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Closed-loop Control of Vasopressor Administration in Patients Undergoing Cardiac Revascularization Surgery: A Case Series

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- J.R: Designed the study, analysed the data and drafted the final manuscript.
- M.C: Designed the study, analysed the data and edited the final manuscript.
- S.W.: analysed the data and edited the manuscript
- L.B: collected & analysed the data and edited the final manuscript.
- L.VO: collected & analysed the data and edited the final manuscript.
- A.J: Designed the study, recruited patients, collected and analysed the data and edited the manuscript.

Authors' declarations of interests

- **Alexandre Joosten** is consultant for Edwards Lifesciences, Irvine USA, Aguetant Laboratoire, Lyon, France and Fresenius Kabi, Bad Homburg, Germany
- **Maxime Cannesson and Joseph Rinehart** are consultant for Edwards Lifesciences, Irvine, USA and have ownership interest in Sironis. 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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Keywords

Intraoperative Hypotension; blood pressure; cardiac surgery; norepinephrine; Robotic Surgery; cardiopulmonary bypass

Introduction

Intraoperative hypotension and arterial pressure variability have been shown to negatively impact patient outcomes, increasing risk of stroke, kidney injury, and myocardial injury among others.[1-5] Vasopressors are usually used to rapidly correct hypotension. Vasopressor infusions are typically administered by standard infusion pump with the rate adjusted by bedside providers to reach a predefined target mean arterial pressure (MAP); this requires frequent changes in the infusion rate because of the almost constantly changing hemodynamic status of such patients. Because it is infeasible for human providers to pay constant attention and make second-to-second changes, management is often suboptimal (i.e. large amounts of time are spent in hypotension below the target, or well above the target with the vasopressor drip still running). Indeed, we have shown that patients under continuous vasopressor infusion in both the operating room (OR) and intensive care units (ICU) spent around 50% of treatment time outside a reasonable MAP target when on vasopressors.[6]

We have developed an automated closed-loop vasopressor (CLV) controller to improve the titration of vasopressor (e.g:norepinephrine) in order to maintain MAP within a narrow range (± 5 mmHg of the chosen target) in the perioperative setting. We have published engineering and animal studies and most recently, described the feasibility of norepinephrine titration in 20 patients undergoing major noncardiac procedures [7-10] This initial cohort pilot study showed the controller was able to keep patients within ± 5 mmHg of a target pressure for more than 90% of management time.[7] Cardiac surgery represents, however, unique challenges in MAP management as the manipulation of the heart itself, the use of cardiopulmonary bypass (CPB) and cardioplegia, and the pre-existing cardiac disease all increase the difficulty in maintaining a steady MAP throughout the surgical period. In this case series we describe three cardiac surgical procedures managed with the CLV system (one coronary artery bypass graft (CABG) procedure done under CPB; one robotic minimally invasive direct coronary artery bypass (MIDCAB) procedure (through a mini-thoracotomy), and one off-pump CABG in order to assess the feasibility, efficiency, and behavior of the CLV in three high-risk patients.

Methods

This study was approved on April 19, 2018, by the Ethics Committee (P2018/276) and registered with clinical trial gov ([NCT04232007](https://clinicaltrials.gov/ct2/show/study/NCT04232007)). The study was done in the cardiovascular anesthesia department of Erasme Hospital between May and August 14th, 2018 with written informed consent documented prior to surgery. The controller has been well described in previous publications [7-10] and used norepinephrine for the cases in this series at a dose of 16 mcg/ml. Fluid administration was standardized and consisted on a baseline fluid administration of 3ml/kg/h of Plasmalyte (Baxter, Belgium) and an additional mini fluid

challenge of 100ml of 3% modified fluid gelatin (Geloplasma®, Fresenius Kabi GmbH, Bad Homburg, Germany) to keep stroke volume variation < 13% (before sternotomy and after sternum closure)

