Accuracy and trending abilities of finger plethysmographic blood pressure and cardiac output compared with invasive measurements during caesarean delivery in healthy women. An observational study.

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Abstract

Background: In women presenting for caesarean section under spinal anaesthesia, continuous measurement of circulatory aspects, such as blood pressure and cardiac output, is often needed. At present, invasive techniques are used almost exclusively. Reliable non-invasive monitors would be welcome, as they could be safer and less uncomfortable, while easy and quick to apply. We aimed to evaluate whether a non-invasive, finger plethysmographic device, the ccNexFin monitor, can replace invasively measured blood pressure in the radial artery, and whether cardiac output measurements from this device can be used interchangeably with measurements from the mini-invasive LiDCO monitor, currently in use at our institution.

Methods: Simultaneous invasive measurements were compared with ccNexFin in 23 healthy women during elective caesarean section under spinal anaesthesia. We used Bland Altman statistics for assessing agreement, and polar plot methodology for judging trending abilities with pre-defined limits.

Results: Mean arterial and systolic pressures showed biases (invasive - ccNexFin) of -4.3 and 12.2 mmHg, with limits of agreement of -15.9 - 7.4 and -11.1 - 35.6, respectively. The ccNexFin trending abilities were within suggested limits for mean pressure, but insufficient for systolic pressure compared with invasive measurements. Cardiac output had a small bias of 0.2 L/min, but wide limits of agreement of -2.6 - 3.0. The ccNexFin trending abilities compared with the invasive estimated values (LiDCO) were unsatisfactory.

Conclusions: We consider the ccNexFin monitor to have sufficient accuracy in measuring mean arterial pressures. The limits of agreement for systolic measurements were wider, and the trending ability, compared with invasive measurements, was outside the recommended limit. The ccNexFin is not reliable for cardiac output measurements or trend in pregnant women for caesarean delivery under spinal anaesthesia.

Background

In a normal pregnancy, large alterations in the circulatory physiology occur. Blood volume, stroke volume, heart rate and cardiac output (CO) increase. Blood pressure (BP) and peripheral resistance
decrease [1]. During caesarean section (CS), both spinal anaesthesia and administration of oxytocin can precipitate severe drops in peripheral arterial resistance and blood pressure. Vasopressors and inotropes are administered to counteract the changes in BP and CO [2]. Peroperatively, BP is usually measured intermittently using oscillatory devices, and changes of short duration are mostly unnoticed, even if they might be substantial. In healthy parturients, changes in BP and CO are usually well tolerated and easily corrected, but in patients with pre-eclampsia or cardiac diseases, close monitoring of hemodynamic variables is necessary to prevent harm to the mother or the foetus. Cardiac disease in pregnant women is often not diagnosed; of maternal deaths from a cardiac cause in the UK and Ireland 2009-2014, 77% did not have a known pre-existing cardiac condition [3].

Anaesthetists are trained to observe and interpret heartbeat-to-heartbeat variables and often need to see trends and changes over time. In our department, the current standard tool for continuous cardiovascular monitoring is the LiDCOplus monitor (LiDCO Ltd, London, UK). It offers continuous data on blood pressure, peripheral resistance, CO etc. As it requires intra-arterial access, it is reserved for delivery in high-risk pregnancies.

It would be of great advantage for research and clinical monitoring of pregnant women if detailed and reliable continuous measurements could be obtained using non-invasive technologies. Advanced monitoring could be established more quickly and easily, and with less risk. There is, however, currently insufficient evidence that non-invasive monitors are reliable for pregnant women.

The ccNexFin monitor (NexFin Systems, Edward Lifesciences Corp., Irvine, USA) is non-invasive and easy to apply. The objectives in this study were:

1) To assess the agreement and trending abilities for systolic and mean arterial blood pressure comparing the ccNexFin with invasive blood pressure

2) To assess agreement and trending abilities for cardiac output between the ccNexFin and the LiDCO monitor
3) To determine if the ccNexFin can replace invasive measurements of BP and CO during caesarean section under spinal anaesthesia in healthy, pregnant women.

