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Control of Postoperative Hypotension Using a Closed-Loop System for Norepinephrine Infusion in Patients After Cardiac Surgery: A Randomized Trial

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Authors

Desebbe, Olivier
Rinehart, Joseph
Van der Linden, Philippe
et al.

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Address correspondence to Alexandre Joosten, MD, PhD, Department of Anesthesiology and Perioperative Medicine, Bicêtre Hospital, 78, Rue du General Leclerc, 94270 Le Kremlin-Bicêtre, France. joosten-alexandre@ hotmail.com.

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See Disclosures at the end of the article.

DISCLOSURES

Name: Olivier Desebbe, MD.
Contribution: This author helped design the study; recruit patients; collect and analyze the data; and edit, read, and approve the final manuscript.
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Name: Joseph Rinehart, MD.
Contribution: This author helped analyze the data (statistical analysis); critically revise the manuscript for important intellectual content; and edit, read, and approve the final manuscript.
Conflicts of Interest: J. Rinehart is a consultant for Edwards Lifesciences (Irvine, CA, USA) and has ownership interest in Perceptive Medical Inc (Newport Beach, CA, USA), which is developing closed-loop physiologic management systems. In addition, J. Rinehart has ownership interest in Sironis (Newport Beach, CA, USA), and Sironis has developed a fluid closed-loop system that has been licensed to Edwards Lifesciences, Irvine, USA, and was used in this study as a decision support system (assisted fluid management). The closed-loop system for vasopressor administration used in this study is new and is the sole creation of 3 of the authors (M.C., J.R., and A.J.). A provisional patent has been submitted through the University of California Irvine covering aspects of closed-loop vasopressor administration, but does not cover any of the processes discussed in the current manuscript.
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Contribution: This author helped design the study, recruit patients, collect and analyze the data, draft the manuscript, and read and approve the final manuscript.

Control of Postoperative Hypotension Using a Closed-Loop System for Norepinephrine Infusion in Patients After Cardiac Surgery: A Randomized Trial

Olivier Desebbe, MD[*], **Joseph Rinehart, MD**[†], **Philippe Van der Linden, MD, PhD**[‡], **Maxime Cannesson, MD, PhD**[§], **Bertrand Delannoy, MD**[*], **Marc Vigneron, MD**[‖], **Alain Curtil, MD**[‖], **Etienne Hautin, MD**[*], **Jean-Louis Vincent, MD, PhD**[¶], **Jacques Duranteau, MD, PhD**[#], **Alexandre Joosten, MD, PhD**[#,**]

[*]Department of Anesthesiology and Perioperative Care, Ramsay Santé, Sauvegarde Clinic, Lyon, France

[†]Department of Anesthesiology and Perioperative Care, University of California, Irvine, Irvine, California

[‡]Department of Anesthesiology, Brugmann Hospital, Université Libre de Bruxelles, Brussels, Belgium

[§]Department of Anesthesiology and Perioperative Medicine, David Geffen School of Medicine, University of California, Los Angeles, Los Angeles, California

[‖]Department of Cardiac Surgery, Ramsay Santé, Sauvegarde Clinic, Lyon, France

[¶]Department of Intensive Care, Erasme University Hospital, Université Libre de Bruxelles, Brussels, Belgium

[#]Department of Anesthesiology and Intensive Care, Hôpitaux Universitaires Paris-Sud, Université Paris-Sud, Université Paris-Saclay, Bicêtre and Paul Brousse Hospitals, Assistance Publique Hôpitaux de Paris, Villejuif, France

[**]Department of Anesthesiology, Erasme University Hospital, Brussels, Belgium.

Abstract

BACKGROUND: Vasopressors are a cornerstone for the management of vasodilatory hypotension. Vasopressor infusions are currently adjusted manually to achieve a predefined arterial pressure target. We have developed a closed-loop vasopressor (CLV) controller to help correct hypotension more efficiently during the perioperative period. We tested the hypothesis that patients managed using such a system postcardiac surgery would present less hypotension compared to patients receiving standard management.

METHODS: A total of 40 patients admitted to the intensive care unit (ICU) after cardiac surgery were randomized into 2 groups for a 2-hour study period. In all patients, the objective was to maintain mean arterial pressure (MAP) between 65 and 75 mm Hg using norepinephrine. In the CLV group, the norepinephrine infusion was controlled via the CLV system; in the control group,

Conflicts of Interest: Alexandre Joosten is a consultant for Edwards Lifesciences (Irvine, CA, USA) and has ownership interest in Perceptive Medical Inc (Newport Beach, CA, USA), which is developing closed-loop physiologic management systems.
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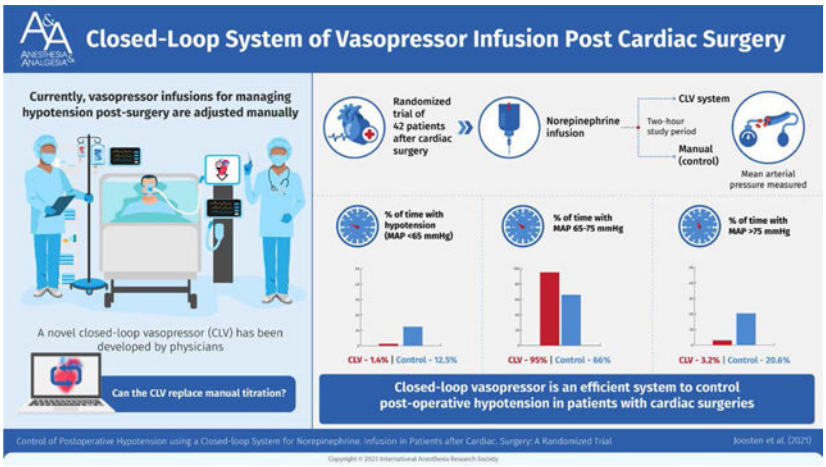
it was adjusted manually by the ICU nurse. Fluid administration was standardized in both groups using an assisted fluid management system linked to an advanced hemodynamic monitoring system. The primary outcome was the percentage of time patients were hypotensive, defined as MAP <65 mm Hg, during the study period.

