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Feasibility of closed-loop titration of norepinephrine infusion in patients undergoing moderate- and high-risk surgery

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Abstract

Background: Vasopressor agents are used to prevent intraoperative hypotension and ensure adequate perfusion. Vasopressors are usually administered as intermittent boluses or manually adjusted infusions, but this practice requires considerable time and attention. We have developed a closed-loop vasopressor (CLV) controller to correct hypotension more efficiently. Here, we conducted a proof-of-concept study to assess the feasibility and performance of CLV control in surgical patients.

Methods: Twenty patients scheduled for elective surgical procedures were included in this study. The goal of the CLV system was to maintain MAP within 5 mm Hg of the target MAP by automatically adjusting the rate of a norepinephrine infusion using MAP values recorded continuously from an arterial catheter. The primary outcome was the percentage of time that patients were hypotensive, as defined by a MAP of 5 mm Hg below the chosen target. Secondary outcomes included the total dose of norepinephrine, percentage of time with hypertension (MAP>5 mm Hg of the chosen target), raw percentage "time in target" and Varvel performance criteria.

Results: The 20 subjects (median age: 64 years [52–71]; male (35%)) underwent elective surgery lasting 154 min [124–233]. CLV control maintained MAP within ±5 mm Hg of the target for 91.6% (85.6–93.3) of the intraoperative period. Subjects were hypotensive for 2.6% of the intraoperative period (range, 0–8.4%). Additional performance criteria for the controller included mean absolute performance error of 2.9 (0.8) and mean predictive error of 0.5 (1.0). No subjects experienced major complications.

Conclusions: In this proof of concept study, CLV control minimised perioperative hypotension in subjects undergoing moderate- or high-risk surgery. Further studies to demonstrate efficacy are warranted.

Trial registry number: NCT03515161 (ClinicalTrials.gov).

Keywords: haemodynamic; hypertension; hypotension; norepinephrine; perioperative care; vasopressor agents

Editorial decision: 30 April 2019; **Accepted:** 8 May 2019

Editor's key points

- Intraoperative hypotension is common and associated with adverse outcomes after noncardiac and cardiac surgery.
- Pressor therapy is often administered but demands close clinical vigilance that may not readily achieve predefined MAP targets.
- Preclinical large animal studies show that closed-loop vasopressor (CLV) control avoids hypotension by automatic adjustment of vasopressor infusion rate targeted at maintaining predefined MAP.
- In this first-in-man study, CLV control minimised perioperative hypotension in patients undergoing elective higher-risk surgery, warranting further study.

Transient episodes of intraoperative hypotension are associated with adverse cardiovascular,[1–6] renal,[7–11] and neurological[12] complications. Rapid correction of hypotension is, therefore, a key consideration for anaesthesiologists responsible for high-risk surgical and critically ill patients.[13–15]

Vasopressors are frequently used to correct hypotension, especially when patients are unresponsive to other interventions including fluid administration. Vasopressor therapy often requires frequent boluses, adjustment of infusion rates, or both in haemodynamically complex patients. Ideally, such changes should be made expediently to avoid periods of hypotension or hypertension, as both can be deleterious.[16] However, vasopressor treatment with continuous norepinephrine infusion may fail to achieve treatment targets in at least 50% of patients.[17]

Using lessons learned in the development and testing of a previous closed-loop system for fluid resuscitation,[18–21] we have developed an automated closed-loop vasopressor (CLV) controller designed to correct hypotension via the automatic adjustment of a vasopressor infusion rate which targets a predefined MAP. Pre-clinical evaluation of CLV in multiple *in silico* studies[22,23] and *in vivo* have established the basic safety profile and overall efficacy of this system.[24]

In this proof-of-concept study, we have assessed the feasibility and clinical performance of CLV control in surgical patients undergoing elective surgery. We tested whether CLV control could maintain MAP within ±5 mm Hg of a target MAP for at least 85% of the intraoperative period, similar to our previous studies on closed-loop fluid management.[20,25]

Methods

Ethics approval

This single-centre prospective proof-of-concept study was approved on April 19, 2018, by the local institutional Ethics Committee (Comité Ethique de l'hôpital Erasme, Brussels, Belgium) under identification number P2018/276-CCB-B406201835963 (Principal Investigator: Alexandre Joosten) and registered with ClinicalTrials.gov (NCT03515161) on May 3, 2018. The study was conducted at Erasme Hospital in Brussels, Belgium, between May 17, 2018 and August 30, 2018. Written informed consent was obtained from all subjects before surgery.

