather than pathological CTGs, indicating mild or evolving hypoxia rather than established or severe hypoxia, or too short time windows to allow reliable CTG classifications. A recent systematic review and meta-analysis shows that there are no relevant differences in umbilical artery pH or other neonatal outcomes between hyperoxygenation and breathing room air, but the authors ask for adequately powered RCTs to assess long- and short-term neonatal morbidity in cases of abnormal CTGs.[11]

Our study contributes to the debate about hyperoxygenation by showing a maternal global vasoconstrictory effect of inhaled 100% O_2 occurring already after 1 min and becoming more pronounced after 3 min. Preeclamptic women show vasoconstriction and hypovolemia,(20) and it should be an important task to investigate whether hyperoxygenation might worsen the condition. Our study does not address the question of whether hyperoxygenation jeopardizes the O_2 supply to the fetus.

The potential increase in ROS in the mother and fetus by hyperoxygenation is a matter of concern, particularly in preeclamptic pregnancy. In a RCT by Khaw et al.[42] comparing 60% O_2 and room air breathing during cesarean section, a significantly increased concentration of malondialdehyde (MDA, a marker for oxidative stress) was measured in the arterial blood of hyperoxygenated women within 10 min, and at birth, isoprostane (formed from free radical-catalyzed peroxidation) was also significantly higher. In arterial and venous umbilical cord blood, MDA, isoprostane, and organic hydroperoxides were significantly higher in the O_2 group. The study was confined to healthy mothers and uncomplicated pregnancies, and neonatal outcome was not affected, but the study raises questions about the toxic effects of ROS in complicated pregnancies. The normal physiological increase in lipid peroxidation in pregnancy is balanced by an increase in antioxidant activity, but in preeclamptic women, the antioxidant capacity is reduced. This leads to an imbalance between the pro- and antioxidant systems and a net increase in oxidative stress.[43] Hyperoxygenations in these women might thus add to this oxidative stress and should probably be avoided.

Hyperoxygenation results in vasoconstriction in most tissues in the body, which is a normal physiological response to protect cells from cytotoxic ROS.[44] Vasoconstriction is caused by multiple mechanisms. Increased free O_2 radicals inhibit nitric oxide (NO) activity by decreasing the availability of the precursor L-arginine, inhibiting NO synthase (NOS), and decreasing the release of NO from erythrocytes.[44] A high pO_2 stiffens erythrocyte cell membranes with impaired release of ATP to plasma. ATP in plasma binds to endothelial P_{2Y} receptors, which regulate the production of NO. Furthermore, serotonin increases and the vasodilatory effect of endothelial prostacyclin decreases.

Strengths and limitations

In line with current knowledge of cardiovascular physiology in pregnant women,[45] our basal measurements showed significantly lower arterial vascular tonus, lower SaO_2, and a higher HR in pregnant women compared with nonpregnant women. To enable comparisons of the magnitudes of changes, expressed as Δ-values, the basal measurements needed to be reset. Longitudinal comparisons with patients serving as their own controls further reduced the risk of confounding, as pO_2 may vary due to differences in physiological condition and breathing technique. Maternal blood gases were not analyzed, and we did not use end-tidal gas analysis. However, pre-oxygenation studies in pregnant and nonpregnant patients show that after 3 min the end-tidal O_2 concentration has usually reached >80%.[25,26] A weakness of the photoplethysmographic DPA method is that body movements or cold fingers can cause erroneous values, but with thorough preparations, including warming hands, we got very few erroneous recordings in this study compared with our previous studies.

Conclusion

This study shows that in healthy third-trimester pregnant women, hyperoxygenation has prompt vasoconstrictive effects on both large and small arteries, as well as a negative chronotropic and a mild hypotonic effect. Such a pattern of change is indicative of a drop in CO, but the study could not reveal whether it is due to a reduction in HR alone or occurring in conjunction with a decreased LV ejection capacity. No subjective side effects were noted, and FHR was not affected. The effects diminished within 5 minutes after the cessation of the O_2 inhalations. In nonpregnant women, the hemodynamic effects were similar, but the vasoconstrictory effects were limited to small arteries, and the hemodynamic effects were significantly less pronounced than in the pregnant group. In pregnant women with complications associated with vasoconstriction and hypovolemia, such as hypertension and preeclampsia, a superimposed vasoconstriction may aggravate the condition, and it is an important task to investigate the adverse effects of hyperoxygenation in these women.

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Supplementary Table 6. Pregnant women. Descriptive statistics from the hyperoxygenation study. Mean, median, range and 95 % confidence intervals (CI) of all variables. Statistically significant changes vs TB are marked in bold (see table 3 for *P*-values).

Variable	TB	T1	T3	T5	T10
AI	n=24	**n=24**	**n=24**	**n=24**	n=24
Mean (CI)	-0.64 (0.11)	**-0.49 (0.10)**	**-0.50 (0.10)**	**-0.49 (0.09)**	-0.58 (0.10)
Median (range)	-0.63 (-1.26 – -0.03)	**-0.46 (-0.92 – -0.08)**	**-0.54 (-0.91 – -0.07)**	**-0.44 (-0.80 – -0.16)**	-0.59 (-1.25 – -0.11)
b/a	n=24	**n=24**	**n=24**	n=24	n=24
Mean (CI)	-0.67 (0.05)	**-0.61 (0.04)**	**-0.60 (0.04)**	-0.62 (0.04)	-0.67 (0.05)
Median (range)	-0.66 (-0.96 – -0.45)	**-0.62 (-0.79 – -0.37)**	**-0.60 (-0.74 – -0.36)**	-0.62 (-0.75 – -0.46)	-0.64 (-1.03 – -0.51)
d/a	n=24	**n=24**	**n=24**	**n=24**	n=24
Mean (CI)	-0.11 (0.03)	**-0.18 (0.04)**	**-0.16 (0.04)**	**-0.18 (0.04)**	-0.14 (0.04)
Median (range)	-0.11 (-0.27 – 0.02)	**-0.18 (-0.35 – 0.02)**	**-0.18 (-0.30 – 0.00)**	**-0.16 (-0.35 – -0.01)**	-0.14 (-0.35 – 0.05)
DI	n=24	**n=24**	n=23	n=24	n=24
Mean (CI)	0.52 (0.07)	**0.58 (0.06)**	0.56 (0.07)	0.56 (0.08)	0.53 (0.07)
Median (range)	0.53 (0.22 – 0.81)	**0.58 (0.18 – 0.86)**	0.55 (0.34 – 0.86)	0.54 (0.21 – 0.92)	0.54 (0.11 – 0.75)
EEI	n=24	**n=24**	**n=23**	**n=24**	n=24
Mean (CI)	1.07 (0.17)	**0.82 (0.12)**	**0.83 (0.14)**	**0.84 (0.13)**	1.01 (0.15)
Median (range)	1.00 (0.45 – 1.72)	**0.80 (0.28 – 1.56)**	**0.83 (0.25 – 1.51)**	**0.79 (0.37 – 1.63)**	0.92 (0.53 – 1.93)
ETc (ms)	n=23	n=24	n=23	n=24	n=23
Mean (CI)	348 (8.7)	342 (14.5)	345 (9.5)	350 (9.7)	341 (13.2)
Median (range)	350 (289 – 382)	352 (227 – 382)	346 (298 – 375)	357 (292 – 385)	347 (252 – 383)
HR (bpm)	n=24	**n=24**	**n=24**	**n=24**	n=24
Mean (CI)	89.2 (5.8)	**81.5 (5.1)**	**80.0 (6.1)**	**79.8 (5.4)**	85.8 (5.1)
Median (range)	85.0 (65 - 113)	**80.5 (57 - 102)**	**78.0 (50 - 107)**	**76.5 (58 - 101)**	87.0 (56 - 105)
MAP (mmHg)	n=24	n=24	n=23	n=23	n=24
Mean (CI)	84.4 (3.5)	82.3 (3.6)	81.1 (3.2)	80.6 (3.4)	84.3 (3.5)
Median (range)	83.2 (69.3 -99.7)	81.7 (70.3 – 104)	80.7 (69.3 – 96.3)	80.3 (67.7 – 100)	85.7 (59.3 – 94.7)
PH	n=24	n=24	n=24	n=24	n=24
Mean (CI)	7.30 (1.50)	7.49 (1.37)	7.97 (1.34)	8.17 (1.26)	6.19 (1.09)
Median (range)	7.78 (0.77 – 13.5)	7.16 (1.17 – 13.0)	7.88 (3.10 – 14.3)	8.19 (1.88 – 13.2)	6.46 (1.27 – 10.3)
SaO_2	n=24	**n=24**	**n=24**	**n=24**	n=24
Mean (CI)	97.8 (0.53)	**99.4 (0.48)**	**99.2 (0.49)**	**99.1 (0.6)**	97.7 (0.7)
Median (range)	98.0 (95-100)	**100 (95-100)**	**100 (95-100)**	**99.5 (94-100)**	98.0 (94-100)
ST index I (mV)	n=24	n=24	n=24	n=24	n=24
Mean (CI)	0.21 (0.07)	0.14 (0.06)	0.16 (0.05)	0.21 (0.07)	0.26 (0.07)
Median (range)	0.20 (-0.1 – 0.6)	0.10 (-0.1 – 0.4)	0.15 (0.0 – 0.4)	0.25 (0.0 – 0.6)	0.30 (-0.2 – 0.5)
ST index II (mV)	n=24	n=24	n=24	n=24	n=24
Mean (CI)	0.18 (0.14)	0.14 (0.15)	0.21 (0.14)	0.18 (0.16)	0.25 (0.16)
Median (range)	0.20 (-0.5 – 0.8)	0.05 (-0.4 – 1.1)	0.30 (-0.5 – 0.8)	0.20 (-0.6 – 1.2)	0.30 (-0.7 – 1.2)
ST index V5 (mV)	n=24	n=24	n=24	n=24	n=24
Mean (CI)	0.05 (0.09)	0.07 (0.09)	0.11 (0.11)	0.11 (0.08)	0.09 (0.08)
Median (range)	0.00 (-0.3 – 0.5)	0.00 (-0.4 – 0.6)	0.10 (-0.7 – 0.7)	0.05 (-0.2 – 0.5)	0.00 (-0.3 – 0.7)

Supplementary Table 7. Nonpregnant women. Descriptive statistics from the hyperoxygenation study. Mean, median, range and 95 % confidence intervals (CI) of all variables. Statistically significant changes vs. TB are marked in bold (see table 3 for *P*-values).