Per our previous publication [7], the primary outcome measure was the percentage of time patients were hypotensive, as defined by a MAP > 5 mmHg below the chosen target. Secondary outcome measures included the total dose of norepinephrine administered and the percentage of treatment time spent in a hypertensive state, defined as a MAP > 5 mmHg above the chosen target MAP with an active norepinephrine infusion (i.e., > 75 mmHg). We also evaluated the raw percentage of time spent during surgery with a MAP within ± 5 mmHg of the predefined MAP goal. However, as a MAP above the set target can occur with no vasopressor infusion (CLV dose = zero), we also decided to calculate an “ideal performance”, defined as: (“time in target (%)”) + (time (%) above target MAP with a CLV infusion rate of zero). An alternate method of calculating this time that leads to slightly more conservative estimates would be (“time in target(%)”) / (Total management time – [time over target without vasopressor]). We have included both methods in our result reporting along with all raw values to provide as complete a picture as possible of performance. Lastly, we also recorded major and minor postoperative complications and hospital length of stay.

Perioperative management

In the operating room, all three described patients were monitored with a non-invasive blood pressure cuff, a 5-lead electrocardiogram, pulse oximetry and a bispectral index (BIS) depth of anesthesia monitor (BIS™ monitor, Aspect Medical System Inc, Natick, USA) and a radial arterial line coupled with the EV1000 monitoring device (Edwards Lifesciences, Irvine, USA), placed before anesthesia induction. They were also equipped with an internal jugular triple lumen central venous catheter (Arrow International, Inc, Reading, USA) where a special lumen was dedicated to norepinephrine infusion. Total intravenous anesthesia using target-controlled infusion of propofol and remifentanyl was used during induction and maintenance of general anesthesia. The anesthesia provider modified propofol and remifentanyl concentrations in order to keep BIS values in the 40-60 range. A bolus of rocuronium was given prior to endotracheal intubation and then continuously administered via an infusion pump at a dose of 30 mg/hour. Mechanical ventilation was provided with a tidal volume of 7 mL/kg of ideal body weight, a positive end-expiratory pressure of 5 mmHg; respiratory rate was adjusted to maintain end tidal CO₂ between 32 and 36 mmHg using the Dräger Zeus® Infinity® Empowered monitors (Dräger Medical, Lübeck, Germany). The CLV system was started before anesthesia induction and discontinued at the end of the skin closure. The system supports a MAP target anywhere from 50-140 mmHg; the anesthesiologists supervising the cases chose the target pressure during management and was free to change the target at any time if desired. Administration of vasopressors outside of the system were not permitted unless deemed necessary for an emergency rescue by the supervising anesthesiologist.

Case 1

Case 1 was an on-pump CABG in a 72 year old male (85 kg, 1.6m) with a history of hypertension and CAD, baseline ejection fraction (EF) of 60%, and Euroscore-2 [11] of 3.2%. Total surgical time was 243 minutes. The CLV system was switched off once CPB began, as data could not be captured from the EV-100 while on bypass. The system was then restarted on separation from CPB after a pump run of 87 minutes. The target was 70 mmHg for the entire case. Total CLV management time was 155 minutes, and the CLV was infusing vasopressor for 132 minutes of that time (85.2 % of time). Mean infusion rate was 2.2 mcg/min and maximum rate was 5 mcg/min. The controller made an average of 2.9 rate changes per minute. Estimated Blood Loss (EBL) was approximately 400ml. No intotropes were used during the case.

MAP was < 65 mmHg for 1.0% of management time, and > 75 mmHg for 19% of management time. MAP was > 75 mmHg for only 5.5% of management time with vasopressor still running. Ideal management time (specifically defined as time in target + time over target with zero vasopressor rate divided by total management time) was 93.5% of case time, while the alternate calculation of (total time in target) / (total time – time above target without vasopressors) was 92%.

Post-operatively, the patient developed enterobacter pneumonia and acute respiratory distress syndrome, which subsequently led to a prolonged hospital course including atrial fibrillation and acute kidney injury. These complications were not thought to be related to vasopressor management during the case. The patient was discharged on postoperative day 91.