Inclusion criteria

Patients aged >18 yr with an ASA physical status (ASA score) 1–3 scheduled for intermediate and high-risk surgical procedures known to commonly require a vasopressor infusion were considered for inclusion.

Exclusion criteria

Exclusion criteria were patients younger than 18 yr, pregnancy, cardiac arrhythmias, and left ventricular ejection fraction <30%, right ventricular failure, or both. For safety reasons, the principal investigator (AJ) with the most experience operating our CLV system remained in the operating room and ICU for each patient throughout the entire period the system was functioning. In all cases, AJ was not the primary anaesthesia provider or the ICU physician managing the patient, but rather focused solely on supervising the CLV system.

Anaesthesia protocol

Subjects were monitored with a five-lead electrocardiogram, noninvasive pulse oximetry, an upper arm blood pressure cuff, end-tidal carbon dioxide partial pressure, a rectal temperature probe and a bispectral (BIS™) monitor (Aspect Medical System Inc., Natick, MA, USA). In addition, a 20-gauge radial arterial catheter was placed before induction and connected via the Flotrac sensor to an advanced cardiac output (CO) and stroke volume variation (SVV) monitor (EV1000™; Edwards Lifesciences, Irvine, CA, USA).

Total intravenous anaesthesia was performed in all subjects and consisted of propofol and remifentanil administered via target-controlled infusion systems using the pharmacokinetic models of Schnider and colleagues[26] and Minto and colleagues,[27] respectively. We used two dedicated Base Primea infusion pumps (Fresenius Kabi, Schelle, Belgium) to manually adjust the effect site concentrations in order to reach BIS values between 40 and 60. Rocuronium (0.6 mg kg^{-1}) was administered during the induction of anaesthesia and continuously administered during the case using a standard syringe pump manually adjusted by the anaesthesiologist to maintain the train-of-four ratio <2 measured using a curarisation monitor (Tofscan®; Idmed, Marseille, France). After tracheal intubation, the lungs were ventilated using a protective strategy with a 1:1 mixture of oxygen and air (2.5 L min^{-1} using the Infinity C700 Anaesthesia Machine; Dräger Medical GmbH, Lübeck, Germany), a tidal volume of 8 ml kg^{-1} of predicted body weight, a positive end-expiratory pressure (PEEP) of 5–7 cm H_2O, and recruitment manoeuvres when necessary. The ventilatory frequency was set to achieve an end-tidal carbon dioxide pressure between 4.3 and 4.8 kPa. Prophylactic antibiotics were administered before skin incision. Anticoagulation was achieved with heparin for vascular and endovascular cerebral aneurysm surgeries and was reversed with protamine (1:2 ratio) at the end of the clamping period for patients undergoing vascular surgery. Postoperative pain was treated

