Randomized comparison of closed-loop feedback computer-controlled with manual-controlled infusion of phenylephrine for maintaining arterial pressure during spinal anaesthesia for Caesarean delivery†

W. D. Ngan Kee*, K. S. Khaw, F. F. Ng and Y. H. Tam

Department of Anaesthesia and Intensive Care, The Chinese University of Hong Kong, Prince of Wales Hospital, Shatin, Hong Kong, People’s Republic of China

* Corresponding author. E-mail: warwick@cuhk.edu.hk

Editor’s key points

- Computer-controlled phenylephrine infusion for arterial pressure (AP) control was compared with manual phenylephrine infusion in a prospective randomized controlled trial in 222 healthy patients undergoing Caesarean delivery under spinal anaesthesia.
- Slightly more subjects (2%) were maintained within 20% of baseline AP with the computer-controlled algorithm, which required significantly fewer manual interventions.
- Incorporation of additional parameters might result in further improvements in haemodynamic control, and perhaps clinical outcome.

Background. Closed-loop feedback computer-controlled infusion has not been described for administering phenylephrine to maintain arterial pressure (AP) during spinal anaesthesia for Caesarean delivery. We aimed to compare AP control using this automated system with a previously described manual infusion system.

Methods. We randomly allocated 222 healthy subjects having spinal anaesthesia for scheduled Caesarean delivery to have systolic AP maintained near baseline with phenylephrine (100 μg ml⁻¹) by computer-controlled infusion utilizing a proportional algorithm or manual-controlled infusion utilizing an on–off algorithm. AP control was assessed by comparing the proportion of systolic AP measurements within ±20% of baseline and by performance error (PE) calculations.

Results. A total of 212 subjects finished the study. In the computer-control group, 97% of systolic AP recordings fell within ±20% of baseline compared with 95% in the manual-control group (P=0.0004). For computer-control compared with manual-control, wobble was smaller [median 3.5 (inter-quartile range 2.5–4.8)% vs 4.2 (3.3–5.9)%, P=0.003], but there was no difference in the median PE [2.9 (0.3–4.7)% vs 1.9 (0–4.2)%], median absolute PE [4.7 (3.5–5.6)% vs 4.7 (3.8–6.7)%], or divergence [−0.01 (−0.03–0)% vs −0.06 (−0.26–0.08)%]. Fewer interventions per subject for controlling AP were required in the computer-control group [2 (2–2) vs 10 (8–13), P<0.001]. There were no differences in measured clinical outcomes.

Conclusions. Within the constraints of the studied algorithms, closed-loop feedback computer-controlled phenylephrine infusion provided better AP control with fewer interventions required compared with manual-controlled infusion.

Keywords: anaesthesia, spinal; arterial pressure, hypotension; Caesarean delivery

Accepted for publication: 27 July 2012

Phenylephrine infusion is an effective technique for maintaining maternal arterial pressure (AP) during spinal anaesthesia for Caesarean delivery.¹⁻³ In previous work, we have described an on–off simple algorithm for giving phenylephrine designed to be easy to use and to avoid the need for frequent calculation of different infusion rates.¹ ² Others have utilized more complicated infusion protocols that adjust the rate of phenylephrine infusion according to the difference between the measured and target (usually baseline) AP.⁴ Although a variable rate of phenylephrine infusion potentially might improve the accuracy of AP control, it necessitates repeated dose computations that are time-consuming and have potential for error if done manually. As an alternative, we recently developed an automated system of phenylephrine administration that uses closed-loop feedback computer control.⁵ The potential advantage of a computer-controlled system is that it allows the use of complicated algorithms without the risk of human computational errors, and thus might provide better AP control with fewer interventions compared with manual-controlled infusion.

This study aimed to compare computer-controlled infusion with manual-controlled infusion of phenylephrine

†This work was previously presented as a poster at Obstetric Anaesthesia 2011, Edinburgh, UK, 26–27 May 2011.
in patients undergoing elective Caesarean delivery using spinal anaesthesia. The primary outcome was the accuracy of AP control. The secondary outcomes included the number of manual interventions required, the incidence of maternal symptoms, and neonatal outcome.