Case 2

Case 2 was a robotic minimally invasive direct coronary artery bypass (MIDCAB) single-graft LIMA-IVA procedure performed off-pump through a mini-thoracotomy in a 66 year-old female (81 kg, 1.75m) with a history of myocardial infarction and hypertension, EF of 68%, and Euroscore-2 1.0%. Total surgical time was 240 minutes. CLV management time was 189 minutes, the target was 70 mmHg for the entire case, and vasopressor was actively infusing during 82 minutes of that time (43.4%). Mean infusion rate was 0.4 mcg/min and maximum rate was 6.5 mcg/min. The controller made an average of 1.8 rate changes per minute. EBL was 650 ml.

MAP was <65 mmHg for 0.9% of management time, and > 75 mmHg for 49% of management time. The CLV system was delivering drug for only 3.5% of the time that MAP was >75 mmHg; thus, the patient was physiologically above this threshold without support for the vast majority of that time. Ideal management time was 95.5%, and the alternate calculation of (total time in target) / (total time – time above target without vasopressors) was again 92%. No intotropes were used during the case.

The patient had no major or minor complications (definitions given in our previous publications, [12-14]) and was discharged from the hospital on post-operative day 7. Figure 1 depicts the system in our operating room in Brussels, Belgium during the MIDCAB robotic surgery.

Case 3

Case 3 was a performed "off-pump" cardiac procedure (one graft: Left internal mammary artery (LIMA) to interventricular artery) in a 70 year-old male (60 kg, 1.4m) with a history of myocardial infarction, chronic obstructive pulmonary disease, and hypertension, with baseline EF of 70% and Euroscore-2 3.7%. Total case management time was 154 minutes, the target was 70 mmHg for the entire case, and the CLV was infusing vasopressor for 130 minutes of that time (84.6%). Mean infusion rate was 2.4 mcg/min and maximum rate was 5.8 mcg/min. The controller made an average of 2.8 rate changes per minute. EBL was 150ml. No intotropes were used during the case.

The patient spent 8.4% of management time with MAP < 65 mmHg, and 20% of management time with MAP > 75 mmHg. 10.3% of case time was over-target with infusion still running. Ideal management time was 81.3%, and (total time in target) / (total time on target + time out of target on vasopressors) was 79%. The patient had no major or minor post-operative complications and was discharged from the hospital on post-operative day 8. Perioperative data and performance of the closed-loop system of the three cases are shown in table 1 and table 2.

Discussion

In this three-case series, the only cardiac surgery patients trialed to date using this controller, the CLV controller effectively maintained MAP within ± 5 mmHg (or higher, with no vasopressor running), for 96%, 94%, and 82% of management time using a low norepinephrine median infusion rate between 0.5 and 2.2 $\mu\text{g}/\text{min}$. (By the alternate calculation, for 92%, 92%, and 79% of management time). All of these times are significantly higher than our historical general surgery standard of care times, and consistent with our results in our first clinical feasibility trial.[6, 7] In addition to the typical challenges of intraoperative blood pressure management, these patients had protamine injections, pulmonary recruitment manoeuvres, sternotomy and sternum closures, all of which can rapidly affect MAP. Our results support the notion that the controller can remain effective in maintaining target pressure in a challenging cardiac surgery patient cohort with rapid and accurate responsiveness.

The lowest ideal management time (79%) was recorded in the off-pump CABG case. This is a lower performance than typical for the CLV but perhaps not surprising given the rapid and dramatic swings in pressure that are commonly seen in these cases as the heart is elevated under suction, lowered, and in general manipulated by the surgeons in order to perform the procedure. Moreover, there are limits to what a controller can reasonably achieve in a living system via a drug infusion pump; control of blood pressure via pharmacologic infusion is not like a mechanical actuator with an instant response that can be tuned to the millisecond. Delivered drug takes time to circulate and reach effect sites and needs to be metabolized or redistributed to end its effect. These pharmacokinetic factors create long delays measured in term of seconds or even minutes and limit any controller's ability to change the drug effect.