RESULTS: Over the 2-hour study period, the percentage of time with hypotension was significantly lower in the CLV group than that in the control group (1.4% [0.9–2.3] vs 12.5% [9.9–24.3]; location difference, −9.8% [95% CI, −5.4 to −15.9]; $P < .001$). The percentage of time with MAP between 65 and 75 mm Hg was also greater in the CLV group (95% [89–96] vs 66% [59–77]; location difference, 27.6% [95% CI, 34.3–19.0]; $P < .001$). The percentage of time with an MAP >75 mm Hg (and norepinephrine still being infused) was also significantly lower in patients in the CLV group than that in the control group (3.2% [1.9–5.4] vs 20.6% [8.9–32.5]; location difference, −17% [95% CI, −10 to −24]; $P < .001$).

The number of norepinephrine infusion rate modifications over the study period was greater in the CLV group than that in the control group (581 [548–597] vs 13 [11–14]; location difference, 568 [578–538]; $P < .001$). No adverse event occurred during the study period in both groups.

CONCLUSIONS: Closed-loop control of norepinephrine infusion significantly decreases postoperative hypotension compared to manual control in patients admitted to the ICU after cardiac surgery. (Anesth Analg 2022;134:964–73)

Graphical Abstract



Recent evidence indicates that postoperative hypotension, by decreasing the perfusion pressure to the heart, brain, and kidney, is strongly associated with adverse events.[1–7] Prolonged hypotension can also compromise organ function and the viability of myocardial cells, causing myocardial cell damage that alters cardiac pump function.[6,7] In a large prospective, randomized controlled trial, maintaining arterial pressure at an individualized target value in patients undergoing major surgery, was associated with reduced postoperative organ dysfunction.[8] It is, therefore, potentially desirable for perioperative hypotension to be corrected rapidly.

In the postoperative context, the current approach to vasopressor administration is manual adjustment of the infusion rate of the vasopressor agent, most often norepinephrine, by

nurses, to achieve a predefined arterial pressure target. This manual titration is just 1 of many complex tasks that nurses need to perform at the same time, inevitably leading to delays in arterial pressure control. Moreover, the nurse to patient ratio postoperatively is rarely 1:1 as it is in the operating room, limiting the time available to dedicate to vasopressor infusion adjustments. Large variations have been reported in the amount of time patients receiving vasopressor infusions spend within an "optimal" arterial pressure range.[9]

We have developed a closed-loop vasopressor (CLV) controller system that automatically adjusts a vasopressor infusion to achieve a predefined arterial pressure target.[10–14] The overall goal of this system is to help reduce the amount of time that patients spend outside optimal arterial pressure thresholds, as determined by the managing physician. Very recently, we reported that the CLV controller was superior to manual management in reducing intraoperative hypotension in patients undergoing major abdominal surgery.[15] In a small prospective pilot study, we also showed that use of this system was feasible in a small cohort of postoperative cardiac patients.[16]

In this prospective randomized trial, standard-of-care arterial pressure management was compared to management using our CLV system in the immediate period postcardiac surgery. The goal of arterial pressure control after cardiac surgery in our institution is to keep mean arterial pressure (MAP) >65 mm Hg to ensure adequate organ perfusion while minimizing mediastinal blood loss. Our hypothesis was that patients managed with the CLV system would experience less hypotension (MAP <65 mm Hg) compared to those receiving standard management.

METHODS

This single-center, 2-arm, parallel-group, randomized controlled superiority study was approved on November 12, 2020, by the Comité de Protection des Personnes Nord-Ouest II under the number 2019-A03191–56 and registered prior patient enrolment with ClinicalTrials.gov (NCT04586218—Principal investigator: Olivier Desebbe—date of registration: October 14, 2020). Importantly, since 2018, clinical research protocols are not reviewed by the local institutional review board (IRB) but rather are randomly directed to a different institution's review board in France to reduce bias in reviews. The study was conducted over a period of 3 weeks (November 26–December 17, 2020) at the Sauvegarde Clinic, Lyon (a nonuniversity hospital with a high volume of patients having cardiac surgery). Written informed consent was obtained from all patients before surgery.

Patient Inclusion and Noninclusion Criteria

All adult (>18 years) French-speaking patients, undergoing elective cardiac surgery (with or without cardiopulmonary bypass [CPB]) during the study period, were considered for inclusion. Exclusion criteria were severe preoperative cardiac arrhythmias, renal insufficiency (estimated glomerular filtration rate <30 mL min^{-1} 1.73 m^{-2}), uncontrolled or severe preoperative hypertension, left ventricular ejection fraction <40%, preoperative infection, and pregnancy.

