Haemodynamic effects of glycopyrrolate pre-treatment before phenylephrine infusion during spinal anaesthesia for caesarean delivery

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ABSTRACT

Background: Phenylephrine given during spinal anaesthesia for caesarean delivery often induces a decrease in heart rate which may decrease cardiac output. Anticholinergic drugs may be given to attenuate this effect but may also cause more labile blood pressure. This study evaluated the effects of glycopyrrolate pre-treatment on non-invasively measured cardiac output and accuracy of blood pressure control.

Methods: At induction of spinal anaesthesia for caesarean delivery, 104 patients randomly received intravenous glycopyrrolate 4 μg/kg or saline placebo. Systolic blood pressure, measured at 1-min intervals, was maintained near baseline using closed-loop feedback computer-controlled phenylephrine infusion with crystalloid cohydration. Cardiac output and stroke volume were measured using suprasternal Doppler ultrasonography at baseline and 5-min intervals for 20 min. Blood pressure control was assessed using performance error calculations.

Results: Eleven patients were excluded. Patients who received glycopyrrolate (n = 45) had greater cardiac output over time (P < 0.001), greater heart rate over time (P < 0.001), similar stroke volume over time (P = 0.95), and lower median phenylephrine infusion rate (P = 0.006) compared with control (n = 48). There was no difference in the incidence of hypotension between groups. Analysis of blood pressure control showed greater positive bias, greater inaccuracy and greater wobble in the glycopyrrolate group (all P < 0.05). Neonatal outcome was similar between groups.

Conclusions: Glycopyrrolate 4 μg/kg given at the start of a phenylephrine infusion increased heart rate and cardiac output but also decreased accuracy of blood pressure control, increased the incidence of hypertension and caused an increased incidence of dry mouth postoperatively compared with control.

Keywords: Caesarean section; Caesarean delivery; Anaesthesia; Spinal; Arterial blood pressure; Hypotension

Introduction

An infusion of phenylephrine is commonly used to prevent and treat hypotension during spinal anaesthesia for caesarean delivery. However, because phenylephrine is an alpha adrenoreceptor agonist without significant beta activity, its use is often associated with a reflex slowing of maternal heart rate (HR). Anecdotal experience indicates that this may occur even when blood pressure (BP) is not substantially elevated above baseline.

Previously, it has been shown that this decrease in HR may be accompanied by a corresponding decrease in cardiac output (CO) and it has been suggested that this could have a detrimental effect on fetal wellbeing. A possible method for attenuating or preventing the reflex decreases in HR and CO associated with phenylephrine is co-administration of an anticholinergic drug such as glycopyrrolate. Although glycopyrrolate has been investigated previously as an adjunctive agent for preventing hypotension during caesarean section, few data are available for its use specifically when phenylephrine is used as the primary vasopressor.

The aim of this study was to investigate the haemodynamic effects of administering a single bolus of glycopyrrolate immediately before commencement of a phenylephrine infusion used to maintain BP in patients having spinal anaesthesia for elective caesarean delivery. The primary outcome was defined as maternal CO, mea-
sured non-invasively. Secondary outcomes included the dose and infusion rate of phenylephrine required until delivery, serial changes in BP and HR, the accuracy of BP control and the incidence of side effects such as nausea, vomiting and dry mouth.

**Methods**

This randomized, double-blinded study was approved by the Joint Chinese University of Hong Kong – New Territories East Cluster Clinical Research Ethics Committee (Shatin, New Territories, Hong Kong, China) and was registered in the Centre of Clinical Trials Clinical Registry of the Chinese University of Hong Kong (registration no. CUHK_CCT00274). All patients gave informed, written consent to participate. Inclusion criteria were: American Society of Anesthesiologists physical status 1 or 2, age >18 years, term singleton pregnancy, and scheduled elective caesarean delivery under spinal anaesthesia. Exclusion criteria were: pre-existing or gestational hypertension, abnormality of the fetus, onset of uterine contractions, cerebrovascular or cardiovascular disease, coagulopathy, thrombocytopenia, or any contraindication to the use of spinal anaesthesia, height >180 cm or <140 cm, weight >100 kg or <50 kg.