One limitation of the existing prototype setup noted during this case series was that use of peripheral monitoring devices (in the case the Edwards Lifesciences EV-1000) was not feasible during cardiopulmonary bypass. We are presently incorporating direct waveform capture capabilities directly from clinical monitors so that pressures can be measured continuously and closed-loop vasopressor therapy continued during bypass if desired. None of the patients in this case series received inotropes. These agents are commonly used in cardiac surgery and while there should not be any interference with the CLV operation this remains to be shown clinically. Moreover, this subset of patients represents a narrow range of the possible cardiac surgery patient spectrum and did not include valve replacements. Finally, the closed-loop system is not available at this time commercially so validation by outside institutions will be limited.

Conclusion

Closed-loop management of blood pressure during cardiac surgery using norepinephrine infusion was feasible and associated with a low incidence of hypotension during surgery. A randomised controlled trial is now needed to demonstrate the added value of this strategy when compared to manually-adjusted vasopressor management using the same anesthetic technique.

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References

1. Roshanov PS, Sheth T, Duceppe E, Tandon V, Bessissow A, Chan MTV, Butler C, Chow BJW, Khan JS and Devereaux PJ, Relationship between Perioperative Hypotension and Perioperative Cardiovascular Events in Patients with Coronary Artery Disease Undergoing Major Noncardiac Surgery. *Anesthesiology*, 2019 130(5): p. 756–766. [PubMed: 30870165]
2. Ruetzler K, Khanna AK and Sessler DI, Myocardial Injury After Noncardiac Surgery: Preoperative, Intraoperative, and Postoperative Aspects, Implications, and Directions. *Anesth Analg*, 2019.
3. Sun LY, Chung AM, Farkouh ME, van Diepen S, Weinberger J, Bourke M and Ruel M, Defining an Intraoperative Hypotension Threshold in Association with Stroke in Cardiac Surgery. *Anesthesiology*, 2018 129(3): p. 440–447. [PubMed: 29889106]
4. Rettig TCD, Peelen LM, Geuzebroek GSC, van Klei WA, Boer C, van der Veer JW, Hofland J, van de Garde EMW and Noordzij PG, Impact of Intraoperative Hypotension During Cardiopulmonary Bypass on Acute Kidney Injury After Coronary Artery Bypass Grafting. *J Cardiothorac Vasc Anesth*, 2017 31(2): p. 522–528. [PubMed: 27727080]
5. Jinadasa SP, Mueller A, Prasad V, Subramaniam K, Heldt T, Novack V and Subramaniam B, Blood Pressure Coefficient of Variation and Its Association With Cardiac Surgical Outcomes. *Anesth Analg*, 2018 127(4): p. 832–839. [PubMed: 29624524]
6. Rinehart J, Ma M, Calderon MD, Bardaji A, Hafiane R, Van der Linden P and Joosten A, Blood pressure variability in surgical and intensive care patients: Is there a potential for closed-loop vasopressor administration? *Anaesth Crit Care Pain Med*, 2019 38(1): p. 69–71. [PubMed: 30513357]
7. Joosten A, Alexander B, Duranteau J, Taccone FS, Creteur J, Vincent JL, Cannesson M and Rinehart J, Feasibility of closed-loop titration of norepinephrine infusion in patients undergoing moderate- and high-risk surgery. *Br J Anaesth*, 2019 123(4): p. 430–438. [PubMed: 31255290]

