ANESTHESIOLOGY

Automated Titration of Vasopressor Infusion Using a Closed-loop Controller

In Vivo Feasibility Study Using a Swine Model

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ABSTRACT

Background: Multiple studies have reported associations between intraoperative hypotension and adverse postoperative complications. One of the most common interventions in the management of hypotension is vasopressor administration. This approach requires careful and frequent vasopressor boluses and/or multiple adjustments of an infusion. The authors recently developed a closed-loop controller that titrates vasopressors to maintain mean arterial pressure (MAP) within set limits. Here, the authors assessed the feasibility and overall performance of this system in a swine model. The authors hypothesized that the closed-loop controller would be able to maintain MAP at a steady, predefined target level of 80 mmHg for greater than 85% of the time.

Methods: The authors randomized 14 healthy anesthetized pigs either to a control group or a closed-loop group. Using infusions of sodium nitroprusside at doses between 65 and 130 μg/min, we induced four normovolemic hypotensive challenges of 30 min each. In the control group, nothing was done to correct hypotension. In the closed-loop group, the system automatically titrated norepinephrine doses to achieve a predetermined MAP of 80 mmHg. The primary objective was study time spent within ±5 mmHg of the MAP target. Secondary objectives were performance error, median performance error, median absolute performance error, wobble, and divergence.

Results: The controller maintained MAP within ±5 mmHg of the target for 98 ± 1% (mean ± SD) of the time. In the control group, the MAP was 80 ± 5 mmHg for 14.0 ± 2.8% of the time ($P < 0.0001$). The MAP in the closed-loop group was above the target range for 1.2 ± 1.2% and below it for 0.5 ± 0.9% of the time. Performance error, median performance error, median absolute performance error, wobble, and divergence were all optimal.

Conclusions: In this experimental model of induced normovolemic hypotensive episodes in pigs, the automated controller titrated norepinephrine infusion to correct hypotension and keep MAP within ±5 mmHg of target for 98% of management time.

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EDITOR'S PERSPECTIVE

What We Already Know about This Topic

- Intraoperative hypotension has been associated with adverse postoperative outcomes.
- A randomized controlled trial of individualized blood pressure management in patients undergoing major abdominal surgery found reduced postoperative adverse events in patients in the blood pressure management intervention group *versus* the standard of care group.

What This Article Tells Us That Is New

- In this study of pigs with normovolemic hypotension induced by administration of sodium nitroprusside, an automated closed-loop vasopressor administration device was able to maintain mean arterial pressure within 5 mmHg of 80 mmHg for 98% of the intraoperative period. This suggests that norepinephrine can be accurately titrated using an automated infusion device in order to maintain target blood pressure.

In a multicenter study published 7 yr ago, Sabaté *et al.* reported that intraoperative hypotension was an independent predictor of major adverse cardiac and cerebrovascular events in patients undergoing noncardiac surgery.[1] More recent large retrospective studies have established strong links between even transient hypotensive episodes and postoperative cardiovascular,[2–4] renal,[5,6] and neurologic[7,8] complications. Finally, a recent prospective randomized controlled trial of individualized systolic blood pressure management in major abdominal surgery patients showed a reduced risk of postoperative complications compared to standard therapy.[9] Rapid correction of hypotension is therefore a key consideration in the management of high-risk surgical and/or critically ill patients.

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Submitted for publication May 23, 2018. Accepted for publication November 20, 2018. From the Department of Anesthesiology (A.J., A.D.), and the Department of Intensive Care (F.S., J.C., J.-L.V.), Erasme University Hospital, Université Libre de Bruxelles, Brussels, Belgium; the Department of Anesthesiology and Intensive Care, Hôpitaux Universitaires Paris-Sud, Université Paris-Sud, Université Paris-Saclay, Hôpital De Bicêtre, Assistance Publique Hôpitaux de Paris, Le Kremlin-Bicêtre, France (A.J.); the Department of Anesthesiology, University of California, San Diego, San Diego, California (B.A.); the Department of Anesthesiology and Perioperative Medicine, David Geffen School of Medicine, Los Angeles, California (M.C.); and the Department of Anesthesiology and Perioperative Care, University of California, Irvine, Orange, California (J.R.).