Variable	TB	T1	T3	T5	T10
AI	n=25	n=25	n=25	n=25	n=25
Mean (CI)	-0.62 (0.067)	-0.62 (0.09)	-0.58 (0.09)	-0.60 (0.09)	-0.71 (0.09)
Median (range)	-0.62 (-0.93 – -0.30)	-0.65 (-1.03 – -0.22)	-0.61 (-0.98 – -0.19)	-0.60 (-0.99 – -0.14)	-0.71 (-1.17 – -0.33)
b/a	n=25	n=25	n=25	n=25	n=25
Mean (CI)	-0.67 (0.03)	-0.68 (0.05)	-0.64 (0.04)	-0.67 (0.04)	-0.70 (0.04)
Median (range)	-0.67 (-0.80 – -0.53)	-0.68 (-1.00 – -0.47)	-0.64 (-0.87 – -0.45)	-0.68 (-0.86 – -0.45)	-0.69 (-0.90 – -0.48)
d/a	n=25	n=25	n=25	n=25	n=25
Mean (CI)	-0.17 (0.04)	**-0.22 (0.05)**	**-0.21 (0.04)**	**-0.21 (0.03)**	-0.18 (0.03)
Median (range)	-0.20 (-0.43 – -0.01)	**-0.23 (-0.42 – -0.01)**	**-0.23 (-0.37 – -0.03)**	**-0.21 (-0.36 – -0.06)**	-0.19 (-0.33 – 0.02)
DI	n=25	n=25	n=25	n=25	n=25
Mean (CI)	0.80 (0.06)	0.80 (0.04)	0.81 (0.05)	0.75 (0.04)	0.76 (0.04)
Median (range)	0.81 (0.55 – 0.98)	0.79 (0.59 – 0.96)	0.79 (0.64 – 1.00)	0.73 (0.49 – 0.93)	0.76 (0.55 – 0.91)
EEI	n=25	n=25	n=25	n=25	n=25
Mean (CI)	0.70 (0.09)	0.63 (0.11)	0.62 (0.08)	0.73 (0.09)	0.78 (0.10)
Median (range)	0.63 (0.41 – 1.24)	0.63 (0.0 – 1.22)	0.62 (0.27 – 1.08)	0.75 (0.37 – 1.36)	0.71 (0.48 – 1.57)
ETc (ms)	n=24	n=25	n=25	n=25	n=25
Mean (CI)	331.7 (9.55)	336,8 (11.4)	332.7 (11.4)	343.2 (9.41)	329.8 (8.04)
Median (range)	331 (295 – 385)	338 (290 – 393)	326 (281 – 381)	340 (311 – 391)	328 (293 – 375)
HR (bpm)	n=25	n=25	n=25	n=25	n=25
Mean (CI)	69.0 (6.00)	67.2 (5.20)	**63.3 (4.27)**	66.9 (4.75)	68.0 (4.09)
Median (range)	67 (45 – 104)	65 (46 – 95)	**63 (47 – 84)**	64 (50 – 93)	69 (47 – 84)
MAP (mmHg)	n=25	n=25	n=25	n=25	n=25
Mean (CI)	82.7 (3.34)	**79.4 (3.25)**	**77.7 (2.93)**	**78.6 (2.91)**	81.5 (2.95)
Median (range)	83.7 (69 – 108)	**80.3 (64.0 – 98.7)**	**77.7 (65.0 – 89.3)**	**78.3 (65.3 – 92.0)**	82.0 (67.0 – 101.3)
PH	n=25	n=25	n=25	n=25	n=25
Mean (CI)	3.06 (0.98)	2.85 (0.83)	3.17 (0.87)	3.10 (0.89)	2.85 (0.96)
Median (range)	1.92 (0.19 – 9.46)	1.84 (0.53 – 7.93)	3.03 (0.76 – 8.66)	2.71 (0.75 – 9.63)	1.98 (0.41 – 10.4)
SaO_2	n=25	n=25	n=25	n=25	n=25
Mean (CI)	99.24 (0.40)	**100.0 (0.0)**	**99.96 (0.08)**	**99.96 (0.08)**	99.12 (0.45)
Median (range)	99-0 (96 – 100)	**100 (100 – 100)**	**100 (99 – 100)**	**100 (99 – 100)**	99 (96 – 100)
ST index I (mV)	n=25	n=25	n=25	n=25	n=25
Mean (CI)	0.24 (0.11)	0.13 (0.11)	0.22 (0.09)	0.20 (0.09)	0.28 (0.09)
Median (range)	0.20 (-0.6 – 0.7)	0.10 (-0.6 – 0.9)	0.20 (-0.1 – 0.7)	0.20 (0.0 – 0.7)	0.20 (0.0 – 0.8)
ST index II (mV)	n=25	n=25	n=25	n=25	n=25
Mean (CI)	0.21 (0.16)	0.24 (0.17)	0.23 (0.14)	0.30 (0.17)	0.26 (0.15)
Median (range)	0.20 (-0.6 – 1.2)	0.30 (-0.6 – 1.1)	0.30 (-0.5 – 1.0)	0.30 (-0.6 – 1.1)	0.30 (-0.6 – 1.1)
ST index V5 (mV)	n=25	n=25	n=25	n=25	n=25
Mean (CI)	0.24 (0.10)	0.32 (0.11)	0.23 (0.11)	0.31 (0.11)	0.28 (0.11)
Median (range)	0.20 (-0.3 – 0.7)	0.30 (-0.3 – 0.7)	0.20 (-0.3 – 0.7)	0.30 (-0.3 – 0.8)	0.30 (-0.4 – 0.7)

Paper V

Hemodynamic effects of inhaled nitrous oxide in non-pregnant and third trimester pregnant women. An interventional comparative study using non-invasive pulse wave analysis

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ABSTRACT

Introduction

Inhaled nitrous oxide (N_2O) has extraordinary pharmacokinetic and analgesic properties, making it very suitable for pain of short onset and duration. It is commonly used for labor analgesia. Few studies have compared the direct circulatory effects of N_2O on pregnant and nonpregnant women.

Material and Methods

25 healthy third-trimester pregnant women and 25 healthy nonpregnant women of fertile age were enrolled to inhale both 30% and 50% N_2O mixed with 70% and 50% oxygen (O_2) respectively, for 5 min. Heart rate (HR), mean arterial blood pressure (MAP), ECG ST index, and photoplethysmographic digital pulse wave analysis (DPA) were assessed before, during, and 5 min after the inhalation stopped. One-way ANOVA for repeated measurements with post-hoc analyses was used for longitudinal changes within groups, and the Mann-Whitney U test was used to compare data between groups after 3 min of inhalation (T3).

Results

Pregnant women were more vasodilated and hyperemic than nonpregnant women at baseline. N_2O inhalation caused significant large and small artery vasoconstriction of similar magnitude in both groups. HR and MAP decreased only in pregnant women. Effects were seen within 1 min, becoming more pronounced after 3-5 min. All effects returned to baseline 5 min after cessation of N_2O inhalation. A larger proportion of pregnant women failed to complete the 50% N_2O experiment due to subjective side effects. No fetal heart rate anomalies were noted.

Conclusion

This study showed that pregnant women were more sensitive to N_2O than nonpregnant women, both in terms of subjective side effects and hemodynamic changes. N_2O caused vasoconstriction in both large and small arteries, with a pattern of change that may indicate a negative inotropic effect. As N_2O is mixed with 50–70% oxygen, some effects might be due to hyperoxygenation. Awareness of vasoconstrictive effects is important when N_2O/O_2 treatment is considered for already hypovolemic and vasoconstricted pregnant women.

List of abbreviations

AI: Ageing index; **ANOVA**: Analysis of variance; **APG:** Acceleration plethysmogram; ***b/a***: Second derivative quotient of the acceleration phase of the percussion pulse wave; **BMI**: Body mass index; **BP**: Blood pressure; **CO**: Cardiac output; **CTG**: cardiotocogram, cardiotocography; ***d/a***: Second derivative quotient of the percussion wave clashing with the reflected tidal wave; **DI**: Dicrotic index; **DPA**: Digital pulse wave analysis; **ECG**: Electrocardiogram; **EEI**: Ejection elasticity index; **ETc**: Left ventricular ejection time compensated (for heart rate); **FHR**: Fetal heart rate; **FiO_2**: Fraction of inspired oxygen; **HR**: Heart rate; **LV**: Left ventricle of the heart; **MAP**: Mean arterial blood pressure; **N_2O**: Nitrous oxide; **O_2**: Oxygen; **PH**: Pulse height; **PW**: Pulse wave; **RCT**: Randomized controlled trial; **SaO_2**: Oxygen saturation; **ST-index**: Difference in ECG ST segment from the isoelectric baseline; **SVR**: Systemic vascular resistance.