Randomization and Blinding

Randomization assignments were generated without restriction and were generated on November 24, 2020, using an Internet-based software (http://www.randomization.com- IP: 2a01:cb00:4f5:6300:f92e:b01f:468a:51e3; Timestamp: November 24, 2020, 16:19:33 UTC). According to IRB request, a written informed consent was obtained before surgery. To avoid bias during the study period, patients were also randomized before surgery to postoperative CLV or manual management. This was done by an independent person not involved in the trial. Allocation was concealed in sequentially numbered opaque envelopes. They were kept in the research room of the hospital. Patients, anesthesia providers managing the patient during the surgery, and the investigator collecting the data were all blinded to group allocation. One of the authors, A. Joosten, who has experience with the CLV system, was present in the intensive care unit (ICU) during the study protocol for each of the CLV patients to ensure correct use of the investigational system. However, he was not involved in data collection.

Anesthetic Protocol

Intraoperative Period.—Patients were equipped with standard monitoring, including a 5-lead electrocardiogram, noninvasive pulse oximetry, upper arm blood pressure cuff, end-tidal co_2 monitoring, and an anesthetic depth monitor (GE Entropy Module, GE Healthcare). A radial arterial catheter was inserted before induction of anesthesia, and a triple-lumen central venous catheter was inserted after induction.

Anesthesia was induced and maintained with propofol combined with remifentanil administered using target-controlled infusion systems to achieve a target spectral entropy of 40 to 60. Cisatracurium (0.15 mg kg^{-1}) was administered for tracheal intubation, and muscle relaxation was maintained with additional 10-mg boluses during surgery. The lungs were mechanically ventilated with an Fio_2 of 50% (Aisys CS^2, GE Healthcare), a tidal volume of 8-mL kg^{-1} predicted body weight, and a positive end-expiratory pressure of 5 cm H_2O.

Fluid administration consisted of a baseline infusion of balanced isotonic crystalloid solution (Ringer lactate, B-Brown) at a rate of 3 mL kg^{-1} h^{-1}. Intraoperative cell salvage was used, and the reservoir content of the CPB circuit was reinfused at the end of the CPB. Packed red blood cells were administered perioperatively to maintain the hemoglobin concentration between 7 and 9 g dL^{-1}. Fluid boluses of 250 mL of Ringer's lactate were given at the discretion of the managing anesthesia team. Norepinephrine was continuously administered after CPB through a peripheral vein to keep MAP >65 mm Hg.

Postoperative Period.—Patients were admitted to the ICU postoperatively and kept sedated with propofol and remifentanil infusions for a minimum of 2 hours and 15 minutes before extubation to ensure adequate blood gas parameters and normal body temperature (>36.5°) using an active forced-air warming system (3M Bair Hugger). When the decision was made to wake the patient, paracetamol (15 mg kg^{-1}), nefopam (40 mg), tramadol (2 mg kg^{-1}), and morphine (0.1 mg kg^{-1}) were administered 1 hour before stopping the remifentanil and propofol.

Study Protocol

The study protocol began 15 minutes after patient arrival in the ICU and continued for a period of 2 hours, during which propofol and remifentanil infusions were unchanged. Fluid administration was standardized in both groups and consisted of a baseline infusion of Ringer's lactate (42 mL h^{-1}), and minifluid challenges of 100 mL of the same solution to optimize stroke volume based on the recommendations of a real-time clinical decision support system ("assisted fluid management" or AFM) incorporated into an advanced hemodynamic monitoring device (EV-1000 clinical platform, Edwards Lifesciences). This AFM system makes recommendations about when a bolus of fluid is likely to result in an increase in stroke volume, as described in recent publications.[17–19]

In all patients, norepinephrine infusion was administered using an electric syringe pump (concentration of 32 μg mL^{-1}) on a separate lumen of the central venous catheter during the 2-hour study period to maintain MAP between 65 and 75 mm Hg. In the CLV group, the CLV system adjusted the norepinephrine infusion rate to keep the MAP within this range. Clinicians could override the CLV system at any time point, if MAP management was considered suboptimal.

In the control group, ICU nurses first fixed the upper and lower limit alarms of MAP on the patient monitor (to be alerted whenever MAP was <65 or >75 mm Hg) and then manually adjusted the norepinephrine infusion rate to keep the MAP within this range, according to the current standard of care. In both groups, the nursing coverage ratio was 1 to 2–3, as it was the standard of care in our ICU.

CLV Controller

The CLV management system has been studied in feasibility and operating room trials and is described in detail in those publications.[10–12,15,16] As a brief overview, the system collects arterial pressure data from a clinical monitor and, through a combination of predictive and rules-based control modules, titrates a norepinephrine infusion to maintain MAP around a prespecified target (70 ± 5 mm Hg for the present study) through automated adjustments of the infusion rate. The algorithm is coded in Microsoft Visual C (Microsoft Corp). Version 2.93 of the CLV controller software was used for all the patients in this study. The controller software was run on an Acer laptop using Windows 7 (Microsoft Corp). It was connected to a serial output on an EV-1000 monitor and a Chemyx Fusion 100 syringe pump (Chemyx Inc). Figure 1 shows a photograph of the CLV system setup in 1 patient in the ICU during the study period. Of note, the norepinephrine infusion in the CLV patients was administered via the proximal input of the central line; the peripheral intraoperative norepinephrine infusion was slowly and progressively reduced to 0 over the first 5 minutes of management to enable a smooth handover of management to the automated system. The peripheral line was kept available as backup in case there were errors in the CLV system or the ICU team was not satisfied with the automated management. Administration of any other vasopressor (eg, ephedrine and phenylephrine) was not allowed unless required for safety, in which case it was considered a protocol failure.