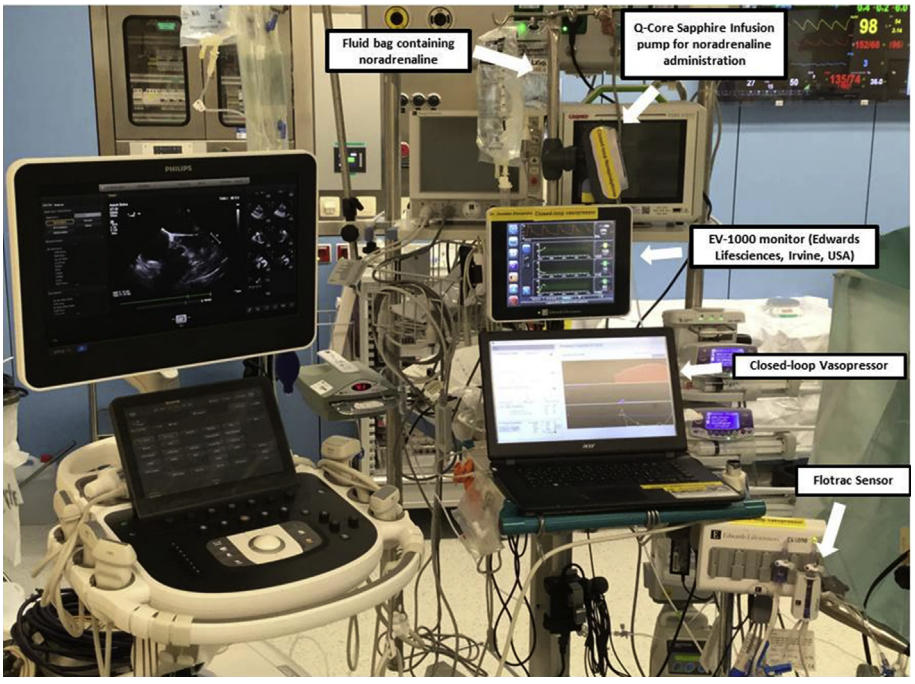

Fig 1. Closed-loop vasopressor system with its different components used in our operating room in Erasme Hospital, Brussels, Belgium, during a cardiac case.

with morphine (0.05 mg kg^{-1}) at incision and 30 min before the end of the procedure together with paracetamol, non-steroidal anti-inflammatory agents, or both. A forced-air warming system (3M™ Bair Hugger™; St. Paul, MN, USA) and a blood-fluid warming system (3M™ Ranger™) were used to maintain normothermia in all patients. Fluid administration consisted of a baseline isotonic balanced crystalloid infusion (Plasmalyte®; Baxter, Lessines, Belgium) set to 3 ml kg^{-1} h^{-1} via an infusion pump (Volumat® Agilia; Fresenius Kabi, Schelle, Belgium) for the duration of the procedure. For subjects who underwent Whipple and major vascular procedures, additional mini-fluid challenges of 100 ml 6% hydroxyethyl starch 130/0.4 (Voluven®; Fresenius Kabi, Bad Homburg, Germany) were delivered using a goal-directed fluid therapy strategy guided by a real-time clinical decision support system (assisted fluid management system) that we have previously described.[28] These colloid boluses were manually administered by the primary anaesthesiologist in charge of the patient to optimise stroke volume and SVV. In other patients, a goal-directed strategy with the assisted fluid management system was not usual care. Packed red blood cells were administered perioperatively to maintain the haemoglobin level greater than 7–9 g dl^{-1}.

CLV controller

The CLV controller used in this study was developed by one of the authors (JR) at the University of California–Irvine (Irvine, CA, USA) and has been described previously.[22–24] Briefly, the system collects real-time MAP values from the EV1000 monitor (Edwards Lifesciences) and, through a combination of proportional integral derivative (PID) and rules-based control modules, titrates a vasopressor to maintain the predefined target MAP. The PID element allows for adjustment of both current and anticipated future error, and the rules-based component allows for additional safety features and functionality such as rate limits and rate-of-change limits. Additionally, the CLV system inputs allow for flexibility in the tightness of control (both above and below target, should error in one direction be preferable in a given clinical setting). The algorithm was coded in Microsoft Visual C (Microsoft Corp., Redmond, WA, USA). Software version 2.804 of the CLV controller 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 the serial output on an EV1000 monitor (Edwards Lifesciences) and to a Q-Core Sapphire Pump (Q-Core Medical Ltd., Netanya, Israel). Figure 1 shows the CLV interface.

CLV protocol

Our current practice is to maintain a MAP of *at least* 65 mm Hg, so we set the target MAP to 70 mm Hg as this results in the CLV controller aiming to keep the MAP between 65 and 75 mm Hg. This initially selected target could be modified during the case if needed. For patients having endovascular embolisation of intracranial cerebral aneurysms, we used our institution's standard MAP target of 80 mm Hg because the coils, flow diverters, and stents used to treat cerebral aneurysms reduce intracerebral blood flow and a higher MAP target is preferred in these cases. The CLV was switched on before induction of anaesthesia (just after the placement of the radial arterial line). For safety reasons, norepinephrine was prepared and connected to an intravenous line using a separate infusion

pump (but the administration rate was zero). In addition, no bolus of vasopressor (either ephedrine, phenylephrine, or even norepinephrine) was allowed during the procedures.

Primary outcome

The predefined CLV goal was to maintain MAP within ±5 mm Hg of the target MAP using automated adjustments of the norepinephrine infusion rate. This target range (±5 mm Hg) was chosen for two reasons. First, it was felt to be a clinically reasonable definition for 'tight' control around a chosen target. Second, in our previous work[17] we have shown that clinicians do not maintain MAP within 10 mm Hg of preoperative values for at least 40% of the intraoperative duration. Therefore, setting a high time-in-target at ±5 mm Hg would represent a significant improvement over current clinical practice.

