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Feasibility of computer-assisted vasopressor infusion using continuous noninvasive blood pressure monitoring in high-risk patients undergoing renal transplant surgery

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- A.J: Designed the study, recruited patients, collected and analysed the data and drafted the manuscript.
- S.C: collected and analysed the data and drafted the manuscript.
- B.A: Analysed the data and edited the final manuscript.
- M.C: Designed the study, analysed the data and edited the final manuscript.
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Authors' declarations of interests

- ***Alexandre Joosten, Maxime Cannesson***, & ***Joseph Rinehart*** are consultants for Edwards Lifesciences (Irvine, California, USA). Maxime Cannesson and Joseph Rinehart have ownership interest in Sironis, and Sironis has developed a fluid closed-loop system that has been licensed to Edwards Lifesciences (Irvine, CA, USA) and is now part of the Assisted fluid management system. The present closed-loop vasopressor system in this study is new, not owned or supported by Edwards, Sironis, or any other commercial entity, and is the sole creation of the co-authors. Neither Edwards, Sironis nor any other commercial entity has provided any funding, directly or indirectly, in support of the current work, to the individual authors or any of their respective departments.
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To the Editor

Intraoperative hypotension is associated with postoperative cardiovascular events [1] and blood pressure variability is associated with 30-day mortality and development of renal failure.[2] Futier et al. highlighted the importance of maintaining systolic blood pressure within 10% of preoperative level, using norepinephrine infusion to reduce organ dysfunction.[3] Tight blood pressure control is therefore essential in the management of high-risk surgical patients. This task is, however, time consuming as tight control requires frequent adjustments and constant vigilance. We developed a closed-loop vasopressor (CLV) controller that corrects hypotension with norepinephrine and extensively tested it in preclinical studies, including a recent pilot trial where blood pressure was measured from an arterial line.[4-6] However, many patients that do not have arterial lines may still benefit from rapid and consistent correction of hypotension. Although intermittent cuffs cannot rapidly detect blood pressure variation, continuous noninvasive monitoring can. Patients undergoing renal can benefit from both continuous noninvasive blood pressure monitoring and CLV therapy since they are at risk of cardiovascular complications due to hypotension and frequently have an arteriovenous fistula, which further complicates traditional blood pressure measurement. We therefore tested the feasibility of our CLV controller guided noninvasively with the ClearSight system (Edwards Lifesciences, USA) in three high-risk patients undergoing renal transplantation.

This study was approved on April 19, 2018, by the Erasme Ethics Committee (P2018/276-CCB-B406201835963) and registered on clinicaltrials.gov (NCT04111055). The study was carried out from June 15 to July 20, 2018 and patients gave written informed consent prior to surgery.

Monitoring consisted of electrocardiogram, pulse oximetry, noninvasive blood pressure, processed EEG monitoring (bispectral monitor, Aspect Medical System Inc, Natick, MA, USA) and central venous pressure. Before induction, the ClearSight system was wrapped around the second phalange of the patient's finger contralateral to any existing fistula. Anesthesia consisted of propofol-remifentanil target-controlled infusions (Base Primea infusion pump, Fresenius Kabi, Belgium) and BIS target was between 40 and 60. Rocuronium ($0.6 mg.kg^{-1}$) was administered and neuromuscular blockade monitored (Tof Scan, Idmed, France). After intubation, the lungs were ventilated with a mixture of oxygen and air [$2 L.min^{-1}$ using the Infinity C700 Anesthesia Machine (Dräger Medical GmbH, Lübeck, Germany)], a tidal volume of $7ml.kg^{-1}$, a positive end-expiratory pressure of $5cmH_2O$ and recruitment maneuvers each hour. Fluid administration consisted of Plasmalyte®, (Baxter, Belgium) at $3ml.kg^{-1}.h^{-1}$ for the duration of the renal transplant. Additional mini-fluid challenges of 100ml of crystalloid were manually administered each time stroke volume variation was above 13% for more than two consecutive minutes. Packed red blood cells were administered at the discretion of the anesthesia staff.