INTRODUCTION

The analgesic effect of inhaled nitrous oxide (N_2O) was discovered in the 18th century, and N_2O has since been widely used in surgery, dentistry, and obstetrics for more than 150 years.[1] Today, its use is especially common in the management of labor pain, being used by as many as 75% of women in western Europe, Australia, and New Zealand.[2] N_2O has extraordinary pharmacokinetic and analgesic properties, making it suitable for reducing pain of short onset and duration. The main side effects are drowsiness, dizziness, nausea, and vomiting, but serious adverse events for mothers or newborns have not been shown. Long-term use or occupational exposure are of concern due to neurotoxicity, but modern rebreathing and ventilation systems have diminished this potential problem in medicine.[3,4]

The anesthetic and analgesic effects are believed to be due to inhibiting excitatory transmission through N-methyl-D-aspartate (NMDA) receptors, but effects on other receptors as well have been implied, including opioidergic neurons, gamma-aminobutyric acid (GABA) interneurons, and noradrenergic pathways.[5–8] Due to its NMDA receptor antagonism, N_2O also has the potency to attenuate opioid-induced hyperalgesia and reduce post-operative morphine consumption.[9,10]

In healthy human subjects, N_2O causes a decrease in heart rate (HR) and blood pressure (BP).[11] Also, vasoconstrictive and cardiodepressant effects have been found.[12]

The latter is thought to be due to a decrease in the transsarcolemmal calcium influx, resulting in reduced availability of calcium in the contractile machinery. The cardiodepressive effect is not always seen clinically, as some of the cardiovascular effects are attenuated by a sympathomimetic effect of N_2O.[13,14]

In pregnant women, few studies exist evaluating the cardiovascular effects of N_2O. Westling and colleagues found increased SV but decreased CO, HR, and MAP during labor,[15] while another study, not conducted during labor, showed decreased central vascular resistance without affecting HR and BP.[16]

To our knowledge, no previous study has compared the direct circulatory effects of N_2O between pregnant and nonpregnant women. In this study, we investigated the effects of inhaled N_2O on maternal mean arterial pressure (MAP), HR, ECG, and arterial vascular tonus in healthy third-trimester pregnant women with an uncomplicated pregnancy. Nonpregnant, healthy women of fertile age served as controls. Using noninvasive digital pulse wave analysis (DPA) we could distinguish vascular tonus between large and small arteries and also evaluate left ventricular (LV) cardiac performance. The women were exposed to N_2O for a time period resembling that of how N_2O inhalations are used during labor, usually between 1 and 3 min at a time and sometimes up to 5 min.

The aim of the study was to explore and compare the circulatory effects of N_2O in pregnant and nonpregnant women. Our hypothesis was that MAP, HR, and arterial vascular tonus would decrease with no effects on ECG ST index, and with similar effects in pregnant and nonpregnant women.

MATERIAL AND METHODS

The Regional Research Ethics Committee in Lund approved the study (Dnr 2011/384). All participating women were volunteers and enrolled after oral and written consent. Pregnant women were recruited at routine ultrasound examinations in gestational week 32, by asking pregnant hospital staff, and by using a Swedish family forum on the internet. The nonpregnant control group consisted mainly of hospital staff and employees at Lund University. A sample size estimation was not made due to a lack of previous data in similar settings.

Inclusion criteria were third-trimester pregnant women with an uncomplicated pregnancy, being able to understand spoken and written Swedish, and with signed informed consent. Exclusion criteria were significant cardiovascular or lung disease, connective tissue disease, gestational hypertension, preeclampsia, diabetes, suspicion of fetal growth restriction, other problems with risk of cardiovascular compromise in the mother or fetus, veganism, body mass index (BMI) <18 kg/m^2, and vitamin B_{12} deficiency.

The women participated on the same occasion in a study on the hemodynamic effects of hyperoxygenation (Rabow et al., submitted),[17] preceding the present experiment. The present study was performed as an individual study after a 10 min washout period after finalizing the hyperoxygenation study, ensuring that all variables affected by O_2 had by then returned to baseline values. New basal recordings (TB) were performed for the present N_2O study, and a separate case report form (CRF) was used. Randomization was not relevant since the effects of N_2O are obvious and the patients served as their own controls.

The study was performed in a calm and quiet delivery room at the maternity unit in Malmö, Skåne University Hospital. Participants were asked to refrain from food, caffeine, and nicotine for at least 2 hours before the experiment. After a 5-min rest in a supine 15° left-tilted position, BP, pulse, ECG, and tissue oxygen saturation (pulse oximetry) were recorded with a Dash 4000 Pro monitoring system (GE Medical Systems Information Technologies, Danderyd, Sweden). The BP cuff was placed on the left arm and the pulse oximeter on the right third finger. The ECG was monitored through 5 channels, and the system was programmed to obtain a continuous ST segment trend. In the case of cold hands, a heat pad was used to warm the hands of the participants.

Simultaneously, pulse waves (PW) were recorded with photoplethysmographic digital PW analysis (DPA) (Meridian™,Salcor AB, Uppsala, Sweden) with an LED probe placed on the right index finger. The device records pulsatile blood volume changes in the finger (plethysmography), and the contour components of the coalescing percussion-tidal PWs are characterized mathematically. In addition to crude PW curve contour analysis, the device also calculates the second derivative plethysmogram for the accelerated plethysmogram (APG).

The device generates variables reflecting heart function and arterial vascular tonus. We selected variables with the best repeatability and best correlation to gold standard arterial applanation tonometry:[18] pulse height (PH), cardiac LV ejection time compensated (ETc), dicrotic index (DI), cardiac ejection elasticity index (EEI), ageing index (AI), and the ratios *b*/*a* and *d*/*a* (representing second derivates of the crude PW curve contour). The variables are described in Table 1. For further details of the DPA variables, see the works by von Wowern et al.[18]

After the basal recordings (TB), inhalation of N_2O 30% mixed with O_2 70% was started at time T0 and continued for 5 min. New Dash and Meridian recordings were performed after 1 min (T1), 3 min (T3), and 5 min (T5) (each Meridian recording takes about 70 s). The Dash recordings were performed immediately after the Meridian recordings. The inhalation was stopped after T5 recordings, and the final recordings were performed 5 min thereafter (T10). Women who could withstand and tolerate 30% N_2O well then went on with 50/50% N_2O/O_2 after another 5 min of rest. The same sequence T0-T10 then followed.

In pregnant women, the fetal heart rate (FHR) was continuously recorded by cardiotocography (CTG) throughout the experiments, and the FHR traces were classified according to national CTG guidelines.[19]

Table 1. Description of digital pulse wave analysis parameters used in the study, revised from von Wowern et al.

Parameter	Physiological background	Conditions with high values	Conditions with low values	Interpretation of increase	Interpretation of decrease
Pulse height (PH)	Circulation in small finger arteries, perfusion of finger tips	High BP, hyperthyroidism, fever, anemia, excessive blood volume, exercise, well-tuned athlete	Peripheral vaso-constriction, low BP, hypovolemia/dehydration, hypothyroidism, increased peripheral resistance	Peripheral vasodilatation	Peripheral vasoconstriction
Left ventricular ejection time compensated (ETc)	Represents systole, i.e. time from onset of the systolic upstroke limb to the closure of the aortic valve	Aortic valve stenosis, increased large artery compliance (low vascular tone)[a]	LV failure, decreased preload, hypovolemia, decreased large artery compliance (high vascular tone) [a]	Increase in LV ejection time, Decreased afterload, decreased SVR, increased preload [a]	Decrease in LV ejection time, Increased afterload, increased SVR, decreased preload
Cardiac ejection elasticity index (EEI)	Index for LV ejection capacity and compliance/elasticity of large arteries	Large artery vasodilatation, anemia, increased LV ejection power, hyperthyroidism, congested heart failure	Large artery vasoconstriction, arteriosclerosis, LV ejection insufficiency	Increase in LV ejection power, large artery vasodilatation	Decrease in LV ejection power, large artery vasoconstriction
Dicrotic index (DI)	Represents the peripheral circulation, indicates peripheral resistance	Small artery vasoconstriction	Small artery vasodilatation	Peripheral vasoconstriction	Peripheral vasodilatation
b/*a*	Early systolic PW peaks identified by second derivatives of the crude PW curve contour; indicates LV ejection capacity and large artery compliance/elasticity	Low large artery elasticity, increased cardiovascular risk, vasoconstriction, atherosclerosis, increases by age	Young persons, athletes	Large artery vasoconstriction, decreased LV ejection	Large artery vasodilatation, increased LV ejection
d/*a*	*d* is a late systolic PW peak identified by second derivative of the crude PW curve contour; mainly reflects the intensity of the tidal PW from small peripheral arteries	High small artery elasticity, young persons	A longer negative *d* peak develops by advancing age, indicating arterial stiffness, atherosclerosis	Small artery vasodilatation	Small artery vasoconstriction
Ageing index (AI)	AI = (*b*-*c*-*d*-*e*)/*a*, representing the global vascular stiffness, i.e. “vascular age”	Atherosclerosis, increases by age	Young persons, athletes	Global arterial vasoconstriction	Global arterial vasodilatation

BP, blood pressure; SVR, systemic vascular resistance; LV, left heart ventricle; PW, pulse wave

Statistical analyses

All Dash and manually obtained recordings were noted in an individual CRF. The CRF variables were manually transferred, whereas the Meridian recordings were digitally transferred to a statistical program spreadsheet data file (SigmaPlot, Alfasoft AS, Norway). For longitudinal comparisons within each group (TB-T1-T3-T5-T10), the software automatically checks for normal distribution with Shapiro-Wilk's test and for equal variance with Brown-Forsythe's test. If these failed, the Friedman non-parametric one-way ANOVA for repeated measurements was performed. If Friedman's test showed significant changes over time (two-sided $P < 0.05$), post-hoc testing with Dunn's method was used to find where in the time series statistical differences were significant. If the tests for normal distribution and equal variance were passed, one-way repeated measures (RM) ANOVA was performed, and if significant ($P < 0.05$), post-hoc pairwise comparisons using the Holm-Sidak method were made. Comparisons between pregnant and nonpregnant women were performed with the two-way RM ANOVA or the Mann-Whitney *U* test, depending on the distribution of data. To correct for possible differences in baseline values between the groups, we created and compared Δ-values. Each Δ-value denotes the difference in change from the particular time point to baseline (for example, T3 minus TB, denoted ΔT3). Categorical data were compared with Fisher's exact test.