The use of vasopressors is a mainstay treatment for correcting all types of vasodilatory hypotension in high-risk surgical and intensive care unit patients. The current approach to optimizing vasopressor infusions is *via* hand-titration by a bedside provider using a target mean arterial pressure (MAP). The ideal target MAP is not currently clear and may vary with the clinical situation and underlying cardiovascular physiology.[10] Vasopressor administration requires continuous modification of the infusion rate over time due to changes in hemodynamic status, patient pharmacokinetics, and pharmacodynamics. Ideally, changes in infusion rate should be made to avoid both hypo- and hypertension, as both can lead to complications. Unfortunately, there are other aspects of patient care that compete for the time and attention of physicians and nurses, meaning continuous, uninterrupted attention to drip titration is not practical. Our own evaluations of performance in clinical practice demonstrated that patients on vasopressors may spend 40% or more of treatment time outside reasonable target ranges.[11]

Titration of vasopressor infusions is a task ideally suited for computer assistance. Using experience gained from the previous bench-to-bedside development of a computer-assisted fluid management system,[12–18] we developed a novel automated closed-loop vasopressor device to treat hypotension using a proportional integral derivative controller that informs a rules-based decision engine.[19,20] The algorithm has undergone extensive *in silico* engineering and robustness testing and can maintain a target MAP in a simulated physiologic model even in the face of random hemodynamic disturbances, infusion-line lag,[19] and patient pharmacodynamic variability (differing individual responses to a given dose of vasopressor). To validate the novel device in an *in vivo* preclinical model, we assessed the performance of the closed-loop controller in healthy pigs, using norepinephrine to treat normovolemic vasodilation induced by sodium nitroprusside. We hypothesized that the closed-loop controller would be able to maintain MAP at a steady, predefined target range of 80 mmHg for more than 85% of the time.

Materials and Methods

Animals

The study protocol was approved by our Institutional Animal Ethics Committee on February 8, 2018, and the experiment was performed in the animal laboratory of the Université Libre de Bruxelles, Brussels, Belgium. This manuscript adheres to the Animal Research: Reporting of In Vivo Experiments Guidelines for reporting animal research. As swine are frequently used for both surgical and preclinical models because they have similar anatomic and physiologic characteristics to humans, we used 16 farm-raised pigs (3 months old) in this study. All pigs were examined by our veterinarian before being enrolled in the study and were housed at a temperature of 23°C in groups of two to three with full access to food and water. The first two pigs were used to test the protocol and the effects of sodium nitroprusside on MAP, and to determine the amount of sodium nitroprusside that induced a decrease in MAP to 50 mmHg. The remaining 14 pigs were randomized into a closed-loop group or control group.

Preparation and Anesthesia Management

All animals were fasted for 12 h before the experiment with free access to water. To prevent unnecessary stress and discomfort, pigs were premedicated in their enclosure by intramuscular injection of a mixture of midazolam (50 mg/kg; Mylan, Belgium), azaperone (200 mg; Eli Lilly Benelux, Belgium), and atropine (0.5 mg) 15 min before moving them to the operating room.

After placing the animal in the supine position on the operating table, a five-lead electrocardiogram was placed to monitor heart rhythm, and a 14-gauge peripheral catheter was inserted into the left ear vein for intravascular access. The neck, hind limb area, and abdomen were then cleaned and disinfected with iodine 2%. Under ultrasound guidance and using the Seldinger technique, the femoral artery was cannulated using a 6F introducer (Terumo Corporation, Japan) under local anesthesia (lignocaine 2% + adrenaline 1/200.000; Kela, Belgium) to monitor invasive arterial blood pressure continuously. This line was connected *via* the Flotrac sensor (Edwards Lifesciences, USA) to a minimally invasive pulse wave monitoring device (EV1000 platform; Edwards Lifesciences). Once the invasive femoral line had been inserted, general anesthesia was induced with intravenous atropine (0.5 mg), propofol 2% (1 mg/kg; Ecuphar, Belgium), sufentanil (2 μg/kg; Janssen-Cilag, Belgium), and rocuronium (1.2 mg/kg; Organon, Netherlands). After tracheal intubation (8.0-mm diameter endotracheal tube), all animals received mechanical ventilation with a tidal volume of 10 ml/kg, respiratory rate of 12 to 14 breaths/min, positive end-expiratory pressure of 5 cm H_2O, and fraction of inspired oxygen of 40%. The right external jugular vein was then cannulated under echography guidance using a 8.5F introducer (Edwards LifeSciences), and a triple lumen catheter was inserted. Finally, the bladder was catheterized by surgical incision, and urine output was recorded continuously.