Patients were given routine antacid premedication. On arrival in the operating theatre, standard monitoring was applied and the patient was placed in the left-tilted supine position. After a brief resting period, BP and HR were measured at 1-min intervals until considered consistent and baseline values were calculated as the mean of three measurements with a difference of <10%. A large bore intravenous cannula was then inserted into an upper limb vein. Spinal anaesthesia was induced with the patient in the right lateral position. Using full aseptic precautions, the skin was infiltrated with lidocaine 1% w/v. A 25-gauge Whitacre spinal needle was inserted via an introducer needle at the estimated L3-4 or L4-5 vertebral interspace. After confirmation of free flow of cerebrospinal fluid, hyperbaric bupivacaine 0.5% w/v 2.2 mL (11 mg) and fentanyl 15 μg was injected intrathecally. At the start of the spinal injection, patients were given a single intravenous bolus of either glycopyrrolate 4 μg/kg diluted in saline to 2 mL (glycopyrrolate group), or 2 mL saline placebo (control group). The dose of glycopyrrolate was based on a previous report because there are no data available on the optimal dose of glycopyrrolate for the prevention of bradycardia associated with phenylephrine, a dose that has previously been investigated was chosen.

Allocation of patients to groups was performed according to computer-generated random codes contained within sealed, opaque, sequentially-numbered envelopes that were opened after measurement of baseline BP. An investigator who was not involved with patient care or assessment prepared the study solutions in identical syringes that were labelled “study drug”.

Rapid intravenous cohydration of warmed lactated Ringer's solution was commenced at the start of spinal injection by fully opening the infusion set with the solution bottles suspended approximately 1.5 m above the top surface of the operating table. This was continued until delivery, or until a volume of 2 L had been given, after which the rate was adjusted to a slow maintenance rate. Immediately after spinal injection, the patient was returned to the tilted supine position. At 1 min after spinal injection, non-invasive BP monitoring was re-started and set to cycle at 1-min intervals until delivery. Supplementary oxygen (6-8 L/min by clear facemask) was only given if the pulse oximeter reading decreased to <95%.

BP was maintained using an infusion of phenylephrine 100 μg/mL administered using a computer-controlled closed-loop feedback infusion delivered through fine-bore extension tubing via a three-way stopcock attached to the intravenous cannula. The infusion was initially commenced at a fixed rate of 30 mL/h (50 μg/min) at the start of spinal injection. After the completion of the first BP measurement after spinal injection, the computer regulated the phenylephrine infusion according to the previously-described algorithm.

Infusion rate (mL/h) = \((10 – \text{error}) \times 3\)

where \text{error} = \frac{(\text{measured systolic BP} – \text{baseline systolic BP})}{\text{baseline systolic BP}} × 100. The infusion rate was constrained to be within the limits 0–60 mL/h (0–100 μg/min).

The upper level of sensory block was assessed using ice 5 min after spinal injection. The assessed level was recorded for intergroup comparison as part of the study although additional checks of block height could also be made as part of clinical assessment.

BP and HR were recorded after the completion of each automatic 1-min cycle. Because the non-invasive BP monitor took varying times to complete individual measurements, the logged time of completion of each measurement was not always equal to elapsed chronological time; during subsequent data analysis this discrepancy was ignored.

A suprasternal Doppler technique (USCOM 1A cardiac output monitor, USCOM Ltd., Sydney, NSW, Australia) was used for non-invasive measurement of CO and a derived value for stroke volume (SV). All measurements were made by the same, blinded experienced investigator (SWYL) and were performed at baseline (after completion of BP and HR measurements) and at 5, 10 and 15 min after spinal injection.