Study Measurements and Outcomes

Hemodynamic variables (MAP, heart rate, stroke volume index, and cardiac index) were recorded every 20 seconds by the EV-1000 monitor and subsequently averaged. At the end of the protocol period, data from the EV-1000 platform were downloaded for analysis. For the CLV group, data from the CLV system were also downloaded.

The primary outcome was the percentage of the study period (the first 2 postoperative hours in the ICU) during which patients were hypotensive, defined as an MAP <65 mm Hg. The primary outcome was calculated on a per-patient basis as: Secondary outcomes included the number of norepinephrine infusion rate modifications, and the amounts of fluid and norepinephrine received during the protocol period; incidence of postoperative acute kidney injury at postoperative day 7; and troponin values measured on all patients on ICU arrival and postoperative day 1. Other exploratory outcomes were: percentage of time during which the MAP was >75 mm Hg with norepinephrine still being infused; percentage of time with an MAP between 65 and 75 mm Hg ("time-in-target"); and percentage of time with an MAP <60 mm Hg. Postoperative complications were recorded at 30 days after surgery. Lengths of stay in the ICU and the hospital were also registered.

Data Collection

All hemodynamic variables were collected at 20-second intervals via the EV-1000 monitor. The study started 15 minutes after patients' arrival in the ICU and for 2 hours.

Statistical Analysis

Data for the primary outcome of time with MAP <65 were analyzed using a modified intention-to-treat approach based on assignment to the control group (manual titration) or the study group (closed-loop titration). The distribution of continuous data was tested for normality using a Shapiro-Wilk test and visually assessed by histogram. Normally distributed variables were compared using a Student *t* test and are expressed as mean ± standard deviation (SD), and those not normally distributed were compared using a Mann-Whitney *U* test and are expressed as median (25–75) percentiles. Discrete data are expressed as numbers and percentages and were compared using a χ^2 or a Fisher exact test when indicated.

Group baselines were assessed with absolute standardized mean differences (ASDs) using the method of Yang and Dalton.[20] For this study, a significant imbalance in baseline characteristics was defined as an ASD >0.65 calculated using the method of Austin 2009.[21]

Differences in groups are described by location difference (the mean of the difference for normally distributed variables and median of the difference between 2 samples using the Hodges-Lechmann estimate for nonnormally distributed data). A 2-sided *P* value of <.05 indicated statistical significance for the primary outcome. All other analyses were considered to be exploratory and hypothesis-generating. No interim analysis was planned on the data. Data were analyzed using Minitab and R.

Study Power

In a review of hemodynamic data from cardiac surgery patients at the Sauvegarde clinic, patients in whom norepinephrine infusion was manually adjusted by ICU nurses spent 20% ± 10% of treatment time with an MAP <65 mm Hg. As such, with a power of 80% and an alpha risk of 0.05, 16 patients per group would need to have been included in our study to detect a 50% relative reduction (from 20% ± 10% in the control group to 10% ± 9% in the CLV group, ie, a 10% absolute reduction) in postoperative hypotension in the CLV group using Student *t* test. In the event a Mann-Whitney test was needed based on the underlying distributions at the time of analysis, a Monte-Carlo simulation using 50,000 simulated trials drawing from normal distributions with the parameters and the alpha/beta risks noted above showed that 17 patients per group were required. To account for this possibility and the potential for drop-out, therefore, we decided to include 20 patients per group (40 patients in total).

RESULTS

Patient Population

Between November 26 and December 17, 2020, 40 of the 45 patients eligible for inclusion were enrolled and randomized (Figure 2). The trial was not stopped before obtaining the sample size goal. There were 3 postrandomization exclusions: 1 patient with severe post-CPB vasoplegic syndrome who required the simultaneous use of a vasopressin infusion (making impossible to include the patient in the study protocol); 1 incidental discovery of severe pulmonary hypertension during surgery; and 1 patient with new-onset atrial fibrillation during the immediate postoperative period, which precludes use of the AFM system (it cannot interpret fluid requirement when atrial fibrillation is present). As a result, 37 patients underwent the postoperative study protocol: 17 in the control group and 20 in the CLV group. All patients but 1 (in the control group) had surgery under CPB.

Baseline characteristics and intraoperative data were well balanced between the 2 groups as assessed by absolute standardized difference, as shown in Tables 1 and 2.

Study period time was 122.4 ± 2.1 minutes in the control group and 122.2 ± 2.2 minutes in the CLV group (location difference, 0.22 [95% CI, −1.2 to 17]; $P = .757$)

No patient required an inotrope support during the 2-hour study period.

Outcome Measures

Patients in the CLV group were hypotensive (MAP <65 mm Hg) for less of the study period than were patients in the control group (1.4% [0.9–2.3] vs 12.5% [9.9–24.3]; location difference, −9.8 [95% CI, −5.4 to −15.9]; $P < .001$) (Figure 3). MAP values in both groups throughout the study period are shown in Supplemental Digital Content 1, http://links.lww.com/AA/D815.

No difference was observed in the total dose of norepinephrine between groups (0.38 mg [0.20–0.57] vs 0.38 mg [0.28–0.57]; location difference, 0.04 [–0.12 to 0.18]; $P = .615$), but the norepinephrine infusion rate was modified more frequently in the CLV group than

that in the control group (581 [548–597] vs 13 [11–14] times; location difference, 568 [578 to −38]; $P < .001$). The percentage of time during which the norepinephrine infusion was running was lower in the CLV group than that in the control group (96% [93–99] vs 100% [100–100]; location difference, −3.2 [95% CI, −0.7 to −5.3]; $P < .001$) (Table 3).