Anesthesia was maintained with inhaled sevoflurane (2%) and continuous intravenous sufentanil (4 $\mu g \cdot kg^{-1} \cdot h^{-1}$) and rocuronium (2 $mg \cdot kg^{-1} \cdot h^{-1}$) until the end of the study protocol. Ventilator conditions were adjusted to maintain 90 to 100 mmHg Pao_2, 35 to 45 mmHg $Paco_2$, and peak airway pressure less than 30 cm H_2O.

Fluid administration was standardized in all pigs. It consisted of a balanced crystalloid solution (PlasmaLyte; Baxter SA, Belgium) given as a standard amount of 500 ml (bolus) during the surgical preparation and anesthesia induction, followed by a 5 $ml \cdot kg^{-1} \cdot h^{-1}$ infusion. Additional fluid boluses of 100 ml of 6% hydroxyethyl starch 130/0.4 (Voluven; Fresenius Kabi, Germany) were administered when necessary to optimize stroke volume and cardiac output based on the EV1000 monitor using the Assisted Fluid Management strategy available on the monitor (Edwards Lifesciences). Assisted Fluid Management is a decision support system integrated into the monitor to provide goal-directed fluid therapy; the system monitors stroke volume variation, mean arterial pressure, cardiac output, and heart rate and makes fluid recommendations based on a validated algorithm and the patient's own previous responses to fluid boluses. For this protocol, all fluid recommendations by the system were followed immediately with a 100-ml bolus. Normoglycemia (arterial blood glucose levels 80 to 120 mg/ml) was strictly maintained throughout the experiment using 20% glucose infusion and insulin as needed. Temperature was kept constant (37° to 39°C) with heating pads to prevent hypothermia.

On completion of the protocol, the animals were euthanized with infusion of propofol (2 mg/kg) followed by 40 ml of saturated KCl 7.45% (B. Braun Melsungen, Germany).

Study Protocol

All animals underwent a 2-h study protocol in which the sodium nitroprusside infusion rate was adjusted every 30 min (doses alternating between 130 and 65 μg/min). Sodium nitroprusside was chosen for this normovolemic vasodilatory model because it is rapidly titratable (allowing adjustments during the study), can be used to predictably maintain relative hypotension, and creates a purely vasodilatory state. First, sodium nitroprusside infusion was initiated at 130 μg/min, the dose that had caused a reduction in MAP to around 50 mmHg in the two initial test pigs. This infusion rate was continued for 30 min. The infusion rate was then decreased to 65 μg/min for 30 min. In the third phase, the sodium nitroprusside rate was increased again to 130 μg/min for 30 min, and finally, in the fourth phase, decreased by half for the last 30 min of study protocol. We continued to record variables for 10 min after the discontinuation of the sodium nitroprusside. Figure 1 describes the different steps of the study protocol. Two coauthors not involved in the creation of the closed-loop system (A.J., A.D.) ran the animal laboratory experiments together.

Closed-loop System Description

The closed-loop system collects MAP values from the EV-1000 monitor, and through a combination of proportional integral derivative and rule-based control modules, titrates vasopressor infusion drip rate to maintain a target MAP. The proportional integral derivative element enables adjustment for both current and anticipated future error, while the rule-based component provides additional safety features in the titration of the vasopressor. The controller sets both a target MAP level and an acceptable error (above or below target), as well as infusion rate limits (upper and lower). The algorithm was coded in Microsoft Visual C