**Methods**

The Joint Chinese University of Hong Kong–New Territories East Cluster Clinical Research Ethics Committee (Shatin, New Territories, Hong Kong, People’s Republic of China) approved this trial. This trial was also registered in the Centre of Clinical Trials Clinical Registry of the Chinese University of Hong Kong (registration no. CUHK_CCT00144).

Informed, written consent was provided by all participating subjects.

The program for computer-controlled infusion was written using Visual Studio 6.0 utilizing Visual C++ running in the operating system Windows XP, and was developed and modified by one of the investigators (Y.H.T.). We used a notebook computer attached to the anaesthesia machine (Dräger Zeus with Infinity C500 monitoring system, Draeger Medical Hong Kong Ltd, Hong Kong, People’s Republic of China) and to a syringe pump (Graseby 3500 Anaesthesia Pump, Graseby Medical Ltd, Watford, Herts, UK) by serial RS232 ports. We prepared phenylephrine (concentration 100 mg l\(^{-1}\)) in a 50 ml plastic syringe and attached this using a fine-bore extension tube and a three-way stopcock to the i.v. cannula. Basic details of this system have been previously described.

In our previous description, the computer-controlled infusion system was designed to emulate our on–off manual-controlled system. However, for the current study, the program was modified to utilize a variable rate infusion based on a proportional algorithm (see below).

We recruited term parturients who were ASA physical status I or II (n=222) and who were on our routine elective operating lists for Caesarean delivery under spinal anaesthesia. Exclusions included subjects with hypertension (pregnancy-induced or pre-existing) or those who had abnormality of the fetus, multiple gestation, cerebrovascular or cardiovascular disease, or onset of uterine contractions.

All patients were administered famotidine 20 mg orally on the evening preceding and during the morning of their operation followed by 30 ml of 0.3 M sodium citrate after they arrived in the operation theatre. We applied standard monitoring [pulse oximetry, ECG, and non-invasive measurement of AP (NIAP)], and monitored fetal heart rate using external cardiotocography up to the time of preparation by the surgeon. Subjects were rested for several minutes undisturbed in the supine left-tilted position, while their AP was measured at an interval of 1–2 min. These AP recordings were repeated until they were considered to be consistent (three successive recordings of systolic AP with <10% difference). The baseline systolic AP was defined as the mean of these three measurements, and this was utilized as the target AP for computer-control.

Next, we placed an i.v. cannula (16 G) under local anaesthesia in the forearm opposite to the AP cuff. We attached to this a warmed a bag of Hartmann’s solution suspended about 1.5 m above the operation table. This was adjusted initially to a minimal rate for the maintenance of patency of the vein. We did not give i.v. prehydration. Next, we placed the subject in the right lateral position and spinal anaesthesia was administered. After dermal infiltration with lidocaine, we inserted a 25 G Whitacre needle at the estimated L2–3 or L3–4 vertebral interspace and injected 2.2 ml hyperbaric bupivacaine 0.5% w/v (11 mg) with fentanyl 15 µg intrathecally. Subjects were then placed back in the supine left-tilted position. We then started i.v. fluid infusion (cohydration) and commenced the infusion of phenylephrine immediately after the intrathecal injection.

We randomly assigned subjects to either the computer-control group or the manual-control according to a closed-sequence randomization code that was generated by a computer. These codes were kept in sealed and opaque envelopes that were numbered sequentially and opened after the recording of baseline AP.