The percentage of time with an MAP <60 mm Hg during the treatment period was significantly lower in the CLV patients than that in the control group (0.0% [0.0–0.0] vs 1.1% [0.0–2.6]; location difference, −1.1% [95% CI, 0.0 to −2.4]; $P < .001$), and the percentage of time within the MAP target range of 65–75 mm Hg significantly higher (94.5% [88.8–96.4] vs 65.6% [59.2–77.2]; location difference, 28% [95% CI, 34 to 19]; $P < .001$). The percentage of time with an MAP >75 mm Hg (and norepinephrine still being infused) was also significantly lower in patients in the CLV group than that in the control group (3.2% [1.9–5.4] vs 20.6% [8.9– 32.5], location difference, −17% [95% CI, −10 to −24]; $P < .001$). All these data are shown in Supplemental Digital Content 2, http://links.lww.com/AA/D816.

Incidence of postoperative complications and lengths of ICU and hospital stay were not different between groups (Supplemental Digital Content 2, http://links.lww.com/AA/D816). Total blood loss recorded at drain removal was lower (805 mL [420–1218] vs 1200 mL [815–1370]; $P = .044$), and diuresis during the protocol period was higher (150 mL [103–260] vs 100 mL [45–180]; $P = .020$) in the CLV group than that in the control group.

There were no system errors and no override with the use of the CLV system. As a result, the ICU clinicians in charge of the patients never needed to use backup vasopressor infusions during the study period.

DISCUSSION

This is the first prospective randomized controlled trial to compare the present CLV system with standard-of-care manual titration in surgical ICU patients. Consistent with our intraoperative reports,[15,18] the CLV system maintained arterial pressure in a much narrower range than did manual titration, resulting in a 90% reduction in hypotension time and >80% reduction in overtreatment (hypertension) time during the 2-hour protocol period. Time-in-target (MAP between 65 and 75 mm Hg) increased from 66% in the manual group to 95% in the CLV group.

There were no significant differences in the incidence of postoperative complications, length of stay, or laboratory data between groups. This is probably not surprising given the overall risk profile of cardiac surgery patients, of the surgical procedure, with or without CPB, and of the postoperative recovery; a 2-hour management period is unlikely to have a major impact on such outcomes. The small number of patients studied also precludes any definitive conclusion regarding these outcomes. Nevertheless, we observed a lower total blood loss in the CLV-managed patients, which could potentially be related to the reduction in the duration of “hypertensive” episodes, and the lower variation in MAP over time. Although interesting, this observation should only be considered exploratory and used for hypothesis generating in further adequately powered studies.

As would be expected, the CLV system made hundreds of changes in the vasopressor infusion rate per hour (an average of 4.5 per minute), compared to a median of 6 to 7 adjustments per patient per hour in the control group. The chief benefit of all forms of automation is the ability to make continuous micro-adjustments at a rate and scale that is not feasible for a human provider. Rate titration is not a cognitively challenging task, but requires some input in terms of time and attention, and bedside provider time is a limited and valuable resource (a fact the COVID-19 epidemic has highlighted). Offloading rate titration to an automated system in the present study resulted in far tighter control with less provider workload. Six to 7 adjustments per hour—1 adjustment every 8 to 10 minutes—may not seem much, but when factoring in the time required to track the patient after each adjustment to ensure an appropriate response and the monitoring between adjustments, it becomes evident there is significant workload associated with this task for bedside providers, much more than is implied by the actual number of rate changes. A corollary to the reduced cognitive workload is, however, the “out-of-the-loop” problems that may be experienced when new automation is introduced. In the present context, when the cognitive workload of directly managing the arterial pressure and norepinephrine infusion is removed by automation, there is a risk that the bedside provider may be slower to recognize signs or symptoms of processes that require intervention because they may be masked by the automated system. For example, a steady and rapid rise in vasopressor requirements may signify volume loss, cardiac decompensation, or a vasodilatory process. If the mode of action of the CLV system is not clearly understood by the bedside provider and efforts are not made by the system to maintain provider situation awareness, this sign may be missed because the closed loop will keep the pressure within the target range despite increasing needs. Such situational awareness considerations must be an integral part of the system design if widespread adoption is to be feasible. The airline industry has significant experience of situational awareness in the context of autopilot.

Limitations

The present study is subject to several limitations. The study period was a short portion of the overall ICU care of the patient, and 3 patients had to be excluded after enrolment before protocol procedures being performed because of perioperative complications not related to the study protocol. The CLV system was set up and supervised by a single experienced user; while performance of the system would not be expected to differ, the overall experience with the CLV may differ in a routine use scenario and, thus, limits generalization of the results to other situations.

CONCLUSIONS

Closed-loop control of norepinephrine infusion significantly decreases the duration of postoperative hypotension compared to manual control in patients admitted to the ICU after cardiac surgery. Future studies are needed to explore whether managing patients with such systems during the entire ICU length of stay may reduce postoperative complications.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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GLOSSARY

ACEI	angiotensin-converting-enzyme inhibitor
AFM	assisted fluid management
ARB	angiotensin II receptor blocker
ASA	American Society of Anesthesiologists
ASD	absolute standardized mean difference
BNP	B-type natriuretic peptide
CABG	coronary artery bypass graft
CLV	closed-loop vasopressor
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	coronavirus disease 2019
CPB	cardiopulmonary bypass
ICU	intensive care unit
IRB	institutional review board
MAP	mean arterial pressure
SD	standard deviation

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KEY POINTS

- **Question:** Is a new closed-loop system for vasopressor titration superior to standard-of-care manual vasopressor titration (titration adjusted by intensive care unit nurses) in patients admitted in the intensive care unit after cardiac surgery?
- **Findings:** The closed-loop system maintained arterial pressure in a much narrower range than did manual titration, resulting in a 90% reduction in hypotension time during the 2-hour study period.
- **Meaning:** Closed-loop vasopressor titration significantly outperforms manual titration by reducing postoperative hypotension in patients admitted in the intensive care unit after cardiac surgery.