The CLV controller has been previously described.[4-6] An ACER laptop using Windows 7 (Microsoft Corp, Redmond, CA) connected to the serial output on the EV1000 monitor and to a Q-Core Sapphire Pump (Q-Core Medical Ltd., Netanya, Israel) ran the controller software (version 2.804). Two patients had preoperative baseline MAP levels of 72 and

74mmHg. For these patients, hypotension was predefined as a MAP equal to 65mmHg or below. We therefore selected a target MAP of 70mmHg in these patients and the CLV controller's goal was to keep the MAP within ± 5mmHg of the target. The third patient had a higher preoperative MAP (86mmHg). As such, his threshold was 75mmHg and we set the controller's goal at 80mmHg ± 5mmHg. The CLV was activated before induction, just after ClearSight finger cuff placement. The clinician could, if deemed necessary, modify the selected MAP target during the case.

The primary outcome was the percentage of case time patients were hypotensive (i.e., MAP of at least 5mmHg below the chosen CLV target). Secondary outcomes included the percentage of treatment time spent in a hypertensive state (i.e., MAP >5mmHg above the chosen target MAP with an active norepinephrine infusion), average dose of norepinephrine administered, raw percentage of "time in target" (i.e., percentage of time spent with a MAP within ± 5mmHg of the predefined MAP goal), postoperative complications, and hospital length of stay. Variables are presented as median values [25-75th percentile]. Hemodynamic variables were recorded every 20 seconds and averaged for analysis.

The controller was tested in three high-risk ASA 3 patients (37, 62, and 59 years old) with significant comorbidities (hypertension, hyperlipidemia, ischemic heart disease). Anesthesia lasted over two hours in all cases. Patients spent 5.7% [3.7-8.2] (ranges: 1.6 to 10.6%) of case time with hypotension and 2.9% [1.7-5.3] with hypertension with norepinephrine still running. It is important to note that the patient who spent the lowest amount of time in target and who was hypotensive for 10.6% of case time developed a severe anaphylactic reaction, and thus severe vasoplegia, during anesthesia induction. This patient recovered after 15 minutes using a combination of epinephrine, salbutamol, and ketamine. The median [25-75 percentiles] time in target was 91.4% [86.6-94.7]. Norepinephrine infused for 97.3% of case time (ranges: 81.4 to 98.1%). The median dose of norepinephrine was 3.7 $\mu g.min^{-1}$ and the controller did 189 modifications per hour. The system stopped functioning six times (thrice in the two first patients). The causes were due to a pump communication error (N=5) related to third-party software, and once due to an accidental plug disconnection during surgery. An audible alarm alerted the clinician when this occurred and restarting the system immediately fixed the problem in less than one minute. All patients were extubated in the operating room and stayed hospitalized 7 to 9 days. Kidney function dramatically improved for all three patients after surgery. One patient developed a urinary tract infection and was treated. No adverse event occurred after a 90 day follow-up.

Several other CLV systems using ephedrine or phenylephrine guided by noninvasive blood pressure monitoring already exist and have been tested in healthy patients undergoing C-section under spinal anesthesia. However, none has investigated the potential of this technology using norepinephrine in high-risk patients undergoing renal transplantation. The pathophysiological alterations associated with chronic kidney disease increase the risk of postoperative mortality; fluid optimization and tight blood pressure control are consequently key perioperative goals.

Noninvasively-guided CLV technology helps clinicians increase compliance to blood pressure goals in patients that do not have invasive arterial catheters. Some safety

considerations will be required before widespread clinical use would be practical, specifically errors in monitoring (e.g., accidental disconnection or miscalibration), component errors (e.g., pump error), and human error (e.g. setup of the system with the wrong drug).

In conclusion, we demonstrated the feasibility of guiding our CLV controller with a continuous and noninvasive blood pressure monitor. System improvements are required to further minimize the incidence of perioperative hypotension in high-risk patients undergoing renal transplantation.

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