**Computer-control**

In the computer-control group, the computer was set to start the infusion of phenylephrine initially at the fixed rate of 100 µg min\(^{-1}\) (60 ml h\(^{-1}\)) at the initiation of spinal injection. One minute after intrathecal injection, NIAP measurement was recommenced and set to cycle each minute. After the first AP recording, the computer program was immediately changed to closed-loop feedback control. The infusion rate \(I\) was controlled according to the following algorithm that was developed empirically:

\[
I(\text{ml h}^{-1}) = (10 - \text{error}%) \times 3
\]

where \(\text{error}\% = (\text{measured systolic AP} - \text{baseline systolic AP})/\text{baseline systolic AP} \times 100\) and the value of \(I\) was constrained to be within the limits 0–60.

This algorithm allowed phenylephrine to be infused within the range 0–100 µg min\(^{-1}\) with adjustment made after each 1 min AP recording according to the algorithm. Visual alarms were incorporated into the program interface that provided a warning if systolic AP increased to >120% of baseline or <80% of baseline or if heart rate decreased to below 50 beats min\(^{-1}\). An unblinded investigator was always present to monitor the function of the closed-loop controller and had discretion to override the system manually if there was any perceived error or any gross fluctuations of AP or heart rate. This investigator could give manual boluses of vasopressors or anticholinergic drugs as required.

**Manual-control**

In the manual-control group, the same syringe pump used in the computer-control group was manually controlled to either deliver phenylephrine at the fixed rate of 100 µg min\(^{-1}\) (60 ml h\(^{-1}\)) or be turned off. Similar to the computer-control group, the syringe pump was initially set to start the
infusion of phenylephrine at the fixed rate of 100 µg min⁻¹ (60 ml h⁻¹) at the initiation of intrathecal injection. One minute after completion of the intrathecal injection, the NIAP monitor was recommenced and set to cycle each minute. The manual-control algorithm was started immediately after the first AP measurement. After each AP measurement, infusion was either continued at the fixed rate if systolic AP was ≤ baseline or was stopped if systolic AP was > baseline.¹ ²

The infusion regimens in both groups were continued until delivery after which we terminated the study and allowed continued management by the attending anaesthetist according to his or her discretion. We continued cohydration to a maximum of 2 litres after which we adjusted fluids to a slow rate sufficient to continuously flush the phenylephrine through the i.v. cannula. Supplemental oxygen 5 litre min⁻¹ was given if the pulse oximeter reading decreased to < 95%. We noted any episodes of nausea or vomiting and the total volume of Hartmann’s solution administered up to the time of incision of the uterus.

We assessed the upper sensory level of anaesthesia 5 min after spinal injection by assessing the loss of discrimination to pinprick. We made additional checks of block height before surgery but did not utilize these levels for the purposes of the study. We also noted the times of skin incision, incision of the uterus, and delivery of the baby.

We recorded the number of interventions performed by the investigator that were related to the management of AP; these including starting, stopping, and adjusting the computer program, manual adjustment of the syringe pump, and any manually administered drug boluses. We also noted the total amount of phenylephrine that was administered until the time of incision of the uterus, and also the number of episodes of hypotension (defined by systolic AP < 80% of baseline) and hypertension (defined by systolic AP > 120% of the baseline).

After delivery of the baby, we gave 5 IU oxytocin by slow i.v. injection. Apgar scores at the first and fifth minute after birth were recorded. Umbilical arterial and umbilical venous blood specimens were drawn from a section of cord that had been double-clamped and blood gases were immediately measured using a Rapid Point 400 analyzer (Bayer Diagnostics Mfg (Sudbury) Ltd, Sudbury, UK).

Haemodynamic recordings measured after the completion of each NIAP 1 min cycle until delivery were entered into a spreadsheet for subsequent analysis. Because the NIAP apparatus was observed to take a varying time to complete individual measurements, the logged time of completion of each haemodynamic measurement set was not always exactly equal to chronological time elapsed. However, for the purposes of analysis and comparison, this error was ignored.