Methods

Ethics approval

The study was approved by the Regional Committee for Medical and Health Research Ethics, Southern Norway (REC ID: 2012/1155). All participants gave written informed consent. The study followed the Declaration of Helsinki and was conducted according to Good Clinical Practice.

Patient population

Healthy, non-smoking, normotensive women with singleton pregnancies scheduled for elective caesarean delivery under spinal anaesthesia were asked to participate. Participants were recruited in collaboration with "The Placenta Project" (REC ID: 2011/2419) and are a subset of the study population of that project. As part of the study protocol for "The Placenta Project", all participants received an intra-arterial line used for blood sampling at delivery. The protocol for the placenta study is published previously[4]. Exclusion criteria were considerable pre-existing morbidity, pregnancy complications, contractions prior to scheduled C-section, and also prior Raynaud phenomena, as this is not compatible with use of the ccNexFin monitor. Two women with hypothyroidism, each supplemented with a low dose of L-thyroxine (50 and 75 mg daily, respectively) and one woman with mild asthma and occasional use of salbutamol (not taken in the days prior to participation in the study), were included. The inclusion period was from May 2013 until January 2014. Demographic properties are shown in table 1.

|                           | Mean (SD) | Range     |
|---------------------------|-----------|-----------|
| Age (yr.mo)               | 35.10 (3.2)| 29.6 – 42.7|
| Height (cm)               | 167 (5.0)  | 160 – 180  |
| Weight before pregnancy (kg)| 64.0 (10.7)| 50 – 91    |
| Weight at delivery (kg)   | 78.9 (12.3)| 60 – 105   |
| Length of pregnancy (days)| 275 (6.5)  | 260 – 292  |

Table 1: demographic properties of the participants.

Monitoring devices
The LiDCOplus monitor is in routine clinical use and has documented accuracy and trending abilities[5]. It provides information about circulatory changes from heartbeat to heartbeat, and is used when advanced monitoring is indicated, such as during major surgery, or during interventions on patients with circulatory disorders. Mathematical analysis of the intra-arterial pressure curve by pulse power analysis is done using the built-in software PulseCO. It estimates many aspects of the circulation and can be used with or without lithium dilution calibration (LiDCO). In this study, we used calibrated CO, aiming at optimal accuracy. The technology has been used in studies of healthy women and pregnant women with heart disease [6], and is the standard method for perioperative monitoring of pre-eclamptic women at our institution. In the comparison of CO methods it serves as the reference.

The ccNexfin monitor is based on the principle of the unloaded vascular wall [7], the Physiocal criteria [8], and a generalized waveform filter to reconstruct brachial pressure from finger pressure [9]. An inflatable cuff is placed around one of the three middle fingers of either hand. An integrated plethysmograph measures the volume of blood under the cuff using an infrared light source and a photosensor. The monitor initially determines a set point for the finger cuff pressure, where most of the venous blood is displaced, and the arterial diameter is reduced to no more than 50% of the expanded diameter. The set point is intermittently calibrated according to the Physiocal criteria, to account for changes in the vascular state of the finger. The cuff pressure is continuously adjusted to counter the varying intra-arterial blood pressure, keeping the signal from the photosensor, and consequently the blood volume and arterial diameter under the cuff, constant. This way, the artery wall is said to be unloaded, transmural pressure is zero, and the pressure in the cuff thus represents the intra-arterial pressure. The measured finger blood pressure is transformed to reflect brachial blood pressure. The CO calculations in the ccNexFin are based on pulse contour analysis of the derived arterial pressure curve. The monitor is designed to work without external calibration. Our research group has been involved in several projects using finger plethysmographic monitor technology, including the largest population-based study ever utilizing this technology, The Tromsø Study [10].
Conduct of the study

**Design:** A prospective observational study. **Monitoring:** A 20G BD arterial cannula (Becton Dickinson Infusion Therapy Systems Inc, Utah, USA) was placed in the radial artery after skin infiltration with lidocaine (5–10 mg). It was connected to a Siemens Dräger Infinity Gamma XL hemodynamic monitor (Drägerwerk AG & Co. KgaA, Lübeck, Germany) via a Codan X-trans pressure transducer (CODAN pvb Critical Care GmbH, Forstinning, Germany), and the signal calibrated according to standard departmental procedures. Peripheral IV catheters were placed on both arms.