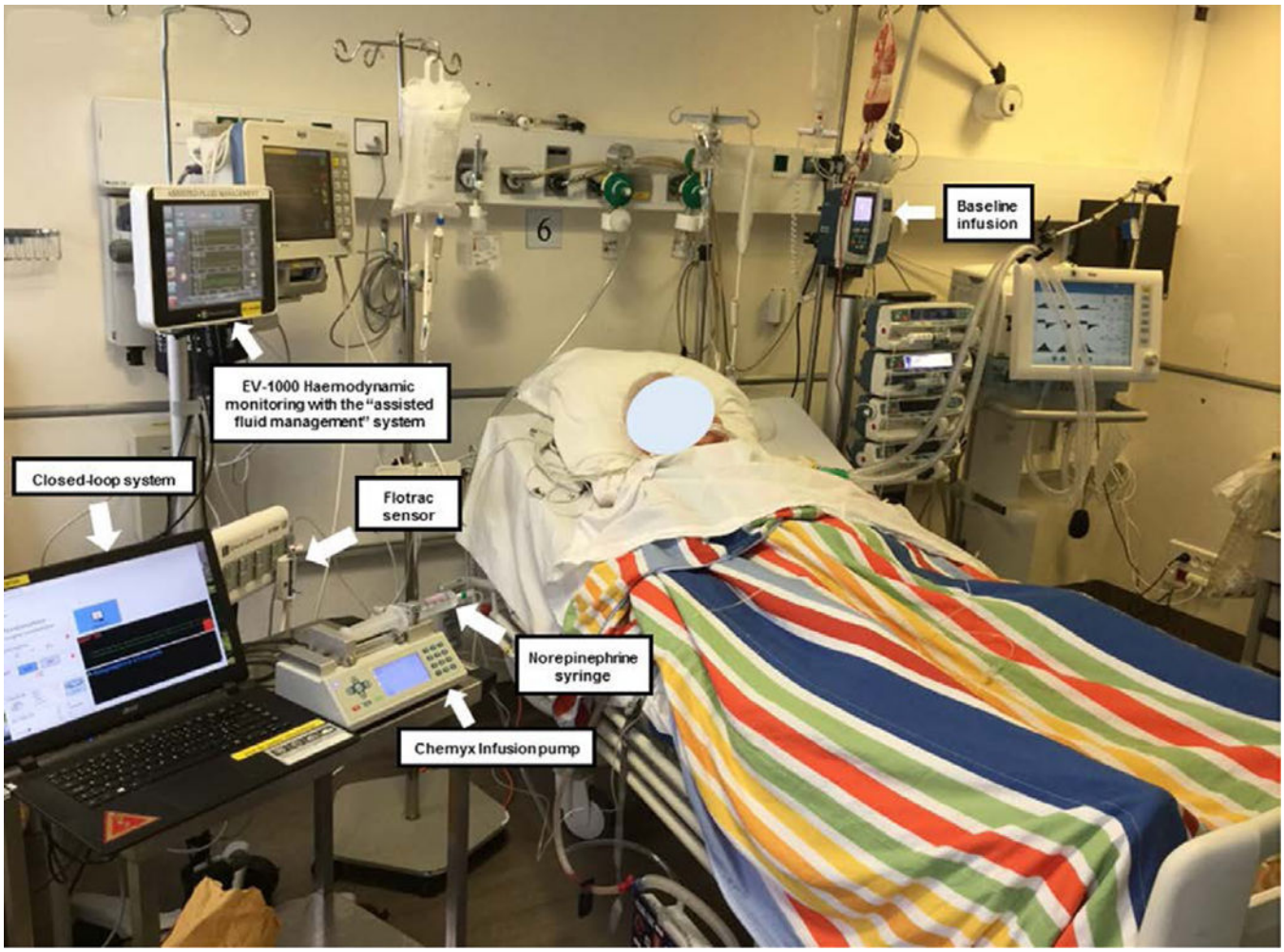

Figure 1.
Closed-loop system set up in the intensive care unit at the Sauvegarde Clinic, Lyon, France.