Table 2. Patient characteristics and baseline measurements.

	Pregnant (n=24) Mean (SD) Median (range)	**Nonpregnant (n=24)** Mean (SD) Median (range)	***P* value**
Age, years	30.1 (4.2) 30 (19 – 37)	26.5 (2.2) 26.5 (23 – 33)	<0.001
Smoker, yes/no	1/23	2/22	1.0
Body mass index, kg/m^2	26.9 (3.8) 25.2 (20.0 – 35.0)	21.4(2.7) 20.7 (18.0 – 26.9)	<0.001
Gestational week	33.5 (2.1) 34 (29 – 38)	-	-
Mean arterial blood pressure, mmHg	85.3 (8,5) 85,7 (69,7 – 96,3)	83.0 (9.2) 82 (68 – 115)	0.2
Heart rate, bpm	85.3 (12.1) 87 (56 – 111)	66.0 (12.1) 67.5 (33 – 85)	<0.001#
SaO_2 (%)	97.8 (1.5) 98 (94 – 100)	99.1 (1.0) 99 (97 – 100)	<0.001
ST-index I	0.20 (0.17) 0.20 (-0.20 – 0.50)	0.24 (0.16) 0.2 (0 – 0.6)	0.4#
ST-index II	0.17 (0.36) 0.20 (-0.60 – 1.20)	0.25 (0.38) 0.25 (-0.8 – 1.0)	0.3
ST-index V5	0.03 (0.16) 0.00 (-0.30 – 0.30)	0.22 (0.58) 0.26 (-0.50 – 0.7)	0.01
AI	-0.60 (0.26) -0.61 (-1.08 – 0.12)	-0.70 (0.19) -0.71 (-1.08 – -0.28)	0.2#
b/a	-0.66 (0.07) -0.65 (-0.82 – -0.53)	-0.69 (0.10) -0.68 (-0.94 – -0.52)	0.3# 0.3
d/a	-0.14 (0.09) -0.12 (-0.32 – 0.00)	-0.19 (0.09) -0.20 (-0.40 – 0.00)	0.09# 0.09
DI	0.54 (0.16) 0.53 (0.26 – 0.83)	0.75 (0.17) 0.81 (0.34 – 0.95)	<0.001#
EEI	0.94 (0.25) 0.89 (0.63 – 1.40)	0.76 (0.30) 0.75 (0.00 – 1.52)	0.02
ETc	348.7 (35.8) 359.0 (249.0 – 401.0)	336.0 (30.4) 335.5 (255.0 – 399.0)	0.2#
PH	6.15 (2.60) 6.26 (1.18 – 11.46)	2.85 (1.83) 2.24 (0.68 – 6.49)	<0.001#

For explanation of variables, se Table 1.
Fisher's exact test were used for categorical data; The unpaired *t*-test was used for normally distributed variables (indicated with #) and the Mann-Whitney *U* test for skewed distributions.

Table 3. Number of women at each measurement point of nitrous oxygen (N_2O) inhalation.

	TB	**T1**	**T3**	**T5**	**T10**
N_2O 30% nonpregnant	24	24	24	24	24
N_2O 30% pregnant	24	24	24	24	24
N_2O 50% nonpregnant	24	22	22	22	22
N_2O 50% pregnant	24	17	14	13	13

TB, time of basal measurement; T1, measurement after 1 min of N_2O inhalation; T3, measurement after 3 min; T5, measurement after 5 min; T10, measurement 5 min after cessation of N_2O.

RESULTS

For demographic characteristics and basal recordings at TB, see Table 2. There was one dropout in each group. Pregnant women were older and heavier than nonpregnant women, and at basal recordings, HR, SaO_2, ST-index lead V, PH, DI, and EEI were significantly different between the groups: higher pulse, lower O_2 saturation, lower ST index in lead V5, and lower vascular tonus in pregnant women.

Twenty-four women in each group completed the 30/70% breathing experiment. Both pregnant and nonpregnant women experienced side effects from breathing N_2O, most commonly euphoria, dizziness, nausea, feelings of unpleasantness, and loss of control. These sensations were aggravated as the N_2O fraction was augmented to 50%. Women in the pregnant group were generally more prone to unpleasant side effects, to the extent that 11 women in this group did not manage to complete the full sequence breathing 50% N_2O. In the nonpregnant group, all but two women completed that part of the experiment (Table 3).

For hemodynamic variables, the most prominent changes were seen at T3 and T5 (Tables 4 and 5 and Figures 1 – 4). In nonpregnant women, HR and MAP remained unchanged regardless of N_2O fraction, whereas in pregnant women, both HR and MAP decreased during 30% N_2O inhalation, but not during 50% N_2O. There were no clinically significant ECG ST segment changes (>0.5 mm) detected in any woman.

Oxygen saturation increased significantly in both groups during 30/70% and 50/50% inhalations. Rises in AI, *b/a*, and PH, and lowerings in EEI and *d/a* were seen in both groups. All longitudinal results are displayed in detail in Tables 4-5, supplementary tables 7-8, and graphically in Figure 1.

Comparisons of Δ-values at T3 (ΔT3) during the 30/70% inhalations reveal that pregnant women exhibit a drop in HR not present among the nonpregnant, and pregnant women show a significantly larger increase in PH (Table 6 and Figures 1 and 2). During the 50/50% inhalations, ETc transiently fell in the pregnant group but increased in the nonpregnant group, while DI increased more in the pregnant group (Table 6).

Table 4. Cardiovascular effects of 30% and 50% N_2O inhalation during 5 min in pregnant women. Measurements were performed before inhalation (basal, TB), after 1 min (T1), 3 min (T3), 5 min (T5), and 5 min after stopping inhalation (T10). Figures denote *P* values and arrows (↑↓) direction of change. For explanation of variables, see Table 1. For descriptive statistics, see supplementary table 7.

Variable	Before-during-after N_2O	Before-during N_2O	Before-during N_2O			Before-after N_2O	Interpretation
	ANOVA TB-T1-T3-T5-T10	ANOVA TB-T1-T3-T5	TB-T1	TB-T3	TB-T5	TB-T10	
AI 30%	<0.001[b]	0.002[b]	(↑ 0.06) 0.1	↑ <0.001 ↑ 0.001	↑ 0.001 ↑ 0.01	1.0 -	Vasoconstriction
AI 50%	<0.001[b]	0.002[b]	1.0 0.6	↑ 0.04 ↑ 0.01	↑ 0.01 ↑ 0.002	1.0	Vasoconstriction
***b/a* 30%**	<0.001[b]	<0.001[b]	0.1 0.2	↑ <0.001 ↑ <0.001	↑ <0.001 ↑ <0.001	1.0	Large artery vasoconstriction
***b/a* 50%**	0.2[b]	0.3[b]	-	-	-	-	*No effect*
***d/a* 30%**	<0.001[b]	<0.001[b]	↓ 0.03 ↓ 0.03	↓ 0.002 ↓ 0.002	↓ 0.01 ↓ 0.03	1.0	Small artery vasoconstriction
***d/a* 50%**	0.002[b]	0.02[b]	↓ 0.03 ↓ 0.02	0.3 0.2	↓ 0.02 ↓ 0.01	1.0	Small artery vasoconstriction
DI 30%	0.03[b]	0.01[b]	↑ 0.04 ↑ 0.04	0.3 0.3	1.0 1.0	1.0	Small artery vasoconstriction
DI 50%	0.006[b]	0.04[b]	↑ 0.01 ↑ 0.02	0.7 0.6	1.0 1.0	↑ 0.014	Small artery vasoconstriction
EEI 30%	<0.001[b]	0.001[b]	0.08 0.1	↓ <0.001 ↓ 0.001	↓ 0.009 ↓ 0.003	1.0	Decreased LV power/ Large artery vasoconstriction
EEI 50%	0.03[b]		↓ 0.044	0.2	↓ 0.031	1.0	Decreased LV power/ Large artery vasoconstriction
ETc 30%	0.5[b]		-	-	-	-	*No effect*
ETc 50%	0.08[b]		-	-	-	-	*No effect*
HR 30%	<0.001[b]	*P* <0.001[b]	(↓ 0.055) 0.1	↓ <0.001 ↓ 0.001	↓ 0.001 ↓0.004	1.0	Decreased HR

HR 50%	0.4[b]	0.3[b]	- -	- -	- -	-	*No effect*
MAP 30%	0.007[b]	0.005[b]	0.8 1.0	0.1 0.1	↓ 0.006 ↓ 0.004	1.0	Decreased MAP
MAP 50%	0.03[b]	0.1[b]	1.0 -	0.9 -	0.4 -	1.0	*No effect*
PH 30%	<0.001[a]	<0.001[a]	0.2 0.11	↑ 0.02 ↑ 0.01	↑ <0.001 ↑ <0.001	0.9	Peripheral vasodilation
PH 50%	0.005[b]	0.02[b]	1.0 1.0	1.0 1.0	↑ 0.01 ↑ 0.02	1.0	Peripheral vasodilation
SaO_2 30%	<0.001[b]	<0.001[b]	↑ <0.001 ↑ <0.001	↑ <0.001 ↑ <0.001	↑ 0.001 ↑ <0.001	1.0	Increased oxygenation
SaO_2 50%	0.002[b]	0.003[b]	↑ 0.047 ↑ 0.02	0.1 (↑ 0.053)	0.4 0.2	1.0	Increased oxygenation
ST index I 30%	0.5[a]	0.5[a]	- -	- -	- -	-	*No effect*
ST index I 50%	0.3[b]	0.2[b]	- -	- -	- -	-	*No effect*
ST index II 30%	0.4[b]	0.9[b]	- -	- -	- -	-	*No effect*
ST index II 50%	0.04[b]	0.5[b]	1.0 -	1.0 -	1.0 -	0.13	*No effect*
ST index V5 30%	0.3[a]	0.3[a]	- -	- -	- -	-	*No effect*
ST index V5 50%	0.7[b]	0.5[b]	- -	- -	- -	-	*No effect*

a) Normal distribution (Shapiro-Wilk and Brown-Forsythe test passed): One-way repeated measurements analysis of variance (ANOVA) with Holm-Sidak post-hoc test was used.
b) Skewed distribution (Shapiro-Wilk or Brown-Forsythe test failed) or fewer than 20 subjects at some observation: Friedman's nonparametric repeated measurements ANOVA was used with Dunn's post hoc test.