The primary outcome measure was the percentage of time patients were hypotensive, as defined by a MAP of 5 mm Hg below the chosen target. (i.e. the time spent with a MAP <65 mm Hg for all cases except endovascular cerebral aneurysm cases, for which the value was <75 mm Hg).

Secondary outcomes

1. Total dose of norepinephrine administered.
2. Percentage of treatment time spent in a hypertensive state, defined as a MAP >5 mm Hg above the chosen target MAP with an active norepinephrine infusion (i.e., >75 or >85 mm Hg for endovascular cerebral aneurysm cases).
3. Raw percentage 'time in target', which we defined as the percentage of time spent during surgery with a MAP within ±5 mm Hg 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' parameter that would not 'penalise' the calculated performance when the patient had an intrinsically higher blood pressure than the target with a CLV rate of 0. This term was defined as: ('time in target [%]') + (time [%] above target MAP with a CLV infusion rate of zero), as the time-over-target could partially result from a poorly tuned controller that consistently overshot the target and then turned off.
4. Standard performance criteria (colloquially known as Varvel's criteria) were median absolute performance error (MDAPE), median prediction error (MDPE), wobble, and divergence (measured as mm Hg min^{-1}). Mathematical definitions and explanations of these terms can be found in the work of Varvel and colleagues,[29] but briefly they represent the expected operating range of inaccuracy, bias, variability over time, and drift away from target over time, respectively. Lastly, we also recorded major and minor postoperative complications (definitions given in our previous sttudies[21,30]) and hospital length of stay.

Statistical analysis

Variables are presented as either a median value (25–75th percentile) or as a numerical amount with relevant percentage values. Haemodynamic variables (MAP, heart rate [HR], stroke volume [SV], CO, SVV) were recorded every 20 s by the EV1000 monitor (Edwards Lifesciences) and were subsequently averaged. Each patient's MAP status was classified as 'in target' (MAP ±5 mm Hg of the MAP target), 'under target' (MAP >5 mm Hg below the MAP target), or 'over target' (MAP >5 mm Hg above the MAP target with ongoing vasopressor infusion).

Sample size calculation

Using the published minimal sample size for feasibility of a pilot study, a sample size of 12 patients was needed.[31] Thus, 20 patients were included for this proof-of-concept study—four patients each from the following procedures: major aortic and vascular surgery, pancreaticoduodenectomy (Whipple procedure), pulmonary lobectomy, endovascular embolisation of intracranial cerebral aneurysm, and cardiac surgery. The four patients who had cardiac surgery were studied in the ICU setting after surgery but before extubation.

Results

Patient characteristics

Of the 25 patients screened for inclusion, five were excluded as three patients declined to participate, one had preoperative atrial fibrillation, and one developed atrial fibrillation during the operation before the start of the study. The baseline

Table 1 Baseline characteristics of the 20 subjects. Population data are listed as 'value (%)' and quantitative data as 'median' (25–75 percentiles). POSSUM, Physiologic and Operative Severity Score for the enUmeration of Mortality and Morbidity.

Variables	
Age (yr)	64 (52–71)
Male (%)	7 (35)
Weight (kg)	73 (61–79)
Height (cm)	167 (162–169)
Body mass index (kg m^{-2})	24 (21–29)
ASA physical status 2/3	7/13
Baseline haemoglobin (g dl^{-1})	12 (11–13)
Baseline lactate (mEq L^{-1})	0.8 (0.7–0.8)
Medications, *n* (%)	
Aspirin	11 (55)
Beta blocker	10 (50)
Angiotensin-converting enzyme inhibitor	4 (20)
Statin	9 (45)
Diuretic	1 (5)
Comorbidities, *n* (%)	
Ischaemic heart disease	6 (30)
Arterial hypertension	13 (65)
Hypercholesterolaemia	9 (45)
Diabetes mellitus	3 (15)
Chronic obstructive pulmonary disease	5 (25)
POSSUM Physiology Score	15 (14–17)
POSSUM Operative Score	10 (10–13)
POSSUM-predicted morbidity	22 (14–32)
POSSUM-predicted mortality	4 (2–6)
Type of surgery, *n* (%)	
Major vascular surgery	4 (20)
Whipple procedure	4 (20)
Thoracic surgery (lobectomy)	4 (20)
Endovascular neuro-aneurysm embolisation	4 (20)
Postoperative cardiac surgery in the ICU	4 (20)