Intra-arterial blood pressure data was passed through to the LiDCOplus monitor. Heart rate ($HR_{inv}$), systolic arterial pressure ($SAP_{inv}$) and mean arterial pressure ($MAP_{inv}$) was recorded at a rate of one sample per heartbeat. $CO_{LiDCO}$, estimated by PulseCO, was also recorded. A single point calibration of CO was performed. The ccNexFin monitor was applied to one of the three middle fingers on the same arm as the intra-arterial cannula. Corresponding variables ($HR_{nex}$, $SAP_{nex}$, $MAP_{nex}$ and $CO_{nex}$) were recorded.

While sitting on the operation table, the subjects received spinal anaesthesia with bupivacaine 10 mg and fentanyl 20 µg, using a 27G pencil point needle. Co-loading with IV NaCl 0.9% 1000 mL was started. The parturients were then placed in the supine position with left lateral tilt, using a wedge under the right hip. Immediately after injection of the drugs, an IV bolus of phenylephrine 25-50 µg was given, followed by an infusion started at 0.25 µg/kg/min and titrated according to invasive blood pressure, aiming for a stable $SAP_{inv} > 90$ mmHg.

**Data recording**

In order to acquire synchronous sampling from both monitors, measurements were sampled in real time by the same computer. Samples were acquired through the RS232 port of the LiDCO monitor and the analogue output from the ccNexfin monitor using a data acquisition card and software from National Instruments. This setup was evaluated for electrical safety and approved by the appointed committee at Oslo University Hospital.

Time-stamped data for inter-beat interval (IBI), SAP, MAP, and CO from both monitoring devices was
recorded to a single dataset per subject, one sample per heartbeat, using software developed in-house in National Instruments LabVIEW®. Events were marked in real time and saved to file using the same software.

Due to subject movement following spinal anaesthesia, placement of a hip wedge, and adjustment of the arterial pressure transducer and the ccNexFin heart reference system, we considered data from the first two minutes after spinal anaesthesia unreliable. The arterial line was used for blood sampling just prior to delivery, causing a pause in our registration, and following delivery, there was again more subject movement causing unreliable data. It is also the experience of our group that the LiDCO needs recalibration after delivery [11]. We included the data between 2 and 12 minutes after spinal anaesthesia for our calculations.

Statistics

Due to differences in processing time between the two monitors, the LiDCO samples were ahead of the ccNexfin samples, on average by around two heartbeats, although they were sampled synchronously from the outputs of the monitors. For each session, this difference was adjusted by calculating the lag by means of a cross-covariance analysis of the IBI time-series, which are assumed to be equal between monitors, and then shifting the ccNexfin recording ahead by the calculated lag in order to align the recordings for comparison at equal beats. This was done in Matlab R2014b (Mathworks, Nantick, Massachusetts, UAS.)

Artefacts were reduced using a previously published method for detecting and removing outliers in continuous blood pressure and cardiac output recordings [12]. Data points for statistical analysis were constructed with one-minute intervals, by averaging data over the first 10 seconds of each minute.