The accuracy of AP control was assessed first by comparing the proportion of systolic AP measurements within the range ± 20% of baseline in each group and second by analysing performance error (PE) calculations using previously described methods.⁵⁻⁷ For the latter, we calculated the following parameters: (i) median absolute PE (MDAPE), which is a measure of bias that describes whether each of the measured values for systolic AP systematically are either above or below the baseline value; (ii) median absolute PE (MDAPE), a measure of inaccuracy representing an average measure of the magnitudes of the differences of measured values for systolic AP higher or lower than baseline value; (iii) wobble (a measure of the intrasubject variability of PE about MDPE); and (iv) divergence (a trend measure describing whether the magnitudes of the differences between measured and target values of systolic AP increase (positive divergence) or decrease (negative divergence) over time). Details of the method of calculation of these parameters are shown in the Appendix. Calculations were made using Microsoft Excel 2010 (Microsoft Corporation, Redmond, WA, USA).

Sample size was based on a priori power analysis using data from our previous work in which computer-controlled phenylephrine infusion using an on–off algorithm resulted in an MDAPE of 6.0 (SD 3.1)% and wobble of 5.5 (SD 2.3)% ⁵ Based on these data, we calculated that to determine a relative 20% difference in MDAPE between the groups (e.g. 6.0% vs 4.8%) with α = 0.05 and β = 0.8, 105 patients in each group would be needed. This sample size would also have a power of 80% to detect a 16% difference in wobble (e.g. 5.5% vs 4.6%) between the two groups. To make allowance for an estimated rate of dropouts of 5%, the sample size was increased to 111 per group. Student’s t-test and the Mann–Whitney U-test were utilized as appropriate for analysing numerical scale data and Fisher’s exact test or the χ² test was used to analyse the categorical or nominal data. All of the statistical analyses were made using PASW Statistics 18.0.0 (IBM SPSS Inc., Chicago, IL, USA) and Microsoft Excel 2010.

Results

In total, 212 subjects completed the study. Subject recruitment and flow is shown in Figure 1. Subject characteristics (Table 1) were similar between the groups. The number of interventions required to manage AP for each subject was greater in the manual-control group than with the computer-control group (P < 0.001), but there were no between-group differences in total dose and median infusion rate of phenylephrine, total volume of Hartmann’s solution given, number of subjects with hypertension or hypotension, and number of subjects noted to have nausea or vomiting (Table 2). No subject required manual boluses of vasopressor or anticholinergic drugs in the computer-control group. Neonatal outcome was not different between the groups (Table 3).

In the computer-control group, 2198 out of 2259 (97%) systolic AP recordings were within ± 20% of baseline compared with 2172 out of 2279 (95%) in the manual-control group (χ² test, P = 0.0004). Changes in systolic AP over time are shown in Figure 2, changes in percentage PE over time are shown in Figure 3, and PE calculations are summarized and shown in Table 4. MDPE was similar between the groups; the median value was 1.9% in the manual-control group and 2.9% in the computer-control group, indicating a bias for systolic AP to be maintained on average slightly
above baseline in both groups. MDAPE and divergence were similar between the groups. Wobble was smaller in the computer-control group, indicating less variability of PE about MDPE compared with the manual-control group.

Discussion
This study found that the infusion of phenylephrine using a closed-loop feedback computer-controller is a feasible alternative to conventional manual-controlled infusion. Compared with the manual-control group, the computer-control system reduced intraoperative workload by the anaesthetist, as evidenced by fewer required interventions for managing AP. In addition, computer-control provided slightly better AP control, as evidenced by the greater proportion of systolic AP recordings within 20% of baseline and the smaller value for wobble.

The better control of AP in the computer-control group was likely achieved because of the more complex proportional algorithm used to control the phenylephrine infusion. It is possible that the same degree of control, or better, could be achieved by the utilization of a more complex manual algorithm. However, the automated nature of computer-control has the inherent advantage of accuracy and also frees the anaesthetist from potential distractions allowing focus on other aspects of patient care. This is offset by the more complicated setup needed for computer-control and the
possibility of hardware malfunctions. However, with further development and testing, potential improvements could include migration to hand-held devices, incorporation into syringe pump software, and elimination of cables using wireless networking or Bluetooth technology. With the continued development of monitoring technology, it is conceivable that in the future, parameters such as heart rate and cardiac output could also be incorporated into the algorithm, which could result in improved haemodynamic control.