8. Joosten A, Delaporte A, Alexander B, Su F, Creteur J, Vincent JL, Cannesson M and Rinehart J, Automated Titration of Vasopressor Infusion Using a Closed-loop Controller: In Vivo Feasibility Study Using a Swine Model. *Anesthesiology*, 2018.
9. Rinehart J, Joosten A, Ma M, Calderon MD and Cannesson M, Closed-loop vasopressor control: in-silico study of robustness against pharmacodynamic variability. *J Clin Monit Comput*, 2018.
10. Rinehart J, Ma M, Calderon MD and Cannesson M, Feasibility of automated titration of vasopressor infusions using a novel closed-loop controller. *J Clin Monit Comput*, 2017.
11. Nashef SA, Roques F, Sharples LD, Nilsson J, Smith C, Goldstone AR and Lockowandt U, EuroSCOREII. *Eur J Cardiothorac Surg*, 2012 41(4): p. 734–44; discussion 744-5. [PubMed: 22378855]
12. Joosten A, Coeckelenbergh S, Delaporte A, Ickx B, Closset J, Roumeguere T, Barvais L, Van Obbergh L, Cannesson M, Rinehart J and Van der Linden P, Implementation of closed-loop-assisted intra-operative goal-directed fluid therapy during major abdominal surgery: A case-control study with propensity matching. *Eur J Anaesthesiol*, 2018 35(9): p. 650–658. [PubMed: 29750699]
13. Joosten A, Hafiane R, Pustetto M, Van Obbergh L, Quackels T, Buggenhout A, Vincent JL, Ickx B and Rinehart J, Practical impact of a decision support for goal-directed fluid therapy on protocol adherence: a clinical implementation study in patients undergoing major abdominal surgery. *J Clin Monit Comput*, 2019 33(1): p. 15–24. [PubMed: 29779129]
14. Joosten A, Delaporte A, Ickx B, Touihri K, Stany I, Barvais L, Van Obbergh L, Loi P, Rinehart J, Cannesson M and Van der Linden P, Crystalloid versus Colloid for Intraoperative Goal-directed Fluid Therapy Using a Closed-loop System: A Randomized, Double-blinded, Controlled Trial in Major Abdominal Surgery. *Anesthesiology*, 2018 128(1): p. 55–66. [PubMed: 29068831]

Figure 1 –.

Operating room showing physical setup of closed-loop vasopressor system.

Data is collected from an EV-1000 device via serial cable which in turn is used to drive a Q-Core Sapphire pump. The system is seen in the photo between the transesophageal echo and the surgical drapes. The laptop at bottom is running the software.

Table 1:

Intraoperative data

	Baseline crystalloid (ml)	Mini Fluid challenge (ml)	Blood loss (ml)	Urine output (ml)	Fluid balance (ml)	Mean CI L/min/m ²	Mean SV (ml)	Mean SVV (%)	Baseline lactate	ICU lactate
On Pump	500	1200	400	1200	100	2.2	64.0	10.8	2.1	2.2
MIDCAB	500	1000	650	290	560	2.9	93.7	9.5	0.8	0.7
Off-pump	200	800	100	100	800	2.1	53.6	9.9	0.8	0.7
Median	500	1000	400	290	560	2.1	64	9.9	0.8	0.7
25 th percentile	350	900	250	195	330	2.1	58.8	9.7	0.8	0.7
75 th percentile	500	1100	525	745	680	2.5	78.9	10.4	1.5	1.5

Legend: CI: cardiac index; SV: stroke volume; SVV: stroke volume variation.

Table 2:

Performance of the Closed-loop vasopressor system

Cardiac cases	Ideal Performance (%) [*]	Ideal Performance (Alt. Calc, %) ^{**}	Mean Percentage of Case Time with					Total number of		Mean Rate of VP (mcg/min)
			MAP < 5 mmHg of target MAP	MAP±5 mmHg of target MAP	MAP > 5 mmHg of target MAP	MAP >5 mmHg of target MAP w/VP	% CLV Giving VP	CLV rate changes per case	CLV rate changes per minute	
On-Pump	93.5	92.4	1.0	80.4	18.5	5.5	85.2	453	2.9	2.2
MIDCAB	95.5	92.0	0.9	50.5	49.5	3.5	43.4	340	1.8	0.4
Off-pump	81.3	79.3	8.4	71.2	20.4	10.3	84.6	432	2.8	2.4

Legend: %: percentage; MAP: mean arterial pressure; VP: vasopressor; w/: with

CLV: closed-loop vasopressor

^{*} Ideal performance is specifically defined as (MAP±5 mmHg) + time above target when CLV is zero.^{**} MAP ± 5 when VP is active is calculated as Time-in-target / (Total_Case_Time – [MAP_above_target_and_VP_zero_time])