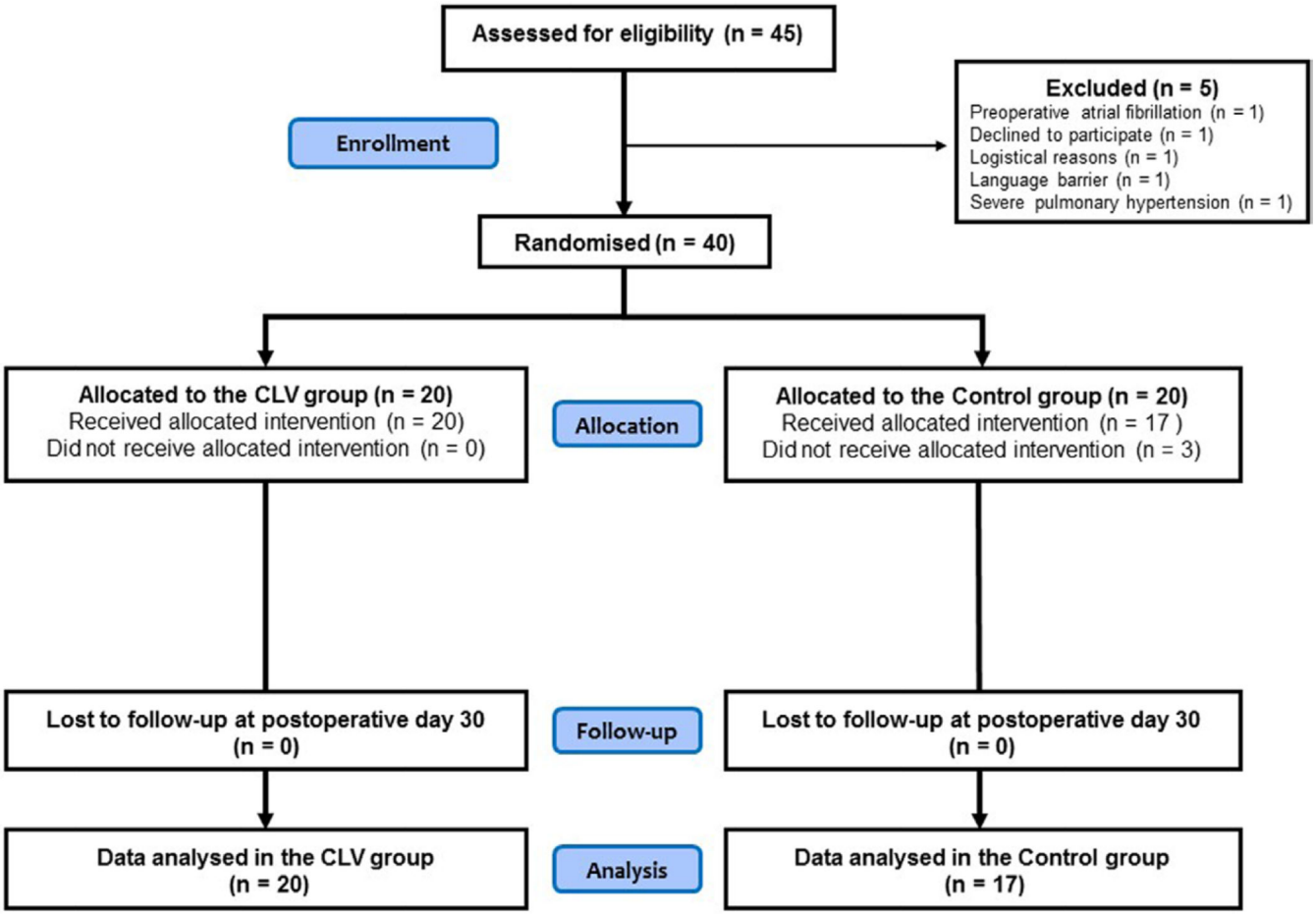

Figure 2.

CONSORT diagram of patient flow. Flow diagram illustrating patient enrolment and reasons for exclusion. CLV indicates closed-loop vasopressor; CONSORT, Consolidated Standards of Reporting Trials.

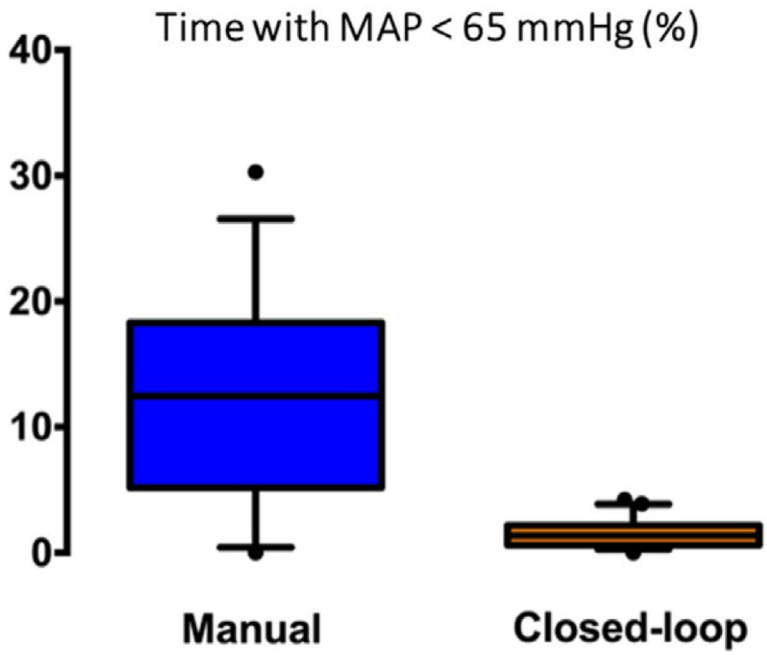

Figure 3.
Boxplots show the percentage of protocol time with hypotension (MAP <65 mm Hg) in the 2 groups. MAP indicates mean arterial pressure.

Table 1.