Table 2 Perioperative data of the 20 subjects. Data are expressed as median (25th percentile–75th percentile)

Variables	
Anaesthesia duration (min)	231 (191–310)
Surgery duration (min)	154 (124–233)
Intraoperative haemodynamic variables	
Stroke volume (ml)	75.1 (63.4–77.9)
Stroke volume variation (%)	8.8 (7.5–11.6)
Cardiac output (L min^{-1})	4.8 (3.9–5.7)
Cardiac index (L min^{-1} m^{-2})	2.8 (2.2–3.2)
Intraoperative Fluid IN	
Total Crystalloid (ml)	1500 (975–1825)
Total Colloid (ml)	0 (0–550)
Total IN (ml)	1500 (1500–3700)
Intraoperative Fluid OUT	
Estimated blood loss (ml)	200 (88–800)
Urine output (ml)	405 (300–625)
Total OUT (ml)	750 (408–1400)
Net Fluid Balance (ml)	650 (485–1154)
Postoperative Fluid IN–OUT	
Total IN in the ICU (ml)	2424 (1474–3527)
Total OUT in the ICU (ml)	1400 (890–1638)
Net Fluid Balance in the ICU (ml)	765 (–28 to 2014)
Haemoglobin on arrival in the ICU (g dl^{-1})	11.4 (10.5–11.9)
Lactate on arrival in the ICU (mEq L^{-1})	1.0 (0.9–1.3)
Length of stay in the ICU (h)	23 (20–24)
Length of stay in the hospital (days)	8 (5–12)

characteristics of the remaining 20 patients are summarised in Table 1. Intraoperative data are shown in Table 2. Haemodynamic variables are provided in Appendix 1.

CLV control characteristics

The predefined MAP target was set at 70 mm Hg in 16 subjects and at 80 mm Hg in the four patients who underwent endovascular embolisation of intracranial cerebral aneurysm. Across all cases, the CLV controller was active for 3877 min (64.6 h) and was administering vasopressor for 97.1% of this time (3764 min, Table 3); the controller was active but not administering norepinephrine for 2.9% of case time because the patient's blood pressure was already at or above the target pressure. During the treatment time, the system made a total of 11 576 infusion rate changes (a median of three infusion rate changes per minute, a minimum of zero and maximum of four). Technical errors occurred in six of the 20 subjects. The system stopped functioning twice in two subjects and once in four subjects. All errors were attributable to a pump communication error between the CLV system and the Q-core infusion pump related to third-party software in which the Commands Server software lost contact with the remote pump. An audible alarm sounded to alert the supervisor when this occurred and restarting the system immediately fixed the problem in every case. These processes lasted less than 2 min. The system was overridden once during a thoracic case when the MAP goal was deliberately decreased to 65 mm Hg for 30 min to help control bleeding. The system was never stopped for inappropriate drip rate management, and the additional line with the norepinephrine manually delivered by an infusion pump was never used.

Primary outcome—hypotension

Subjects were hypotensive (as defined by a MAP of 5 mm Hg below the chosen target) for 2.6% (1.6–4.6) of the total case time (range, 0–8.4%). Two subjects never had hypotension. The maximum hypotension time seen was 8.4% in a postoperative cardiac subject although this episode did not lead to any postoperative complications.

Secondary outcomes

Norepinephrine dose

The total dose of norepinephrine administered was 14 382 μg (i.e., 653 [499–810] μg per patient or a median dose of 3.9 μg min^{-1} (Table 3). The maximum infusion rate reached was 15.74 μg min^{-1} during a cerebral aneurysm procedure. Figure 2 depicts the norepinephrine infusion rate (μg min^{-1}) over time for the 20 cases.

Percentage of treatment time spent in a hypertensive state

Subjects had a MAP over target for 2.4% (1.4–3.8) of case time when the CLV was still infusing norepinephrine. Patients had a MAP >10 mm Hg below target for 0.3% (0–0.6) of the time and a MAP >10 mm Hg above target (with active vasopressor infusion) for 0.2% (0–0.7) of the time. Thus, the system was more than 10 mm Hg away from the target around half-a-percent of case time in total.