The computer-controlled infusion of phenylephrine was continued until the time of uterine incision when the study was terminated. Subsequent care was according to the discretion of the attending anaesthesiologist. The total dose and median rate of infusion of phenylephrine, the total amount of intravenous fluid given,
and the number of episodes of hypotension (defined by systolic BP <80% of baseline), hypertension (defined by systolic BP >120% of baseline) and maternal bradycardia (defined by HR <50 beats/min) were recorded. Any instances of nausea (reported by patients) or vomiting (observed by investigators) up to the time of uterine incision were recorded. The times of uterine incision and delivery of the baby were recorded. Neonates were assessed routinely by recording birthweight, Apgar scores and umbilical cord blood gases. After arrival in the recovery room, patients were asked to grade any feeling of dry mouth according to the following scale: 0 = none, 1 = mild, 2 = severe.

Statistical analysis
Sample size was determined by a priori power analysis based on data from our previous, unpublished work where cardiac output during spinal anaesthesia for caesarean delivery had been measured using the same apparatus, and on data from a previously-published study. A sample size of 47 patients per group would have >90% power with \( \alpha = 0.05 \) to detect a 20% difference be-

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Table 1  Patient characteristics and anaesthetic and surgical times

<table>
<thead>
<tr>
<th></th>
<th>Glycopyrrolate group ((n = 45))</th>
<th>Control group ((n = 48))</th>
<th>(P) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>33 [20–40]</td>
<td>32 [24–42]</td>
<td>0.67</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>66.2 ± 7.8</td>
<td>69.2 ± 7.8</td>
<td>0.35</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>159 ± 6.0</td>
<td>158 ± 5.4</td>
<td>0.76</td>
</tr>
<tr>
<td>Block height at 5 min (dermatome)</td>
<td>T4 (T5–T4)</td>
<td>T4 (T5–T3)</td>
<td>0.18</td>
</tr>
<tr>
<td>Induction-to-uterine incision interval (min)</td>
<td>30.8 (27.9–33.4)</td>
<td>31.3 (26.8–35.2)</td>
<td>0.80</td>
</tr>
<tr>
<td>Uterine incision-to-delivery interval (s)</td>
<td>86 (50–146)</td>
<td>83 (53–122)</td>
<td>0.58</td>
</tr>
</tbody>
</table>

Data are mean [range], mean ± SD, or median (interquartile range).
between groups in CO 5 min after spinal injection based on estimated mean control value of 5.4 (SD 1.5) L/min. This sample size also had 80% power to detect a 30% difference in median absolute performance error for systolic BP measurements (see below) between groups based on estimated mean control value of 6.0% (SD 3.1). To account for potential dropouts the sample size was increased by 5%, giving a final total sample size of 104 patients.

Univariate intergroup comparisons were performed using Student’s t-test or the Mann–Whitney U-test as appropriate for numerical scale data and Fisher’s exact test for nominal data. Summary comparisons of changes in CO, HR and SV over time were performed by calculating the area under the curve (AUC) for values plotted against time using the trapezium rule; the AUC values for patients in each group were then compared using the Mann–Whitney U test. Serial changes in BP were assessed using performance error calculations as previously described (Appendix A). The following parameters were calculated: (1) median percentage performance error (MDPE, a measure of bias), (2) median absolute performance error (MDAPE, a measure of inaccuracy), (3) wobble and (4) divergence. All analyses were performed using Microsoft Excel 2010 (Microsoft Corporation, Redmond, WA, USA) and PASW Statistics 18.0.0 (IBM SPSS Inc, Chicago, IL, USA).

Results

Patient recruitment and flow is shown in Fig. 1. Fifty patients were allocated to the glycopyrrolate group and 54 patients were allocated to the control group. Eleven patients were excluded for technical problems or because severe shivering prevented accurate measurement of BP, leaving a total of 93 patients who completed the study and underwent data analysis (45 in the glycopyrrolate group and 48 in the control group). Patient characteristics and anaesthetic and surgical details were similar between groups (Table 1).