Method comparison statistics were done using Matlab and Stata v15 (Statacorp LLC, College Station, Texas, USA). We used the method first described by Bland and Altman to investigate the agreement of the ccNexFin monitor with invasive blood pressure and LiDCO cardiac output measurement [13,14]. Early versions of this method did not sufficiently consider structure in the data, and could produce too narrow limits of agreement, and too narrow confidence intervals, with repeated measurements per subject. We calculated limits of agreement based on the repeated observations method as described
by Zou [15]. Confidence intervals for the limits of agreement were calculated using the MOVER algorithm [15]. This method is preferred when the true value varies, when there is a different number of measurements from each subject, and the between-subject variance is large with respect to the within-subject variance. The MOVER method also allows the construction of asymmetric CIs. Diagnostic plots suggested by Bland and Altman were inspected to check for underlying assumptions.

Polar plots were used to assess trending abilities for both blood pressure and CO [16]. As suggested by Critchley, the smallest changes were considered most likely to represent noise, and excluded from the polar plot analysis. Data points with an average change of more than 5 mmHg (for BP) or 0.5 L/min (for CO) from the previous measurement were included.

Results
Of 63 subjects approached, 45 agreed to participate. Of these, 7 went into labour prior to the caesarean section, and for 12 subjects study personnel were not available at the time of the caesarean section. A further 2 were excluded due to technical problems with the recording equipment, and in one patient we did not succeed in placing an intra-arterial line. This left us with 23 subjects eligible for analysis of blood pressure. Two additional subjects were excluded from the analysis of cardiac output, due to unsuccessful calibration of the LiDCO monitor (Figure 1).

Mean (SD) time from spinal anaesthesia to blood sampling was 16.1 (5.5) minutes, with extreme values of 5.6 and 31.7 minutes. We had some missing data, mostly due to delivery sooner than 12 minutes after spinal anaesthesia, or misalignment of the ccNexFin heart reference system. For the blood pressure analysis, 209 of a theoretical maximum of 230 data points remained (90.9%). For the 21 subjects included in the CO analysis, 187 of 210 possible data points remained (89.0%).

The Bland Altman plots and the polar plots are shown (Figure 2) and the results of the Limits of Agreement and the polar plot analyses are shown in table 2.
Table 2: Results of bias (invasive - ccNexFin), the Limits of Agreement and polar plot analyses

|     | bias (95% CI) | LoA (95% CI) to | mean polar angle (SD) |
|-----|---------------|----------------|-----------------------|
| MAP | -4.3 mmHg (-6.6, -1.9) | -15.9 (-20.7, -12.8) to 7.4 (4.2, 12.2) | 2.3° (10.0°) |
| SAP | 12.2 mmHg (7.5, 17.0) | -11.1 (-20.7, -4.8) to 35.6 (29.2, 45.2) | 5.0° (17.3°) |
| CO  | 0.2 L/min (-0.3, 0.7) | -2.6 (-3.5, -2.0) to 3.0 (2.5, 3.9) | -10.4° (27.2°) |

Discussion

Context

Even though the anaesthetist aims to keep the patient as stable as possible during caesarean delivery, rapid and major fluctuations in blood pressure and CO is common. Both spinal anaesthesia, and injections of oxytocin, give sudden drops in the peripheral resistance, with drops in blood pressure and concomitant rises in CO [2,17]. Fluids and vasopressors are given to counter this. Surgery, bleeding, anxiety and discomfort also affect the cardiovascular system. Thus, this clinical setting is challenging for any monitoring device, especially regarding trending abilities.

Blood pressure varies with measurement site and the modality used

The definition of a gold standard for blood pressure is debatable. Although auscultatory blood pressure, measured on the upper arm, still may be considered the gold standard, it is too slow and impractical to be used in the setting of caesarean delivery. For most patients, intermittent oscillometric measurements are sufficient, but in more challenging cases, continuous measurements are needed. These are usually obtained invasively. For invasive measurements, the gold standard might be the blood pressure in the ascending aorta, but his measurement is of course not obtainable. The radial artery is the preferred site, as it is conveniently located, easy to cannulate, and the incidence of complications is low [18]. Still, peripherally measured intra-arterial blood pressure is not equal to the central pressure. The pressure curve is modified as it travels along the branches of the arterial tree, both by the elastic properties of the central vessels and by reflected waves from the periphery.