Table 5. Cardiovascular effects of 30% and 50 % N_2O inhalation during 5 min in nonpregnant women. Measurements were performed before inhalation (basal, TB), after 1 min (T1), 3 min (T3), 5 min (T5), and 5 min after stopping inhalation (T10). Figures denote *P* values and arrows direction of change. For explanation of variables, see Table 1. For descriptive statistics, see supplementary table 8.

Variable	Before-during-after N_2O	Before-during N_2O	Before-during N_2O			Before-after N_2O	Interpretation
	ANOVA TB-T1-T3-T5-T10	ANOVA TB-T1-T3-T5	TB-T1	TB-T3	TB-T5	TB-T10	
AI 30%	<0.001[b]	<0.001[b]	1.0 1.0	↑ 0.02 ↑ 0.02	↑ 0.002 ↑ 0.002	1.0	Vasoconstriction
AI 50%	<0.001[b]	<0.001[b]	0.7 0.3	↑ <0.001 ↑ <0.001	↑ 0.003 ↑ 0.001	1.0	Vasoconstriction
***b/a* 30%**	<0.001[a]	0.002[a]	0.9 0.7	0.2 0.2	↑ 0.007 ↑ 0.006	0.9	Large artery vasoconstriction after 5 min
***b/a* 50%**	0.01[a]	0.03[a]	0.4 0.2	0.2 0.07	(↑ 0.057) ↑ 0.02	0.5	Large artery vasoconstriction after 5 min
***d/a* 30%**	0.08[b]	0.08[b]	- -	- -	- -	-	No effect
***d/a* 50%**	0.02[b]	0.016[b]	0.10 0.14	↓ 0.005 ↓ 0.007	0.9 0.9	0.7	Small artery vasoconstriction
DI 30%	0.01[b]	0.005[b]	0.2 0.2	0.4 0.3	1.0 0.7	0.8	*No effect*
DI 50%	0.005[b]	0.001[b]	↑ 0.045 ↑ 0.04	1.0 0.9	1.0 1.0	1.0	Small artery vasoconstriction
EEI 30%	0.03[b]	0.03[b]	0.4 0.2	↓ 0.02 ↓ 0.009	0.3 0.2	1.0	Decreased left ventricular ejection power/Large artery vasoconstriction
EEI 50%	0.2[b]	0.04[b]	- 0.2	- ↓ 0.04	- (↓ 0.051)	-	Decreased left ventricular ejection power/Large artery vasoconstriction
ETc 30%	0.6[b]	0.6[b]	- -	- -	- -	-	*No effect*
ETc 50%	0.08[b]	0.03[b]	- 1.0	- (↑ 0.059)	- 0.2	-	*No effect*
HR 30%	0.4[b]	0.2[b]	- -	- -	- -	-	*No effect*
HR 50%	0.08[b]	0.3[b]	-	-	-	-	*No effect*
MAP 30%	0.1[b]	0.3[b]	- -	- -	- -	-	*No effect*

MAP 50%	0.08[b]	0.6[b]	- -	- -	- -	-	*No effect*
PH 30%	<0.001[a]	<0.001[a]	↓ 0.045 ↓ 0.03	0.8 0.8	↑ <0.001 ↑ <0.001	0.5	Initial peripheral vasoconstriction, later vasodilation
PH 50%	<0.001[a]	<0.001[a]	0.5 0.5	(↑ 0.076) ↑ 0.04	↑ 0.002 ↑ <0.001	0.4	Peripheral vasodilation
SaO_2 30%	<0.001[b]	<0.001[b]	↑ 0.008 ↑ 0.004	↑ 0.008 ↑ 0.004	↑ 0.01 ↑ 0.008	1.0	Increased oxygenation
SaO_2 50%	<0.001[b]	<0.001[b]	↑ 0.007 ↑ 0.003	↑ 0.02 ↑ 0.01	0.09 0.07	1.0	Increased oxygenation
ST index I 30%	0.9[b]	0.9[a]	-	-	-	-	*No effect*
ST index I 50%	0.8[b]	0.6[a]	-	-	-	-	*No effect*
ST index II 30%	0.7[b]	0.8[a]	-	-	-	-	*No effect*
ST index II 50%	0.1[b]	0.1[b]	-	-	-	-	*No effect*
ST index V5 30%	0.4[a]	0.2[a]	-	-	-	-	*No effect*
ST index V5 50%	0.6[a]	0.7[a]	-	-	-	-	*No effect*

a) Normal distribution (Shapiro-Wilk test): One-way repeated measurements analysis of variance (ANOVA) with Holm-Sidak post-hoc test was used.
b) Skewed distribution: Friedman's nonparametric repeated measurements ANOVA was used with Dunn's post hoc test.

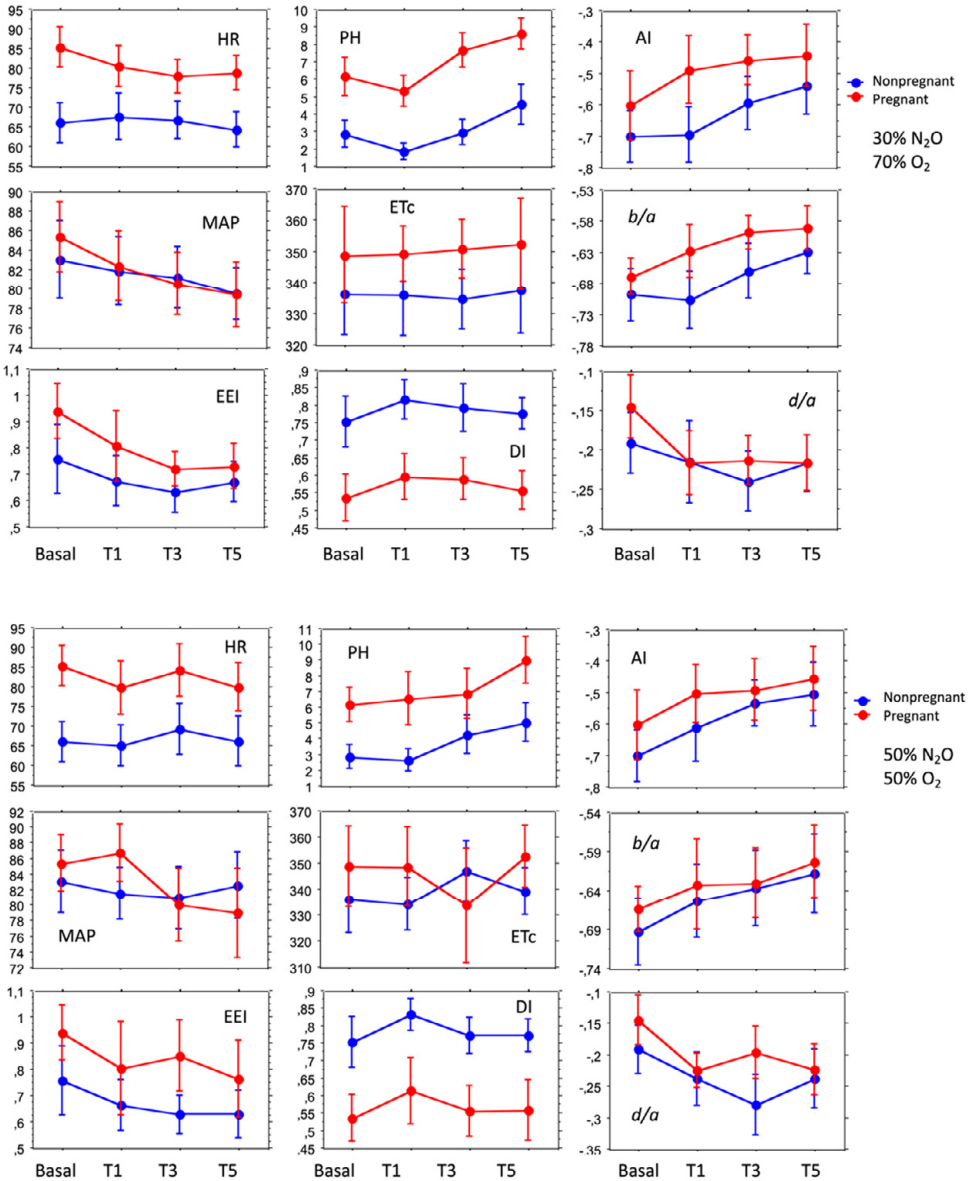

Figure 1. Cardiovascular effects of inhalation of 30% N_2O (above) and 50% N_2O (below) in 24 third-trimester healthy pregnant women and 24 healthy nonpregnant women of fertile age. Measurements of heart rate (HR, bpm), mean arterial blood pressure (MAP, mmHg), and digital photoplethysmographic (PPG) pulse wave analysis of cardiac ejection elasticity index (EEI), pulse height (PH), left ventricular ejection time compensated (ETc, ms), dicrotic index (DI), and the second derivative (APG) indices ageing index (AI), *b/a*, and *d/a* of the crude digital pulse wave curve contour were performed before nitrous oxide inhalations (Basal), and after 1 min (T1), 3 min (T3), and 5 min (T5). Mean values with 95% confidence interval.