The primary outcome, CO 5 min after spinal injection, was greater in the glycopyrrolate group versus the control group (median 7.6 [interquartile range 6.4–8.9] versus 6.1 [5.3–6.9] L/min, \( P < 0.001 \)). Values for CO over time and corresponding values for HR and SV are shown in Fig. 2. Comparison of the AUC showed that both CO and HR were greater over time in the glycopyrrolate group versus the control group (both \( P < 0.001 \)) but there was no difference in SV over time (\( P = 0.95 \)).

Haemodynamic changes, phenylephrine consumption, total intravenous fluid given and maternal symptoms are summarized in Table 2. The glycopyrrolate group had greater values for the highest recorded systolic BP, highest recorded HR, and lowest recorded
Table 2  Haemodynamic variables, phenylephrine consumption, intravenous fluids and maternal symptoms

<table>
<thead>
<tr>
<th></th>
<th>Glycopyrrolate group (n = 45)</th>
<th>Control group (n = 48)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Highest recorded systolic blood pressure (mmHg)</td>
<td>139 (130–152)</td>
<td>130 (123–136)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Lowest recorded systolic blood pressure (mmHg)</td>
<td>109 (99–114)</td>
<td>104 (95–113)</td>
<td>0.24</td>
</tr>
<tr>
<td>Highest recorded heart rate (beats/min)</td>
<td>120 (106–135)</td>
<td>104 (95–115)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Lowest recorded heart rate (beats/min)</td>
<td>76 (70–82)</td>
<td>62 (56–69)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Patients with one or more episode of hypotension (systolic blood pressure &lt;80% of baseline)</td>
<td>2 (4.4%)</td>
<td>7 (14.6%)</td>
<td>0.16</td>
</tr>
<tr>
<td>Patients with one or more episode of hypertension (systolic blood pressure &gt;120% of baseline)</td>
<td>20 (44.4%)</td>
<td>8 (16.7%)</td>
<td>0.007</td>
</tr>
<tr>
<td>Patients with one or more episode of bradycardia (heart rate &lt;50 beats/min)</td>
<td>0</td>
<td>2 (4.2%)</td>
<td>0.50</td>
</tr>
<tr>
<td>Total dose of phenylephrine (µg)</td>
<td>980 (565–1180)</td>
<td>1020 (780–1440)</td>
<td>0.013</td>
</tr>
<tr>
<td>Phenylephrine infusion rate (µg/min)</td>
<td>30.5 (20.9–36.7)</td>
<td>34.1 (26.6–43.9)</td>
<td>0.009</td>
</tr>
<tr>
<td>Total intravenous fluid (mL)</td>
<td>1975 (1500–2020)</td>
<td>2000 (1500–2020)</td>
<td>0.86</td>
</tr>
<tr>
<td>Nausea or vomiting</td>
<td>7 (15.6%)</td>
<td>3 (6.3%)</td>
<td>0.19</td>
</tr>
<tr>
<td>Dry mouth in recovery room</td>
<td>None</td>
<td>45 (93.8%)</td>
<td>0.001</td>
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</tr>
</tbody>
</table>

Data are number (%), or median (interquartile range).

Fig. 3  Systolic blood pressure for all patients plotted against time. Values on the x-axis corresponded to the number of each consecutive blood pressure measurement made with the monitor set to record at 1-min intervals, and are not exactly equal to chronological time.

Fig. 4  Percentage performance error for all patients plotted against time. Values on the x-axis corresponded to the number of each consecutive blood pressure measurement made with the monitor set to record at 1-min intervals, and are not exactly equal to chronological time.
HR (all \( P < 0.001 \)), but there was no difference in the lowest recorded systolic BP. The number of patients who had one or more episodes of hypertension was greater in the glycopyrrolate group (\( P = 0.007 \)), but there was no difference in the number of patients with hypotension. Two patients in the control group versus no patient in the glycopyrrolate group had an episode of bradycardia (\( P = 0.5 \)); for both these patients, the minimum recorded HR was 49 beats/min, and the bradycardia lasted for <5 s, resolving without treatment. For the glycopyrrolate group compared with the control group, the total dose of phenylephrine was lower (\( P = 0.013 \)) and the median rate of infusion of phenylephrine was lower (\( P = 0.009 \) (Table 2). The number of patients who reported a feeling of dry mouth in the recovery room was greater in the glycopyrrolate group compared with the control group (\( P = 0.001 \)). Other measurements were similar between groups.