Baseline Characteristics

Variables	CLV group (N = 20)	Control group (N = 17)	Absolute standardized difference
Age (y)	69 ± 7	67 ± 13	0.21
Sex, Male	14 (70)	14 (82)	0.29
Weight (kg)	78 ± 16	82 ± 16	0.24
Height (cm)	169 ± 9	171 ± 8	0.35
Body surface area (m^2)	1.8 ± 0.2	1.9 ± 0.2	0.31
Body mass index ($kg.m^{-2}$)	26.3 (24.5–29.3)	25.9 (24.7–29.4)	0.09
ASA physical status II/III	0/20	1/16	0.35
Predicted 30-d mortality (Euroscore II)	1.5 (0.8–2.4)	1.4 (1.0–2.4)	0.03
Preoperative haemoglobin ($g\ Dl^{-1}$)	13.9 ± 1.7	13.8 ± 1.8	0.06
Preoperative plasma creatinine ($mmol\ L^{-1}$)	82 ± 16	89 ± 21	0.37
Preoperative pro-BNP ($ng\ L^{-1}$)	531 (118–1449)	145 (76–1301)	0.01
Preoperative left ventricular ejection fraction (%)	61 (60–65)	61 (60–65)	0.03
Medication, n (%)			
Aspirin	7 (35)	6 (35)	0.01
Clopidogrel	3 (15)	1 (6)	0.30
β-blocker	10 (50)	7 (41)	0.18
ACEI	4 (20)	7 (41)	0.47
ACEI or ARB	9 (52)	12 (60)	0.14
Statin	10 (50)	9 (53)	0.06
Diuretic	4 (20)	5 (29)	0.22
Calcium blocker	2 (10)	0 (0)	0.47
Comorbidities, n (%)			
Myocardial injury	10 (50)	10 (58)	0.18
Arterial hypertension	15 (75)	13 (76)	0.03
Hyperlipidaemia	11 (55)	9 (53)	0.04
Diabetes	3 (15)	4 (24)	0.22
Chronic obstructive pulmonary disease	3 (15)	2 (12)	0.10
Type of surgery, n (%)			

Variables	CLV group (N = 20)	Control group (N = 17)	Absolute standardized difference
CABG	8 (40)	9 (53)	0.41
Valve	7 (35)	3 (18)	
Combined procedures	2 (10)	2 (12)	
Others[a]	3 (15)	3 (18)	

Data are listed as number and (%) or mean ± standard deviation or median and (25–75) percentiles.

Abbreviations: ACEI, angiotensin-converting-enzyme inhibitor; ARB, angiotensin II receptor blockers; ASA, American Society of Anesthesiologists; BNP, B-type natriuretic peptide; CABG, coronary artery bypass graft; CLV, closed-loop vasopressor.

[a]Included aortic surgery (Bentall procedure) and atrial myxoma.

Table 2.

Intraoperative Data

Variables	CLV group (n = 20)	Control group (n = 17)	Absolute standardized difference
Anesthesia duration (min)	224 ± 37	223 ± 36	0.02
Surgery duration (min)	165 ± 40	158 ± 32	0.19
Cardiopulmonary bypass duration (min)	78 ± 35	79 ± 37	0.05
Aortic clamp duration (min)	53 ± 28	57 ± 34	0.15
Total crystalloid (mL)	625 (500–1000)	500 (500–1500)	0.03
Total priming (mL)	1500 (1500–1500)	1500 (1500–1500)	0.46
Hemofiltration (mL)	0 (0–438)	0 [0–375]	0.06
Total fluid received (mL)[a]	2333 ± 666	2206 ± 787	0.06
Urine output (mL)	300 (163–465)	300 (200–400)	0.23
Total dose of norepinephrine (mg)	1.3 ± 0.7	1.1 ± 0.9	0.33

Data are expressed as mean ± standard deviation or median and (25–75) percentiles.

Abbreviation: CLV, closed-loop vasopressor.

[a]No patient received blood products.

Table 3.

Outcome Data

Variables	CLV group (n = 20)	Control group (n = 17)	Location difference[a] and 95% CI	P value
Primary outcome				
Percentage of protocol period with an MAP <65 mm Hg (%)	1.4 (0.6–2.2)	12.5 (5.2–18.3)	−9.8 (–5.4 to −16.0)	<.001
Secondary outcomes (during the 2-h study period)				
Total dose of norepinephrine received (mg)	0.38 (0.20–0.57)	0.38 (0.28–0.57)	0.04 (–0.12 to 0.18)	.615
Number of norepinephrine infusion rate modifications	581 (548–597)	13 (11–14)	568 (578–538)	<.001
Percentage of time with norepinephrine infusion running (%)	96 (93–99)	100 (100–100)	–3.2 (–0.7 to −5.3)	<.001
Amount of baseline crystalloid fluid received (mL)	84 (84–84)	84 (84–84)	0 (0–0)	.522
Amount of crystalloid received (AFM recommendations) (mL)	985 ± 342	809 ± 402	176 (425–72)	.159
Total fluid received (mL)	1070 ± 343	904 ± 412	166 (418–86)	.190
Other secondary outcomes				
Acute kidney injury, n (%)	4 (20)	4 (24)	3 (0–27)	.795
Troponin values on ICU arrival (ng mL^{-1})	335 (214–656)	172 (149–613)	100 (245–36)	.115
Troponin values on postoperative day 1 (ng mL^{-1})	303 (272–531)	253 (171–545)	79 (208–40)	.161

Data are expressed as number and (%), mean ± standard deviation, or median and (25–75) percentiles.

AFM, assisted fluid management; CI, confidence interval; CLV, closed-loop vasopressor; ICU, intensive care unit; MAP, mean arterial pressure.

[a]Defined as the mean or median of the difference between a sample from each group.