Table 6. Comparison of changes between pregnant and nonpregnant women from basal measurements to 3 min (denoted ΔT3) of 30% and 50% nitrous oxide inhalation, respectively.

Variable	ΔT3 in nonpregnant Median (range)	ΔT3 in pregnant Median (range)	*P* value	Interpretation
AI 30%	0.135 (0.71)	0.175 (1.47)	0.4	No difference
AI 50%	0.160 (0.39)	0.125 (0.86)	0.5	No difference
***b/a* 30%**	0.050 (0.42)	0.060 (0.37)	0.7	No difference
***b/a* 50%**	0.050 (0.52)	0.030 (0.23)	0.5	No difference
***d/a* 30%**	0.045 (0.37)	0.070 (0.42)	0.5	No difference
***d/a* 50%**	0.090 (0.50)	0.050 (0.37)	0.5	No difference
DI 30%	0.020 (1.17)	0.035 (0.52)	0.4	No difference
DI 50%	-0.020 (0.64)	0.070 (0.30)	0.047	↑ in pregnant
EEI 30%	-0.140 (1.21)	-0.220 (0.89)	0.1	No difference
EEI 50%	-0.055 (1.03)	-0.235 (0.65)	0.3	No difference
ETc 30%	-4.00 ms (173)	2.00 ms (206)	0.7	No difference
ETc 50%	12.50 ms (155)	-11.00 ms (162)	0.004	↓ in pregnant
HR 30%	1 bpm (34)	-6 bpm (39)	0.003	↓ in pregnant
HR 50%	0.5 bpm (49)	-5.5 bpm (52)	0.1	No difference
MAP 30%	-0.7 mmHg (24)	-5.7 mmHg (22)	0.2	No difference
MAP 50%	0.3 mmHg (53)	-1.7 mmHg (21)	0.5	No difference
PH 30%	0.29 (9.11)	1.80 (12.03)	0.04	↑ in pregnant
PH 50%	0.56 (10.87)	0.28 (7.60)	0.7	No difference
SaO_2 30%	100% (3)	100% (6)	0.1	No difference
SaO_2 50%	100% (4)	100% (2)	0.09	No difference

Statistical analyses with Mann-Whitney *U* test.

DISCUSSION

The study showed that inhalation of N_2O/O_2 for 5 minutes in mixtures of 30/70% and 50/50% had hemodynamic effects in both pregnant and nonpregnant women. Vasoconstriction occurred in both large and small arteries, as indicated by all DPA variables except PH (pulse height). PH increased in both groups, which relates to blood flow in small finger arteries and to cardiac LV ejection performance, stroke volume, and large artery distensibility.[18] DPA variables reflecting LV ejection performance are EEI (cardiac ejection elasticity index) and ETc (LV ejection time compensated). ETc was not affected by N_2O in any group, but in both groups, EEI decreased. EEI is an index for LV ejection capacity and compliance/elasticity of large arteries, and a decrease then reflects decreased LV ejection power and large artery vasoconstriction. The PH and EEI changes thus seem contradictory, but it is notable that at 1 min, PH indicated vasoconstriction during the 30/70% inhalation.

Circulatory physiological changes seen in late pregnancy were reflected in our measurements at baseline. DPA indicated a lower DI and a higher PH, EEI, and ETc in the pregnant group. Higher PH and lower DI suggest peripheral vasodilation and possible hyperemic circulation; higher EEI suggests large artery vasodilation; and higher ETc suggests lower afterload or increased preload.[20] However, the global vascular stiffness measure ageing index (AI) and MAP were similar between groups, indicating that the dignity of the vasodilation in the pregnant group is compensated for by increased HR and increased plasma volume.[21]

The hemodynamic effects of N_2O might seem slightly ambiguous, as some effects were seen after 30% N_2O but not after 50%, and all variables did not change in the same direction. However, the changes in *b/a*, *d/a*, DI, EEI, and AI indicate both small and large artery vasoconstriction and a possible decrease in cardiac LV power. A special note is given to the variable *d/a*, as it has been shown to change in response to vasoactive drugs like angiotensin and glyceryl trinitrate, while *b/a* did not change.[22] The ST indices and the cardiac marker ETc remained basically unchanged. In opposition, there was a rise in PH. A low value of PH is usually seen in conditions with low circulation in the fingertips, such as dehydration, caffeine use, Raynaud's phenomenon, or cold fingers; high values are seen in conditions with less sympathetic tone, warm fingers, or good peripheral perfusion.[23] Our interpretation is that vasoconstriction of both large and small arteries dominates, as the rise in PH may be influenced by many factors, such as locally improved circulation in the finger and the use of heat pads to warm cold hands to enable DPA recordings.[24]

The effects differed more between pregnant and nonpregnant groups than we expected. During 30% N_2O, MAP, HR, and *d/a* decreased in the pregnant group but remained unchanged in the nonpregnant group. The nonpregnant needed 50% N_2O to have a negative effect on *d/a*, while MAP and HR remained unchanged.

Furthermore, the comparison of Δ-values at T3 (ΔT3) shows that vasoconstrictive effects on small arteries are more pronounced in the pregnant group. Vasoconstriction results in higher systemic vascular resistance (SVR) and a higher afterload, which may result in a reduction in stroke volume (SV) and a shortening of LV ejection time, corresponding to a lower ETc.[25] ΔETc was in fact significantly lower in the pregnant group after 3 min of 50% N_2O inhalation. This might be a coinciding finding, considering the high dropout rate during the 50% measurements, but it raises some concern that the heart in pregnant women might be affected by the vasoconstrictive effects of 50% N_2O.

Pregnant women had a lower vascular tonus at baseline, and they were more prone to vasoconstriction from N_2O than the nonpregnant group. Thus, it seems that pregnant women vasoconstrict more easily from their vasodilated state. The oxygen fraction might contribute to these effects, as oxygen has been shown to have vasoconstrictive effects.[17,26] Pregnant women are more susceptible to hemodynamic reactions from oxygen than nonpregnant women. In fact, a common methodological problem in studies with N_2O inhalation is that controls breathe room air while N_2O is mixed with pure oxygen. This might bias the result, as oxygen itself affects cardiovascular parameters.[27,28] Mixing N_2O with ambient room air is not considered safe as it may jeopardize oxygenation.[29]

Effects previously attributed to N_2O include increased sympathetic efferent activity, depressed baroreflex-mediated tachycardia, and weak but dose-dependent negative inotropic effects.[13,14] However, an increase in pulmonary vascular resistance from N_2O has not been shown.[14,30] Quite a few studies with somewhat conflicting results have been published regarding effects on cerebral blood flow (CBF) and cerebral metabolism rate (CMR).[31] In healthy individuals, normocapnic exposure to 50% N_2O increased CBF but did not change cerebral blood volume (CBV) or CMR.[32–34] N_2O does not have any effects on isolated human pial arteries in vitro, suggesting that vasodilation causing increased CBF in vivo is secondary to the release of other mediators. Strong efforts have been made to identify such mediators, but the results are inconsistent. Altered CBF or changes in hemodynamic variables in awake humans may be secondary to other side effects, such as pain relief, nausea, emotional effects, and drowsiness.[15,35]

In pregnant women, we found only two studies evaluating the cardiovascular effects of N_2O. Westling and colleagues used impedance cardiography to evaluate cardiac stroke volume (SV) together with HR and BP in parturients breathing N_2O/O_2 during the first stage of labor.[15] They compared the effects of different gas mixtures, ranging from 0 to 70% N_2O. Hemodynamic variables were recorded during and between uterine contractions. Higher concentrations of inhaled N_2O resulted in lower pain scores, lower HR, lower cardiac output (CO), lower arterial pressure, but a higher SV. The relative increase in CO that normally occurs during contractions was attenuated by N_2O. They conclude that pain relief in itself probably plays a major part in explaining the results.[15] On the other hand, Polvi and coworkers, using

Doppler ultrasound velocimetry on the carotid artery, observed that maternal inhalation of 30% N_2O caused a decreased central vascular resistance in both mother and fetus.[16] Their study was not on laboring women, thus eliminating pain relief as a confounding factor. Still, their conclusions have been challenged due to methodological problems.[36]

In fact, many study results concerning the multitude of effects of N_2O are conflicting. The literature contains in vitro and in vivo studies in both animals and humans, often producing different and sometimes even opposite results. Many studies are very small. Furthermore, many investigations were conducted during general anesthesia with the co-administration of other medications, including O_2, as well as concomitant surgery, blurring the overall picture. Considering possible adverse cardiovascular effects from N_2O, the ENIGMA-II trial was conducted to ultimately establish whether N_2O affects perioperative cardiovascular risk or not. This study randomized 7112 cardiac at-risk patients having non-cardiac non-neurosurgery to receive N_2O or not during anesthesia. Their conclusion was that N_2O administration did not increase the risk of death, cardiovascular complications, or surgical-site infection.[37]

Our results are basically in harmony with the earlier described findings. What we did not know previously is that pregnant women seem more sensitive to N_2O than nonpregnant women, not only hemodynamically but also experiencing more adverse side effects, resulting in a higher dropout rate.

Strengths and limitations

The high dropout rate among pregnant women breathing N_2O at 50% resulted in low statistical power in this part of the experiment. Another limitation is that while breathing 30% N_2O, the women were also breathing 70% O_2. As previously shown, O_2 has vasoconstrictive effects that might have impacted the N_2O effects.[26,38–40] That might be the reason why some vasoactive effects were actually stronger during 30% N_2O than during 50%, as the oxygen fraction is smaller in the 50% group (50% vs. 70% O_2). Furthermore, the central sedative or behavioral effects of N_2O could attenuate the vasoactive effects as concentrations of N_2O rise. Such confounding is present in many studies when performed under general anesthesia. We do not consider it likely that changes in carbon dioxide could have contributed to the cardiovascular effects[41], since other studies failed to show any difference in pCO_2 in subjects inhaling N_2O.[42] The women were carefully instructed and monitored on breathing technique, but we had no resources to control end-tidal gas concentrations in this study setting.