Changes in systolic BP over time are shown in Fig. 3, changes in percentage performance error over time are shown in Fig. 4, and performance error calculations are summarized in Table 3. MDPE, MDAPE and wobble were all greater in the glycopyrrolate group compared with the control group but there was no difference in divergence.

Apgar scores and umbilical cord blood gases were similar between groups (Table 4).

### Discussion

This study found that, in patients having spinal anaesthesia for caesarean delivery, intravenous glycopyrrolate 4 \( \mu \)g/kg given immediately before initiation of a titrated phenylephrine infusion increased maternal HR and CO and decreased phenylephrine requirement compared with control. However, this was at the expense of increased BP variability, a greater incidence of hypertension, and an increased number of patients who had the feeling of a dry mouth immediately postoperatively. There was no difference in the incidence of hypotension or in the number of patients who had nausea or vomiting and no effect on measured indices of neonatal outcome.

There is controversy surrounding the optimal method for maintaining BP during spinal anaesthesia in obstetric patients. Phenylephrine has gained popularity because of its efficacy and titratability, and because, unlike ephedrine, in clinical doses it does not appear to have a depressant effect on fetal acid–base status. However, some investigators have expressed concern that the use of phenylephrine may be associated with a detrimental decrease in CO. Unlike the findings of other investigators, the current study did not observe...
an overall decrease in CO in the control group. This is possibly because the HR in our patients was relatively well maintained; only two patients in the control group had an episode of bradycardia (defined arbitrarily in our study as HR <50 beats/min) and in both cases this lasted for only a few seconds, resolving without treatment. This may reflect the close control of BP and rapid titration of phenylephrine that was facilitated by use of the computer-controlled infusion. Careful titration of phenylephrine, with particular attention to reducing dose when HR decreases, may eliminate the need for other measures to maintain HR and CO. This may be a better strategy for maintaining optimal maternal haemodynamic control than routine use of glycopyrrolate, which has some potential to cause adverse effects. Routine glycopyrrolate administration may be best avoided in patients with preeclampsia due to the risk of severe hypertension.

The current results showed that although both HR and CO were greater over time in the glycopyrrolate group, there was no difference in SV between groups. This supports previous observations that changes in CO and HR are highly correlated, and indicates that CO changes associated with phenylephrine are mediated predominantly by changes in HR rather than contractility.

Although previous studies have shown that large doses of phenylephrine may decrease maternal CO, most studies have investigated low-risk elective cases and have not shown any evidence of a detrimental effect on neonatal outcome, despite the use of large doses of phenylephrine to maintain maternal BP near baseline. Although it has been suggested that CO may be more important than BP for maintaining uteroplacental perfusion, this is controversial; a global measure of CO does not necessarily represent regional uterine blood flow, and flow through the widely dilated uteroplacental vascular bed is considered to be pressure-dependent. In addition, the uteroplacental vasculature is thought to have a “margin of safety” that, within limits, permits tolerance to fluctuations in flow. However, few data are available for situations where there is acute or chronic impairment of uteroplacental blood flow. In these circumstances, it is possible that the decrease in CO associated with large doses of phenylephrine may have more potential for harm and caution with dosage is prudent. In the current study, CO increased above baseline in the glycopyrrolate group, and further studies to investigate whether this increase could be of benefit in patients with uteroplacental insufficiency would be interesting.