Percentage of time spent during surgery with a MAP within ±5 mm Hg of the predefined MAP goal

Subjects were in target (MAP ±5 mm Hg of target) 91.6% (85.6–93.3) of the time. If allowing for correction of time-over-target when the vasopressor drip was zero, the 'ideal performance' percentage of case time was 94.2% (91.8–95.8) (Table 3). There were two cases with 40 min of overall case time with MAP above target and the vasopressor rate was zero, eight such instances in four cases with times of 15–40 min, and the remaining 30 instances were 15 min or less in duration (Fig. 3).

Performance characteristics

The raw standard performance criteria for the controller without any correction were: MDAPE 2.9 (0.8); MDPE 0.5 (1.0); wobble 2.7 (0.8); and divergence (mm Hg m^{-1}) 0.0 (0.3). If allowing for correction of time over target when the vasopressor rate was zero ('ideal performance time'), the performance criteria were: MDAPE 2.1 (0.7); MDPE; 0.0 (0.7); wobble 2.3 (0.7); and divergence (mm Hg m^{-1}) 0.0 (0.3).

Clinical outcomes

Except for the postoperative cardiac cases in the ICU which were kept intubated as part of their routine care, all subjects were extubated in the operating room at the end of the procedure. No subject was re-intubated. No patients experienced any major complications, but six subjects (30%) developed a minor postoperative complication (atrial fibrillation [n=1], pseudo-obstruction of the bowel [n=2], urinary tract infection [n=1], and other infections [n=2]). The PACU or ICU stay lasted 23 (20–24) h and the hospital stay 8 (5–12) days. No subject died during the 90 day follow-up period.

Table 3 Performance of the closed-loop system. *Ideal performance time % = (MAP ±5 mm Hg) + time above target when CLV is zero. CLV, closed-loop vasopressor; VP, vasopressor

Case type	Ideal performance (%)*	Mean percentage of case time with					Total number of		Mean rate of VP (μg min^{-1})
		MAP ±5 mm Hg of target	MAP >5 mm Hg *below* target	MAP >5 mm Hg *above* target	MAP >5 mm Hg above target with VP	CLV giving VP	CLV rate changes per case	CLV rate changes per hour	
Thoracic	96.9	87.6	1.5	10.9	1.6	89.6	445	200	4.01
Thoracic	91.9	78.9	3.2	17.9	4.9	84.5	297	176	1.89
Thoracic	89.5	76.5	2.8	20.7	7.7	74.5	437	163	1.37
Thoracic	94.1	92.6	3.9	3.5	2	98.5	724	216	3.52
Vascular	99.2	99	0	1	0.8	99.3	478	176	4.03
Vascular	95.8	82.3	1.2	16.5	3	86.1	480	163	1.28
Vascular	85.8	83	5.2	11.8	9	96.5	1624	238	4.2
Vascular	88.3	66.2	3.7	30.1	8	75.4	1119	155	3.5
Whipple	99	93	0	7	1	91.8	900	134	2.61
Whipple	94.1	94.1	5.9	0	0	98.3	275	159	4.27
Whipple	95.1	90.9	2.5	6.6	2.4	94.5	697	200	2.71
Whipple	92.6	86.4	2.5	11.2	4.9	89.1	1032	221	2.42
Neuro aneurysm	95.9	95.8	1.5	2.6	2.6	100	415	174	2.56
Neuro aneurysm	95.7	91.6	2.3	6.1	2	95.8	440	143	3.74
Neuro aneurysm	95.9	95.9	1.7	2.4	2.4	100	503	205	9.69
Neuro aneurysm	94.3	92.6	2.2	5.2	3.5	97.7	453	170	4.9
ICU postop cardiac	94.9	94.9	4.6	0.5	0.5	100	250	108	4.06
ICU postop cardiac	90.2	90.2	6.7	3.1	3.1	100	386	245	6.93
ICU postop cardiac	91.6	91.6	8.4	0	0	99.5	322	153	4.12
ICU postop cardiac	93.2	91.8	4.8	3,4	2	98.5	299	152	7.65
Median	94.2	91.6	2.6	5.6	2.4	97.1	449	172	3.9
25th percentile	91.8	85.6	1.6	2.5	1.4	89.5	370	154.5	2.6
75th percentile	95.8	93.3	4.6	11.3	3.8	99.3	703.8	201.2	4.2