MDPE was positive in both groups, indicating a bias for both systems to maintain systolic AP slightly above baseline. Adjustments of the algorithms could be performed to result in values of MDPE nearer to or even slightly below zero. This would likely decrease the average dose of phenylephrine and have less potential for decreasing maternal heart rate and cardiac output, concern about which has previously been expressed by other investigators using phenylephrine.89 However, this might concomitantly increase the risk of transient episodes of hypotension and thus increase the risk of maternal symptoms such as nausea. Given the excellent maternal and neonatal outcomes in our subjects, we continue to favour relatively aggressive maintenance of AP in low-risk elective cases, but with the caveat that this might not be appropriate if there is fetal compromise or impaired uteroplacental circulation.

MDPE and MDAPE were similar between the groups, indicating that on average, the two systems tended to maintain systolic AP a similar distance from baseline. However, wobble was smaller in the computer-control group. Small values for wobble reflect the ability of the system to achieve stable

### Table 1
Subject characteristics and surgical times. Values are mean (sd), mean (range) for age, or median (inter-quartile range)

<table>
<thead>
<tr>
<th></th>
<th>Manual-control group (n=103)</th>
<th>Computer-control group (n=108)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>33 (20–44)</td>
<td>33 (23–46)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>67.9 (10.1)</td>
<td>68.0 (8.9)</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>157 (5.1)</td>
<td>157 (5.3)</td>
</tr>
<tr>
<td>Block height at 5 min (dermatome)</td>
<td>T4 (T3–T5)</td>
<td>T4 (T3–T5)</td>
</tr>
<tr>
<td>Induction-to-uterine incision interval (min)</td>
<td>28.4 (23.4–34.0)</td>
<td>26.1 (22.4–32.6)</td>
</tr>
<tr>
<td>Uterine incision-to-delivery interval (s)</td>
<td>92 (64–133)</td>
<td>96 (69–124)</td>
</tr>
</tbody>
</table>

### Table 2
Number of interventions to manage AP, phenylephrine consumption, volume of i.v. fluid given and incidence of hypotension, hypertension, and nausea/vomiting. Values are median (inter-quartile range) or number (%)

<table>
<thead>
<tr>
<th></th>
<th>Manual-control group</th>
<th>Computer-control group</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of interventions to manage AP</td>
<td>10 (8–13)</td>
<td>2 (2–2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Total dose of phenylephrine (µg)</td>
<td>1220 (825–1600)</td>
<td>1070 (840–1400)</td>
<td>0.20</td>
</tr>
<tr>
<td>Phenylephrine infusion rate (µg min⁻¹)</td>
<td>42 (32–52)</td>
<td>40 (34–48)</td>
<td>0.63</td>
</tr>
<tr>
<td>Total i.v. fluid given up to the time of delivery (ml)</td>
<td>2000 (1550–2020)</td>
<td>1950 (1500–2010)</td>
<td>0.44</td>
</tr>
<tr>
<td>Patients with one or more episodes of hypotension (systolic AP&lt;80% of baseline)</td>
<td>9 (8.7%)</td>
<td>10 (9.3%)</td>
<td>0.89</td>
</tr>
<tr>
<td>Patients with one or more episodes of hypertension (systolic AP&gt;120% of baseline)</td>
<td>28 (27%)</td>
<td>27 (25%)</td>
<td>0.72</td>
</tr>
<tr>
<td>Nausea or vomiting</td>
<td>4 (3.9%)</td>
<td>3 (2.8%)</td>
<td>0.72</td>
</tr>
</tbody>
</table>