It is documented that oscillometric non-invasive BP measured in the upper arm underestimates high blood pressures, overestimates low blood pressures, while mean pressures are rather similar.
compared to intra-arterial measurements in the radial artery [19]. In 1990, Gravlee et al, compared intra-arterial blood pressure in brachial artery with four methods of non-invasive BP measurements on the upper arm before, during and after cardiopulmonary bypass. Averaging over-all measurements, they found the auscultatory method to report lower systolic, but higher mean and diastolic pressures than the invasive measurements, while the oscillometric method reported an equal systolic, and higher mean and diastolic values compared to invasive measurements. Judging from the graphs, the same is true when considering the first two measurements, i.e. before open chest surgery, separately [20].

In 1951, Wood et al, measured the blood pressure in radial and brachial arteries simultaneously in 17 healthy subjects, and found SAP in the radial artery to be 6 mmHg higher, and MAP and DAP slightly lower (2 and 1 mm Hg), than in the brachial artery. For hypertensive subjects, the difference in systolic pressure was increased [21]. Pauca et al, measured pressures in the radial artery and in the ascending aorta during bypass surgery. They found small differences in MAP and DAP, but greater differences between centrally and peripherally measured SAP, with pressures in the radial artery being on average 12 mmHg higher. Systolic values were also found to have a much greater variance than mean and diastolic values [22].

The ccNexFin measures blood pressure in a finger. The waveform is transformed to approximate invasive brachial blood pressure [9], but the model used relies on measurements and assumptions in a group of 53 men, some healthy, and some with varying degrees of hypertension and cardiovascular disease. We found the MAP values to be similar between the monitors, with the ccNexFin reporting values on average 4 mm higher than the invasive measurements. Systolic values were on average about 12 mm lower. A slightly lower systolic value is expected, as the ccNexFin aims to represent a more central pressure, but the difference is larger than can reasonably be explained by this effect.

The inaccuracy is small and will likely be of minor importance during caesarean delivery under spinal anaesthesia.
Varying definitions of hypotension

An analysis by Klöhr et al, reviewing definitions of hypotension after spinal anaesthesia for caesarean delivery, found that in research, relative limits seem to be more popular than absolute thresholds [23]. This and other papers reference a survey by Burns et al, from 2001 as an argument that anaesthetists prefer absolute thresholds in this setting [24], but actually they did not. Indeed, they claimed that a relative rather than an absolute decrease may be more important. They add that not only the degree of hypotension, but also the duration might be important. Still, as absolute limits do not require a baseline to be determined, it may be reasonable to assume that this simpler approach would be preferred by many. In a recent consensus document, Kinsella et al, suggest taking a baseline BP measure before spinal anaesthesia, using repeated measurements if the BP is not stable, if it is higher than expected or if the woman is in labour [25]. They recommend aiming for a SAP ≥ 90% of the baseline, and to avoid a decrease to < 80% baseline. It is also suggested that the SAP is a less important variable than mean arterial pressure (MAP) as a determinant of organ perfusion. Still, recommended limits are based on the SAP, as this has been the primary outcome in most of the available research. MAP is unlikely to be used to define hypotension in this clinical setting without more supportive data [25].

Auscultatory, oscillometric, invasive and finger plethysmographic techniques use different principles to measure or estimate blood pressures. In addition, measurements are done at different anatomic sites. It is important to be aware of the measurement techniques used in scientific studies, their definitions of safe limits for blood pressure, and to consider the characteristics of these methods as compared to the ones being used in clinical practice.

In this perspective the inaccuracy of ccNexFin compared to invasive arterial pressure is of minor impact and we recommend finger plethysmographic measurement in clinical use and in research.