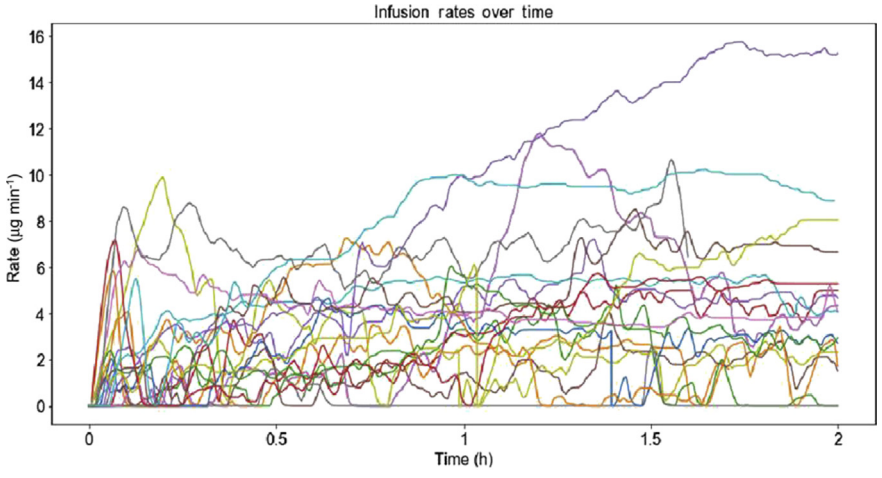

Fig 2. Graph of infusion rates over the first 2 h in all cases. The closed-loop vasopressor controller was started after placement of the arterial line and before anaesthetic induction. In most patients the controller gives an initial large dose of vasopressor concurrent with induction as the blood pressure decreases because of the effects of the anaesthetic drugs. After this, infusion rates diverge depending on the patient and case.

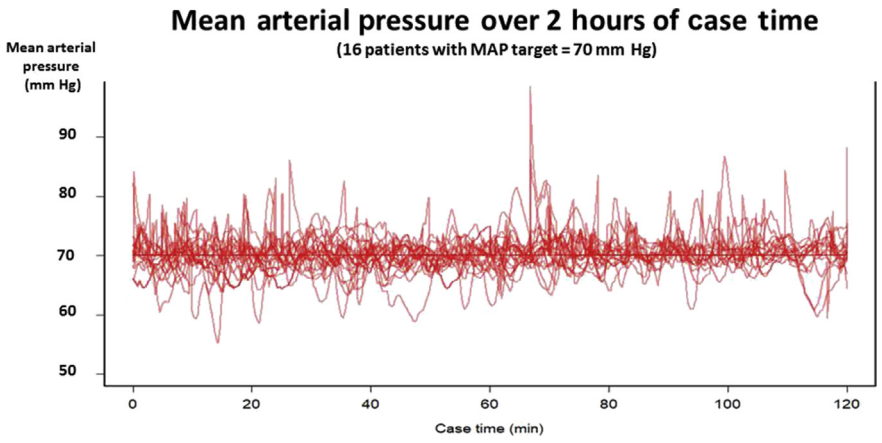

Fig 3. MAP during the procedures for the included patients with MAP targets of 70 mm Hg. Time-over-target when the vasopressor infusion was completely halted by the system is shown as zero error.

Discussion

This proof-of-concept study found that titration of norepinephrine by the CLV controller was able to maintain MAP within ±5 mm Hg of the predefined target for more than 90% of operative duration in subjects undergoing moderate- or high-risk surgery. The MAP was under target (hypotension) for 2.6% of the time (primary outcome) and above target (hypertension) with an infusion still running for 2.4% of the time. This contrasts with patients receiving manually adjusted vasopressor infusions, where a predetermined target MAP is achieved for <50% of operative time with >30% operative time exceeding the same MAP target.[17] Although several closed-loop systems for vasopressor infusions are being developed,[32–34] no other clinical study has assessed CLV titration of norepinephrine using an arterial line coupled to an advanced haemodynamic monitor in perioperative patients undergoing major surgical procedures under general anaesthesia.