The inhalation time spent during labor has previously been shown to be rather short, often about 1 min.[42] At that time, significant cardiovascular effects were scarce, but more prominent after 3 and 5 min. During active labor, many parturients also inhale N_2O in between uterine contractions, and some experience short intermissions due

to long contractions, making inhalation times longer. We thus considered group comparisons after 3 min of inhalation clinically relevant.

In many clinical situations, N_2O is used with longer inhalation times. The rate and time of N_2O uptake are dependent on pulmonary, ventilatory, and circulatory factors. Subjective effects are already experienced after 30 s, and it has been shown that within 3-5 min, 90% of the inhaled fraction of N_2O has reached the alveoli.[43] In our study, T3 and T5 results were quite similar, indicating that maximal effects were already reached after 3 min.

No woman experienced any drop in O_2 saturation. In fact, saturation rose in both groups. Worries of hypoxic events or desaturations from N_2O treatment in pregnant women during labor have been expressed,[42] but that was clearly not the case in our setting. Interestingly, maternal desaturation can occur during labor regardless of N_2O use.[44]

The DPA method for PW analyses in the present setting is not yet widely used, the literature is scarce, and the interpretation of the DPA indices is sometimes challenging. The method has hitherto been used in studies for the evaluation of hypertensive disorders, vascular age, and pharmacological studies.[18,20,22,45–49] Missing values from movement artifacts or cold fingers can be a problem, but due to quite vigorous preparations, including warming of cold hands, we had very few missing DPA values in this study.

Conclusion

This study showed that pregnant women were more sensitive to N_2O than nonpregnant women, both in terms of subjective side effects and hemodynamic changes. N_2O caused vasoconstriction in both large and small arteries, with a pattern of change that may indicate a negative inotropic effect. HR and MAP were basically unaffected in nonpregnant women but decreased in pregnant women. Some of the hemodynamic effects ascribed to N_2O might, however, be effects of the high oxygen fraction in the inhaled gas, as we have previously demonstrated vasoconstrictive and possibly negative inotropic effects from hyperoxygenation. Our findings can have implications for parturients with heart disease or vasoconstrictive states, such as hypovolemia and preeclampsia, where caution is warranted.

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Supplementary Table 7. Pregnant women. Descriptive statistics from the N_2O study. Mean, median, range and 95 % confidence intervals (CI) of all variables. Statistically significant changes vs TB are marked in bold (see table 4 for *P*-values).

Variable	TB	T1	T3	T5	T10
AI 30% Mean (CI) Median (range)	n = 24 -0.60 (0.11) -0.62 (-1.08 – 0.12)	n = 24 -0.49 (0.11) -0.44 (-1.06 – 0.0)	**n = 24** **-0.46 (0.08)** **-0.48 (-0.71 – -0.11)**	**n = 24** **-0.44 (0.10)** **-0.50 (-0.79 – 0.17)**	n = 24 -0.54 (0.11) -0.54 (-0.88 – -0.01)
AI 50% Mean (CI) Median (range)	n = 24 -0.60 (0.11) -0.62 (-1.08 – 0.12)	n = 17 -0.50 (0.09) -0.48 (-0.80 – -0.21)	**n = 14** **-0.49 (0.10)** **-0.50 (-0.79 – -0.25)**	**n = 13** **-0.46 (0.10)** **-0.41 (-0.69 – -0.17)**	n = 17 -0.67 (0.08) -0.64 (-0.94 – -0.44)
***b/a* 30%** Mean (CI) Median (range)	n = 24 -0.66 (0.03) -0.65 (-0.82 – -0.53)	n = 24 -0.62 (0.04) -0.62 (-0.82 – 0.43)	**n = 24** **-0.59 (0.03)** **-0.60 (-0.71 – -0.47)**	**n = 24** **-0.59 (0.03)** **-0.60 (-0.71 – -0.38)**	n = 24 -0.64 (0.03) -0.63 (-0.81 – -0.48)
***b/a* 50%** Mean (CI) Median (range)	n = 24 -0.66 (0.03) -0.65 (-0.82 – -0.53)	n = 17 -0.63 (0.06) -0.61 (-0.84 – -0.47)	n = 14 -0.63 (0.04) -0.62 (-0.82 – -0.53)	n = 13 -0.60 (0.05) -0.61 (-0.69 – -0.42)	n = 17 -0.68 (0.03) -0.66 (-0.77 – -0.57)
***d/a* 30%** Mean (CI) Median (range)	n = 24 -0.14 (0.04) -0.12 (-0.32 – 0.0)	**n = 24** **-0.22 (0.04)** **-0.22 (-0.43 – -0.03)**	**n = 24** **-0.21 (0.03)** **-0.22 (-0.35 – -0.09)**	**n = 24** **-0.22 (0.04)** **-0.20 (-0.39 – -0.05)**	n = 24 -0.16 (0.03) -0.16 (-0.32 – -0.04)
***d/a* 50%** Mean (CI) Median (range)	n = 24 -0.14 (0.04) -0.12 (-0.32 – 0.0)	**n = 17** **-0.22 (0.03)** **-0.23 (-0.30 – -0.06)**	n = 14 -0.20 (0.04) -0.20 (-0.38 – -0.09)	**n = 13** **-0.22 (0.04)** **-0.23 (-0.38 – -0.12)**	n = 17 -0.15 (0.03) -0.16 (-0.25 – -0.0)
DI 30% Mean (CI) Median (range)	n = 24 0.54 (0.07) 0.53 (0.26 – 0.83)	**n = 24** **0.60 (0.07)** **0.62 (0.33 – 0.86)**	n = 24 0.59 (0.06) 0.60 (0.33 – 0.84)	n = 24 0.56 (0.06) 0.54 (0.32 – 0.81)	n = 24 0.56 (0.07) 0.58 (0.27 – 0.83)
DI 50% Mean (CI) Median (range)	n = 24 0.54 (0.07) 0.53 (0.26 – 0.83)	**n = 17** **0.61 (0.10)** **0.63 (0.32 – 0.91)**	n = 14 0.56 (0.07) 0.58 (0.38 – 0.80)	n = 13 0.56 (0.09) 0.56 (0.32 – 0.78)	**n = 17** **0.62 (0.08)** **0.60 (0.35 – 0.89)**
EEI 30% Mean (CI) Median (range)	n = 24 0.94 (0.10) 0.89 (0.63 – 1.40)	n = 24 0.81 (0.14) 0.72 (0.36 – 1.61)	**n = 24** **0.72 (0.07)** **0.72 (0.47 – 1.09)**	**n = 24** **0.73 (0.09)** **0.72 (0.31 – 1.05)**	n = 24 0.90 (0.13) 0.86 (0.48 – 1.78)
EEI 50% Mean (CI) Median (range)	n = 24 0.94 (0.10) 0.89 (0.63 – 1.40)	**n = 17** **0.80 (0.18)** **0.72 (0.44 – 1.68)**	n = 14 0.85 (0.14) 0.83 (0.55 – 1.45)	**n = 13** **0.76 (0.15)** **0.79 (0.39 – 1.36)**	n = 17 0.86 (0.08) 0.83 (0.59 – 1.21)

ETc 30% (ms)	n = 23	n = 24	n = 24	n = 24	n = 24
Mean (CI)	348.7 (15.5)	349.2 (8.9)	350.8 (9.4)	352.3 (14.5)	347.4 (14.2)
Median (range)	359 (249-401)	346 (309-400)	352 (314-391)	358 (214-396)	353 (241-394)
ETc 50% (ms)	n = 23	n = 17	n = 14	n = 13	n = 17
Mean (CI)	348.7 (15.5)	348.5 (15.2)	333.6 (22.0)	352.6 (11.9)	345.1 (12.9)
Median (range)	359 (249-401)	352 (295-396)	320 (228-368)	359 (318-376)	348 (295-397)
HR 30% (bpm)	n = 24	n = 24	**n = 24**	**n = 24**	n = 24
Mean (CI)	85.3 (5.1)	80.4 (5.3)	**77.9 (4.2)**	**78.7 (4.3)**	83.4 (4.9)
Median (range)	87.0 (56-111)	75.5 (64-104)	**77.5 (53-99)**	**76.5 (55-95)**	82.0 (60-103)
HR 50% (bpm)	n = 24	n = 17	n = 14	n = 13	n = 17
Mean (CI)	85.3 (5.1)	79.8 (6.8)	84.2 (6.7)	79.8 (6.1)	81.2 (5.1)
Median (range)	87.0 (56-111)	77.0 (60-103)	79.5 (70-109)	76.0 (68-98)	79.0 (63-96)
MAP 30% (mmHg)	n = 24	n = 24	n = 24	**n = 23**	n = 23
Mean (CI)	85.3 (3.6)	82.3 (3.6)	80.5 (3.2)	**79.4 (3.3)**	83.7 (2.9)
Median (range)	85.7 (69.7 –96.3)	83.7 (63.3 – 98.0)	81.3 (62.3 – 98.3)	**82.0 (61.3 – 91.7)**	84.7 (61.3 – 93.3)
MAP 50% (mmHg)	n = 24	n = 16	n = 13	n = 12	n = 16
Mean (CI)	85.3 (3.6)	86.7 (3.6)	80.0 (4.6)	79.0 (5.8)	84.8 (3.9)
Median (range)	85.7 (69.7 –96.3)	86.0 (77.0 – 97.7)	79.3 (66.0 – 95.7)	78.0 (65.0 – 99.3)	86.7 (67.7 – 96.3)
PH 30%	n = 24	n = 24	**n = 24**	**n = 24**	n = 24
Mean (CI)	6.15 (1.10)	5.30 (0.89)	**7.66 (0.99)**	**8.58 (0.89)**	6.23 (1.32)
Median (range)	6.26 (1.18 – 11.5)	4.90 (2.48 – 10.4)	**6.84 (4.91 – 12.0)**	**8.48 (5.47 – 12.6)**	5.98 (0.62 – 15.0)
PH 50%	n = 24	n = 17	n = 14	**n = 13**	n = 17
Mean (CI)	6.15 (1.10)	6.54 (1.68)	6.85 (1.60)	**8.99 (1.49)**	5.39 (1.56)
Median (range)	6.26 (1.18 – 11.5)	7.19 (1.37 – 11.4)	5.94 (2.75 – 11.9)	**8.50 (6.01 – 13.4)**	5.13 (1.56-10.9)
SaO_2 30%	n = 24	**n = 24**	**n = 24**	**n = 24**	n = 24
Mean (CI)	97.7 (0.61)	**99.4 (0.46)**	**99.0 (0.60)**	**98.8 (0.75)**	97.5 (0.65)
Median (range)	98.0 (94-100)	**100.0 (96-100)**	**99.0 (95-100)**	**99.0 (93-100)**	98.0 (93-100)
SaO_2 50%	n = 24	**n = 16**	n = 13	n = 12	n = 16
Mean (CI)	97.7 (0.61)	**99.2 (0.60)**	98.7 (1.0)	98.4 (1.1)	97.1 (1.2)
Median (range)	98.0 (94-100)	**100.0 (97-100)**	99.0 (94-100)	99.0 (94-100)	98 (92-100)