Normal physiological reflexes produce the changes in HR and CO during phenylephrine administration. Since phenylephrine is devoid of significant beta-adrenergic effects at clinical doses, the rise in BP, which is secondary to an increase in systemic vascular resistance, triggers a baroreceptor response mediated by the vagus nerve. The efferent limb of this reflex is blocked by anticholinergic drugs such as glycopyrrolate and atropine. Impairment of the baroreceptor reflex removes a natural physiological buffer. This is reflected in the greater values for MDPE, MDAPE and wobble in the glycopyrrolate group compared with the control group, and explains the greater fluctuation in BP and higher incidence of hypertension that were observed in patients who received glycopyrrolate. The phenylephrine infusion was closely regulated by computer-controlled feedback control, and there was no evidence of harmful effects. However, bolus administration of glycopyrrolate given in response to maternal bradycardia induced by phenylephrine have produced precipitous increases in BP and been associated with headache and other maternal symptoms. At worst, uncontrolled intraoperative hypertension can result in haemorrhagic stroke. In addition, the increased HR associated with anticholinergic administration may increase cardiac work and myocardial oxygen consumption, which may be detrimental in patients with cardiac disease. In normal practice, when bradycardia occurs during phenylephrine administration, we would advocate simply stopping phenylephrine delivery and waiting for HR to spontaneously recover. The use of anticholinergic drugs is reserved when hypotension accompanies bradycardia; ephedrine and intravenous fluids administration may also be considered in these circumstances.

Several previous studies have investigated the use of glycopyrrolate as an adjunctive agent for maintaining BP during spinal anaesthesia for caesarean delivery with varying results. Ure et al. reported that glycopyrrolate 200 µg reduced ephedrine requirement and reduced the frequency and severity of nausea. In contrast, Yentis et al. found that although glycopyrrolate 4 µg/kg increased intraoperative HR, there was no difference in ephedrine requirement or severity of hypotension. The same group in a subsequent study evaluated glycopyrrolate 2 µg/kg in patients with a resting HR of ≤80 beats/min and again found no difference in ephedrine requirement or hypotension compared with control. The primary vaspressor in these studies was ephedrine; unlike phenylephrine, this has positive chronotropic properties that may have masked or reduced any benefit from adding an anticholinergic agent. Our study relied on phenylephrine to maintain BP. Chad et al. used glycopyrrolate 400 µg in a study where hypotension was treated with ephedrine or phenylephrine at the attending anaesthesiologist’s discretion. Glycopyrrolate decreased the incidence of bradycardia but not hypotension compared with control, and HR variability was decreased in patients who received glycopyrrolate, although the clinical significance of this was uncertain. Yoon et al. described the effects of a single intravenous dose of glycopyrrolate 200 µg before a
phenylephrine infusion in patients having spinal anaesthesia for caesarean delivery.\textsuperscript{21} They also reported that glycopyrrolate caused an increase in maternal HR and cardiac index versus control that was observed 8–15 min after induction.

A suprasternal Doppler method for non-invasively measuring CO was used in our study. This measures blood flow in the ascending aorta and uses an algorithm to estimate cross-sectional area and calculate CO. Previous reports have validated the accuracy of this method.\textsuperscript{22,23} However, as with most non-invasive CO monitors, measurements should be assumed to have a margin of error.

Atropine is perhaps the most commonly-used anticholinergic drug. However, glycopyrrolate has a quaternary ammonium structure that results in lower placental transfer than atropine, making it more suitable for use in pregnancy.\textsuperscript{24,25}

More patients in the glycopyrrolate group reported a feeling of dry mouth immediately postoperatively compared with the control group. This antialgesic action of glycopyrrolate has been observed in previous studies.\textsuperscript{5} Whether this affected patient satisfaction was not one of the study parameters.

Phenylephrine was administered using a computer-controlled infusion. The automated infusion largely eliminates bias that may result from manual adjustment. Whilst this technology is not generally available, the computer algorithm is not dissimilar to that used when manually titrating a phenylephrine infusion. The results may reasonably be assumed to apply to the use of manual infusions. Although infusion may be the optimal mode of phenylephrine administration during caesarean section,\textsuperscript{7} we acknowledge that many practitioners may be more familiar with the use of intermittent boluses. Provided boluses are delivered regularly with the objective of maintaining BP near to baseline, we believe the results would also be applicable to bolus administration of phenylephrine.