Trending abilities for blood pressure

The degree to which two monitors agree in their ability to track changes is also crucial. For the polar
plot method we applied, Critchley et al, suggest using a limit of ±5° for angular bias, and radial limits of no more than ±30°, for good trending abilities [16]. Only the MAP measurements satisfied these limits. The low angular bias suggests that the monitors were in good calibration, and with radial limits well within ±30°, the ccNexFin shows good trending ability compared to intra-arterial measurements. The SAP had an angular bias on the border of the suggested range, but the radial limits were too wide. Taken into consideration the hemodynamic variations typical for caesarean delivery under spinal anaesthesia, this is a challenging model, with larger intra-individual variations than in critical care patient. We recommend finger plethysmographic measurements in clinical settings and for research purposes requiring good BP trending, i.e. repeated measurements, ability. In pre-eclampsia or other settings with pregnancy induced hypertension, invasive measurements should replace the finger plethysmographic method due to the tendency to underestimate SAP.

Cardiac Output

Regarding CO, we did not find sufficient agreement between the monitors. Even though the bias was small, the limits of agreement were wide, more than ±40% of the mean CO. Both angular bias and radial limits of agreement were far outside recommended limits, and suggest that the ccNexFin cannot reliably track changes in CO. This is consistent with the results in a study where this technology was compared with echocardiographic estimates of CO [26]. Based on the interpretation of the results we do not recommend using ccNexFin measuring CO or monitoring CO trend in the clinic or research in pregnant women.

Limitations

In this study, the accuracy (bias) and precision (variability) of agreement between two methods were presented. We calculated limits of agreement and assessed the ccNexfin against invasive measurements for blood pressure, and the LiDCO monitor for CO. As described in Hapfelmaier et al, the precision of agreement partly depends on the precision of measurement (repeatability) of both devices. For instance, the limits of agreement will become wider as a consequence of using an imprecise reference technique. This means that the agreement between a new technique and a reference technique needs to be judged in light of the precision that the techniques themselves are
able to achieve [27]. In our study, it was not possible to determine the repeatability (variation around a true value). Obstetric anaesthesia is characterized by constantly changing hemodynamics and repeated measurements during one constant value of BP or CO within the experiment is impossible. Hence, determining the precision of measurement of the LiDCO per se and the Nexfin technique per se, was not possible.

Conclusion
We consider the ccNexFin monitor to have sufficient accuracy in measuring mean arterial pressures. The limits of agreement for systolic measurements were wider, and the trending ability, compared with invasive measurements, was outside the recommended limit. The ccNexFin is not reliable for cardiac output measurements or trend in pregnant women for caesarean delivery under spinal anaesthesia.

Abbreviations
CO – cardiac output
BP – blood pressure
HR – heart rate
SAP – systolic arterial pressure
MAP – mean arterial pressure
IBI – inter-beat interval
LoA – limits of agreement

Declarations
Details of authors contributions
Ivar N. Omenås have contributed during planning, data collection, analyses, interpretation, and manuscript preparation.

Christian Tronstad have contributed during planning, data collection, analyses, interpretation, and manuscript preparation.

Leiv Arne Rosseland is principle investigator, have contributed during planning, approval of protocol, data collection, analyses, interpretation, and manuscript preparation.

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Declaration of interests
Ivar N. Omenås declare no conflict of interest.

Christian Tronstad declare no conflict of interest.

Leiv Arne Rosseland declare no conflict of interest.

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Anonymous data set is available on Springer Nature Data (details will follow after accepted manuscript)

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Figures
Flow chart showing screened, included, excluded and analysed number of patients.
Figure 2

Comparison of invasive measurements with ccNexFin of mean arterial pressure (MAP) with Bland Altman plot (A) and Polar plot (B). Comparison of invasive measurements with ccNexFin of systolic arterial pressure (SAP) with Bland Altman plot (C) and Polar plot (D). Comparison of invasively estimated (LiDCO) with ccNexFin of cardiac output (CO) with Bland Altman plot (E) and Polar plot (F).