This feasibility study highlights several potential contributions of CLV. Despite the relative challenge of tight blood pressure control in the perioperative environment, performance characteristics were strong. As we have previously discussed in our engineering study,[22,23] all automated controllers must maintain a narrow balance between speed of correction and overcorrection resulting in decreased haemodynamic stability. The low divergence and wobble seen in this study suggest the controller is not significantly over-responding, and the low MDAPE and MDPE suggest it is not significantly under-responding. However, in less dynamic clinical environments (e.g. ICU) the controller performance was in target for >90% of case time, whereas in more challenging patient populations (vascular and thoracic surgery), there was more operative time out of target. Although there may be additional room to fine-tune the system gain in specific patient populations or cases, the current balance between response speed and stability appears to be acceptable.

Renewed interest in automated titration of vasopressor drugs has been generated by data demonstrating an association between perioperative hypotension and morbidity after surgery. Multiple retrospective studies based on large patient databases have identified associations between intraoperative hypotension (both magnitude and duration) and adverse events in both surgical and ICU patients.[1–15] Personalising perioperative blood pressure management may be beneficial.[35,36] However, this approach may not be easy to implement given the other tasks anaesthetists have to perform simultaneously. As a result, patients may spend a significant period of time with an inappropriate MAP value.[17] However, CLV systems are still a research tool and significant challenges remain for the future, especially with respect to clinical acceptance, technological integration, and regulatory approval. Nevertheless, we anticipate the gradual introduction of such systems as these hurdles are progressively eliminated.[37,38]

Study limitations

As this protocol was a proof-of-concept study, our CLV system was only tested in a small series of subjects and performed in a single centre with a single user using historical data as a point of reference for performance. Resolution of the pump communication error encountered in the present study will be needed. The behaviour of this CLV system was not tested in situations characterised by more acute haemodynamic changes. In this study, CLV required intra-arterial pressure monitoring, which may not be indicated for patients undergoing lower risk surgery. CLV has been used to titrate phenylephrine based on noninvasive blood pressure monitoring in women undergoing Caesarean section under spinal anaesthesia.[39–41] As fluid and vasopressors are often both needed simultaneously for high-risk surgical and ICU patients, this study was not able to assess the complex interactions between these two treatment modalities. CLV in an experimental small-animal model of haemorrhagic shock has reported promising results.[34]

Conclusions

This proof-of-concept study demonstrates the clinical feasibility of a closed-loop system to reliably minimise perioperative hypotension using a norepinephrine infusion in patients undergoing moderate- and high-risk surgery. A randomised controlled trial is now required to examine whether there are any clinical benefits of this strategy when compared with manually adjusted vasopressor management.

Authors' contributions

Study design: AJ, MC, JR.
Recruitment of patients: AJ
Data collection: AJ
Data analysis: all authors
Drafting of the manuscript: AJ
Drafting of the final manuscript: BA
Editing of the final manuscript: JD, FST, JC, JLV, MC, JR
All authors read and approved the final version of the manuscript.

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Declarations of interest

AJ, MC, and JR are consultants for Edwards Lifesciences. MC and JR 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 CLV 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. The other authors have no conflicts of interest related to this article.

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Appendix 1. Advanced haemodynamic variables of the 20 subjects*

Variables	
Baseline haemodynamic variables	
Stroke volume index (ml m^{-2})	
Stroke volume variation (%)	36.8 (29.4–46.8)
Cardiac index (L min^{-1} m^{-2})	9.8 (7.2–12.3)
	2.5 (1.9–2.9)
Intraoperative haemodynamic variables	
Stroke volume index (ml m^{-2})	
Stroke volume variation (%)	41.1 (34.3–50.1)
Cardiac index (L min^{-1} m^{-2})	8.9 (7.5–11.6)
	2.8 (2.2–3.2)
End haemodynamic variables	
Stroke volume index (ml m^{-2})	45.6 (37.5–49.3)
Stroke volume variation (%)	9.2 (6.2–11.0)
Cardiac index (L min^{-1} m^{-2})	2.9 (2.4–3.3)

*Baseline haemodynamic values represent the average of the first 5 min of the recorded values. Intraoperative haemodynamic variables is the average of the total intraoperative values during the procedures, and end haemodynamic variables represents the average of the last 5 min of the recorded values. The given values represent the median and percentiles (25th–75th) for the 20 cases. Variables are recorded each 20 s by the EV-1000 monitor (Edwards Lifesciences). For each patient, a mean value per category was calculated.