In summary, pre-treatment with intravenous glycopyrrolate 4 µg/kg resulted in an increase in maternal HR and CO and a decrease in vasopressor dose when given before a phenylephrine infusion. However, this dose also resulted in more labile BP and a greater incidence of hypertension which may limit its usefulness for routine clinical care. Evaluation of different doses of glycopyrrrolate and of glycopyrrolate pre-treatment in situations where increased CO might be beneficial would be of interest.

Acknowledgements

The authors wish to thank the staff of the Labour Ward, Prince of Wales Hospital, Shatin, Hong Kong, China for their support and cooperation during the conduct of this study. The closed-loop feedback computer-controlled infusion program was written by Yuk Ho Tam B.Sc., M.Phil., Scientific Officer, Department of Anaesthesia and Intensive Care, The Chinese University of Hong Kong, Prince of Wales Hospital, Shatin, Hong Kong, China.

References

Appendix A. Derivation of performance error calculations

**Performance error (PE):** PE was defined as the difference between each measured value of systolic blood pressure (SBP) and the baseline value, expressed as a percentage of the baseline value. For each patient until the time of uterine incision, it was calculated as follows:

\[
PEij = \left( \frac{\text{meaSBPij} - \text{tarSBPi}}{\text{tarSBPi}} \right) \times 100
\]

where \(PEij\) is the percentage performance error for the \(i\)th patient at the \(j\)th minute. \(\text{meaSBPij}\) is the measured SBP for the \(i\)th patient at the \(j\)th minute and \(\text{tarSBPi}\) is the target SBP (set-point for the closed-loop system) for the \(i\)th patient.

**Median performance error (MDPE):** MDPE is a measure of bias and describes whether the measured values for SBP are systematically either above or below the baseline value. For each patient, it was defined as the median of all values of \(PE\) and was calculated as follows:

\[
MDPEi = \text{median}\{PE_{ij}, j = 1, \ldots, Ni\}
\]

where \(MDPEi\) is the median performance error for the \(i\)th patient and \(Ni\) is the number of values for \(PE\) obtained for the \(i\)th patient.

**Median absolute performance error (MDAPE):** MDAPE is a measure of inaccuracy and represents an average of the magnitudes of the differences of measured values for SBP above or below the baseline value. For each patient, it was defined as the median of the absolute values of \(PE\) (\(|PE|\)) and was calculated as follows:

\[
MDAPEi = \text{median}\{|PE_{ij}|, j = 1, \ldots, Ni\}
\]

where \(MDAPEi\) is the median absolute performance error for the \(i\)th patient.

**Wobble:** Wobble is a measure of the inrasubject variability of PE about MDPE. It was calculated as follows:

\[
WOBBLEi = \text{median}\{|PE_{ij} - MDAPEi|, j = 1, \ldots, Ni\}
\]

where \(WOBBLEi\) is the wobble for the \(i\)th patient.

**Divergence:** Divergence describes the trend of changes in \(|PE|\) with time and is a measure of whether the magnitudes of the differences between measured and target values for SBP increase (positive value for divergence) or decrease (negative value for divergence) with time. It was defined for each patient as the slope of the linear regression equation of the values of \(|PEij|\) for that patient against time. It was calculated as follows:

\[
DIVERGENCE_{Ei} = \frac{N_i \sum_{j=1}^{N_i} (T_{ij} \times |PE_{ij}|) - \sum_{j=1}^{N_i} T_{ij} \times \sum_{j=1}^{N_i} |PE_{ij}|}{N_i \sum_{j=1}^{N_i} T_{ij}^2 - \left( \sum_{j=1}^{N_i} T_{ij} \right)^2}
\]

where \(DIVERGENCE_{Ei}\) is the divergence for the \(i\)th patient and \(T\) is time in minutes.