### Table 3
Neonatal outcome. Values are median (inter-quartile range) or number (%). NS, not significant

<table>
<thead>
<tr>
<th></th>
<th>Manual-control group</th>
<th>Computer-control group</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birthweight (kg)</td>
<td>3.17 (2.97–3.40)</td>
<td>3.25 (2.96–3.60)</td>
<td>0.15</td>
</tr>
<tr>
<td>Umbilical arterial blood gases</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>pH</td>
<td>7.30 (7.27–7.33)</td>
<td>7.30 (7.28–7.32)</td>
<td>0.47</td>
</tr>
<tr>
<td>Pco₂ (kPa)</td>
<td>6.3 (5.6–7.0)</td>
<td>6.2 (5.7–7.1)</td>
<td>0.77</td>
</tr>
<tr>
<td>P₀₂ (kPa)</td>
<td>2.2 (1.9–2.5)</td>
<td>2.1 (1.7–2.6)</td>
<td>0.46</td>
</tr>
<tr>
<td>Base excess (mmol litre⁻¹)</td>
<td>−4.0 (−6.0 to −2.5)</td>
<td>−4.2 (−5.9 to −2.1)</td>
<td>0.58</td>
</tr>
<tr>
<td>Umbilical venous blood gases</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>pH</td>
<td>7.36 (7.34–7.37)</td>
<td>7.35 (7.34–7.37)</td>
<td>0.05</td>
</tr>
<tr>
<td>Pco₂ (kPa)</td>
<td>5.2 (4.5–5.7)</td>
<td>5.1 (4.5–5.8)</td>
<td>0.93</td>
</tr>
<tr>
<td>P₀₂ (kPa)</td>
<td>3.7 (3.0–4.0)</td>
<td>3.5 (3.1–4.1)</td>
<td>0.91</td>
</tr>
<tr>
<td>Base excess (mmol litre⁻¹)</td>
<td>−3.8 (−5.4 to −2.7)</td>
<td>−4.1 (−6.0 to −2.5)</td>
<td>0.53</td>
</tr>
<tr>
<td>Umbilical arterial pH &lt;7.2</td>
<td>3</td>
<td>4</td>
<td>1.0</td>
</tr>
<tr>
<td>1 min Apgar score &lt;7</td>
<td>1</td>
<td>2</td>
<td>1.0</td>
</tr>
<tr>
<td>5 min Apgar score &lt;9</td>
<td>0</td>
<td>0</td>
<td>NS</td>
</tr>
</tbody>
</table>
measured values in individual subjects, albeit in our subjects centred about median values for systolic AP that were slightly above values recorded at baseline. It is possible that a small decrease in the constant by which the error factor is multiplied in the proportional algorithm could reduce MDPE and MDAPE while maintaining a low value for wobble, thus resulting in more optimized AP control overall.

Our computer-control system has the disadvantage of relying on intermittent non-invasive monitoring of AP using oscillometry. However, this monitoring mode is prone to movement and shivering artifact, and the intermittent AP measurement is an important limit to the degree of control.

It would be interesting to investigate the incorporation of other methods that are able to provide more frequent or continuous non-invasive measurement of AP. The placement of an arterial line would provide the greatest degree of control, but invasive monitoring is rarely justified in low-risk obstetric cases.

A limitation of our study design is the lack of blinding of investigators. Although blinding was theoretically possible by running both systems simultaneously with active and placebo vasopressor solutions, this was considered impractical. While we acknowledge this shortcoming of our study, we believe that the use of a strict infusion protocol in the manual infusion group and an automated system in the

---

**Table 4** PE calculations. Data are median (inter-quartile range)

<table>
<thead>
<tr>
<th></th>
<th>Manual-control group</th>
<th>Computer-control group</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median performance error (MDPE) (%)</td>
<td>1.9 (0–4.2)</td>
<td>2.9 (0.3–4.7)</td>
<td>0.37</td>
</tr>
<tr>
<td>Median absolute performance error (MDAPE) (%)</td>
<td>4.7 (3.8–6.7)</td>
<td>4.7 (3.5–5.6)</td>
<td>0.11</td>
</tr>
<tr>
<td>Wobble (%)</td>
<td>4.2 (3.3–5.9)</td>
<td>3.5 (2.5–4.8)</td>
<td>0.003</td>
</tr>
<tr>
<td>Divergence (% min⁻¹)</td>
<td>−0.06 (−0.26 to 0.08)</td>
<td>−0.01 (−0.03 to 0)</td>
<td>0.15</td>
</tr>
</tbody>
</table>

---

Fig 2 Systolic AP for all subjects plotted against time. (A) Manual-control group and (B) computer-control group. Values on the x-axis correspond to the number of each consecutive AP measurement made with the monitor set to record at 1 min intervals, and are not exactly equal to chronological time.