Supplementary Table 8. Nonpregnant women. Descriptive statistics from the N_2O study. Mean, median, range and 95 % confidence intervals (CI) of all variables. Statistically significant changes vs TB are marked in bold (see table 4 for *P*-values).

Variable	TB	T1	T3	T5	T10
AI 30% Mean (CI) Median (range)	n=24 -0.70 (0.08) -0.71 (-1.08 – -0.28)	n=24 -0.70 (0.09) -0.71 (-1.08 – --0.19)	**n=24** **-0.60 (0.08)** **-0.60 (-0.95 – -0.14)**	**n=24** **-0.54 (0.09)** **-0.54 (-0.94 – -0.06)**	n=24 -0.69 (0.10) -0.70 (-1.12 – -0.17)
AI 50% Mean (CI) Median (range)	n=24 -0.70 (0.08) -0.71 (-1.08 – -0.28)	n=22 -0.61 (0.11) -0.64 (-1.08 – -0.06)	**n=22** **-0.53 (0.07)** **-0.55 (-0.83 – -0.18)**	**n=22** **-0.50 (0.10)** **-0.53 (-0.87 – -0.04)**	n=22 -0.72 (0.11) -0.70 (-1.32 – -0.35)
***b/a* 30%** Mean (CI) Median (range)	n=24 -0.69 (0.04) -0.68 (-0.94 – -0.52)	n=23 -0.70 (0.05) -0.69 (-0.94 – -0.49)	n=24 -0.66 (0.04) -0.66 (-0.87 – -0.46)	**n=24** **-0.62 (0.04)** **-0.63 (-0.77 – -0.48)**	n=23 -0.71 (0.05) -0.71 (-0.89 – -0.49)
***b/a* 50%** Mean (CI) Median (range)	n=24 -0.69 (0.04) -0.68 (-0.94 – -0.52)	n=22 -0.65 (0.05) -0.68 (-0.84 – -0.42)	n=22 -0.64 (0.05) -0.64 (-0.89 – -0.33)	**n=22** **-0.62 (0.05)** **-0.60 (-0.88 – -0.40)**	n=22 -0.70 (0.05) -0.68 (-1.20 – -0.55)
***d/a* 30%** Mean (CI) Median (range)	n=24 -0.91 (0.04) -0.20 (-0.40 – -0.0)	n=24 -0.22 (0.05) -0.25 (-0.45 – -0.10)	n=24 -0.24 (0.04) -0.25 (-0.42 – -0.05)	n=24 -0.22 (0.04) -0.22 (-0.42 – -0.02)	n=24 -0.19 (0.04) -0.18 (-0.36 – -0.03)
***d/a* 50%** Mean (CI) Median (range)	n=24 -0.91 (0.04) -0.20 (-0.40 – -0.0)	**n=22** **-0.24 (0.04)** **-0.24 (-0.41 – -0.06)**	**n=22** **-0.28 (0.05)** **-0.28 (-0.62 – -0.12)**	**n=22** **-0.24 (0.05)** **-0.23 (-0.50 – -0.01)**	n=22 -0.22 (0.04) -0.23 (-0.43 – -0.03)
DI 30% Mean (CI) Median (range)	n=23 0.75 (0.07) -0.81 (0.34 – -0.95)	n=24 0.82 (0.06) 0.86 (0.51 – -0.98)	n=24 0.79 (0.07) 0.85 (0.19 – 0.94)	n=24 0.78 (0.05) 0.78 (0.57 – 1.0)	n=23 0.80 (0.06) 0.84 (0.45 – 0.95)
DI 50% Mean (CI) Median (range)	n=23 0.75 (0.07) -0.81 (0.34 – -0.95)	**n=22** **0.83 (0.05)** **0.86 (0.63 – 1.0)**	n=22 0.77 (0.05) 0.81 (0.47 – 0.94)	n=22 0.77 (0.05) 0.78 (0.45 – 0.92)	n=22 0.78 (0.07) 0.85 (0.41 – 0.96)

EEI 30% Mean (CI) Median (range)	n=23 0.76 (0.13) 0.75 (0.0 – 1.52)	n=24 0.67 (0.09) 0.70 (0.18 – 1.10)	**n=24** **0.63 (0.08)** **0.59 (0.35 – 1.20)**	n=24 0.67 (0.08) 0.64 (0.44 – 1.02)	n=23 0.76 (0.13) 0.68 (0.0 – 1.38)
EEI 50% Mean (CI) Median (range)	n=23 0.76 (0.13) 0.75 (0.0 – 1.52)	n=22 0.66 (0.10) 0.66 (0.32 – 1.15)	**n=21** **0.63 (0.07)** **0.62 (0.24 – 0.93)**	n=22 0.63 (0.09) 0.60 (0.32 – 1.17)	n=22 0.70 (0.12) 0.62 (0.27 – 1.36)
ETc 30% (ms) Mean (CI) Median (range)	n=24 336 (12.8) 336 (255-399)	n=24 336 (13.0) 335 (255-389)	n=24 335 (9.7) 329 (290-383)	n=24 337 (13.8) 337 (240-417)	n=24 338 (18.8) 331 (240-506)
ETc 50% (ms) Mean (CI) Median (range)	n=24 336 (12.8) 336 (255-399)	n=23 334 (10.1) 332 (283-391)	n=22 347 (11.7) 341 (308-402)	n=22 339 (9.2) 336 (302-377)	n=22 331 (11.1) 324 (294-387)
HR 30% (bpm) Mean (CI) Median (range)	n=24 66.0 (5.1) 67.5 (33-85)	n=23 67.6 (5.9) 68.0 (33-95)	n=24 **66.7 (4.9)** **66.0 (43-87)**	n=24 **64.2 (4.4)** **61.5 (48-90)**	n=24 66.4 (5.3) 65.5 (46-104)
HR 50% (bpm) Mean (CI) Median (range)	n=24 66.0 (5.1) 67.5 (33-85)	n=23 65.0 (5.2) 65.0 (45-99)	n=22 69.1 (6.5) 65.5 (44-98)	n=22 66.1 (6.3) 63.0 (46-111)	n=22 63.8 (5.0) 59 (48-88)
MAP 30% (mmHg) Mean (CI) Median (range)	n=23 83.0 (4.0) 82.0 (68.0-115.3)	n=24 81.8 (3.5) 81.2 (66.0-98.7)	n=24 81.1 (3.2) 81.5 (71.3-101.7)	n=24 79.5 (2.7) 80.5 (66.0-90.7)	n=23 82.2 (2.6) 82.7 (72.0-92.0)
MAP 50% (mmHg) Mean (CI) Median (range)	n=23 83.0 (4.0) 82.0 (68.0-115.3)	n=23 81.5 (3.3) 82.0 (66.0-98.7)	n=22 80.9 (4.1) 80.8 (64.3-100.7)	n=22 82.5 (4.3) 82.7 (67.0-98.7)	n=22 85.3 (3.8) 84.5 (69.0-99.7)
PH 30% Mean (CI) Median (range)	n=24 2.85 (0.77) 2.24 (0.68-6.49)	**n=23** **1.83 (0.47)** **1.77 (0.59-4.55)**	n=24 2.94 (0.72) 2.58 (0.39-6.22)	**n=24** **4.54 (1.13)** **4.02 (0.53-10.35)**	n=24 2.38 (0.69) 2.16 (0.55-8.28)
PH 50% Mean (CI) Median (range)	n=24 2.85 (0.77) 2.24 (0.68-6.49)	n=23 2.63 (0.71) 2.07 (0.68-6.78)	**n=22** **4.24 (1.22)** **4.26 (0.83-10.3)**	**n=22** **5.02 (1.23)** **5.34 (0.87-9.65)**	n=22 2.32 (0.69) 1.74 (0.43-6.40)
SaO_2 30% Mean (CI) Median (range)	n=24 99.3 (0.41) 99.0 (97-100)	**n=24** **100.0 (0.0)** **100.0 (100-100)**	**n=24** **100.0 (0.0)** **100.0 (100-100)**	**n=24** **100.0 (0.09)** **100.0 (99-100)**	n=24 99.0 (0.56) 99.5 (96-100)
SaO_2 50% Mean (CI) Median (range)	n=24 99.3 (0.41) 99.0 (97-100)	**n=23** **100.0 (0.0)** **100.0 (100-100)**	**n=22** **99.9 (0.13)** **100.0 (99-100)**	n=22 99.8 (0.19) 100.0 (99-100)	n=22 98.6 (0.65) 99.0 (95-100)