Fig 3 Percentage PE for all subjects plotted against time. (A) Manual-control group and (B) computer-control group. Values on the x-axis correspond to the number of each consecutive AP measurement made with the monitor set to record at 1 min intervals, and are not exactly equal to chronological time.
computer-controlled infusion group minimized potential bias that might have occurred in relation to the lack of blinding.

The magnitude of the difference in wobble between the groups was small and the better AP control with computer-control of phenylephrine infusion was not associated with any measured improvement in clinical outcomes, compared with manual-control. Although it is possible that close control of AP could be advantageous in high-risk patients, currently few data are available addressing this issue.

**Declaration of interest**

None declared.

**Funding**

This study was supported by departmental and institutional funding only.

**Appendix**

**Performance error**

PE was defined as the difference between each measured value of systolic AP (SAP) and the baseline value, expressed as a percentage of the baseline value for each subject until the time of uterine incision, calculated as:

\[ \text{PE}_i = \frac{\text{measSAP}_j - \text{tarSAP}_j}{\text{tarSAP}_j} \times 100 \] (A1)

where \( \text{PE}_i \) is the percentage PE for the \( i \)th subject at the \( j \)th minute, measSAP\(_j\) the measured SAP for the \( i \)th subject at the \( j \)th minute, and tarSAP\(_j\), the target SAP (set-point for the closed-loop system) for the \( i \)th subject.

**Median performance error**

MDPE is a measure of bias and describes whether the measured values for SAP are systematically either above or below the baseline value. For each subject, it was defined as the median of all values of PE and was calculated as:

\[ \text{MDPE}_i = \text{median} \{\text{PE}_j, j = 1, \ldots, N_i \} \] (A2)

where \( \text{MDPE}_i \) is the median PE for the \( i \)th subject and \( N_i \) the number of values for PE obtained for the \( i \)th subject.

**Median absolute performance error**

MDAPE is a measure of inaccuracy and represents an average of the magnitudes of the differences of measured values for SAP above or below the baseline value. For each subject, it was defined as the median of the absolute values of PE (|PE|) and was calculated as:

\[ \text{MDAPE}_i = \text{median} \{|\text{PE}_j|, j = 1, \ldots, N_i \} \] (A3)

where \( \text{MDAPE}_i \) is the median absolute PE for the \( i \)th subject.

**Wobble**

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

\[ \text{WOBBLE}_i = \text{median} \{|\text{PE}_j - \text{MDPE}_j|, j = 1, \ldots, N_i \} \] (A4)

where \( \text{WOBBLE}_i \) is the wobble for the \( i \)th subject.

**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 SAP increase (positive value for divergence) or decrease (negative value for divergence) with time. It was defined for each subject as the slope of the linear regression equation of the values of |PE\(_j\)| against time calculated as:

\[ \text{DIVERGENCE}_i = \frac{N_i \sum_{j=1}^{N_i} (T_{ij} \times |\text{PE}_j|) - \sum_{j=1}^{N_i} T_{ij} \times \sum_{j=1}^{N_i} |\text{PE}_j|}{N_i \sum_{j=1}^{N_i} T_{ij}^2 - \left( \sum_{j=1}^{N_i} T_{ij} \right)^2} \] (A5)

where \( \text{DIVERGENCE}_i \) is the divergence for the \( i \)th subject and \( T \) the time (min).

**References**


Handling editor: H. C. Hemmings