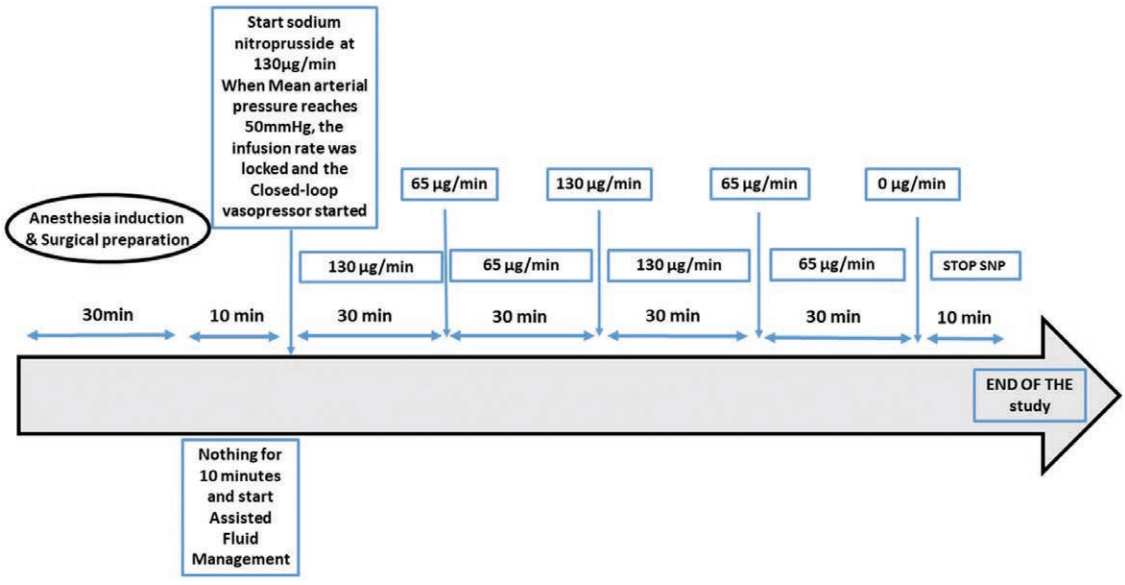

Fig. 1. Study protocol. SNP, sodium nitroprusside.

(Microsoft Corp., USA). Figure 2 shows the closed-loop interface.

For the purpose of the experiment, the goal was to maintain MAP at 80 ± 5 mmHg *via* automated adjustments of the norepinephrine infusion rate. The controller allows for setting "tolerance zones" above and below the precise MAP target that are penalized less heavily than error outside of these zones. By adjusting the lower zone to −2 and the upper zone to +5, the system will correct *mild* hypertension less aggressively than *mild* hypotension, resulting in a slight error "preference" in the controller to be above the target MAP, which is generally preferred by clinicians. The allowable norepinephrine infusion dose ranged from 0 to 50 mcg/min in all pigs, but the maximal rate could be increased manually if needed. Adjustment of the norepinephrine infusion rate was made every 20 s by the closed-loop controller using the MAP recorded from the EV1000 monitor. The infusion rate can be adjusted much more frequently by the closed-loop system, but despite outputting data *via* the serial port every 2 s, the EV-1000 platform only *updates* the MAP value every 20 s, so more frequent adjustment was not warranted in this study.

The controller program was run on an ACER laptop running Windows 7 (Microsoft Corp.), connected to the serial output on the EV-1000 monitor. The laptop was also connected *via* serial connection to a Q-Core Sapphire Pump (Q-Core Medical Ltd., Israel) containing the norepinephrine infusion, the rate of which was controlled by the software.

Data Collection

During the study protocol, data were collected by the closed-loop system every 2 s. Data collection included time-stamp, MAP, infusion rate of norepinephrine, and multiple other parameters related to the closed-loop operation such as target values, drip limits, tolerance settings, individual and global error components for the proportional integral derivative controller, states of flags (binary indicators for specific states in the closed-loop system like bad incoming data or user overrides) in the rules-based components, and data about the fluid pump state. Because the control group did not have the closed-loop intervention, but both groups did have EV-1000 monitoring from the time of placement of the arterial line, the EV-1000 MAP data (sampled once every 20 s) were used for analysis of blood pressures and time-in-target comparisons.

Statistical Analysis

Closed-loop performance was evaluated using the percentage of time that MAP was within ±5 mmHg of the target. MAP was recorded by the system every 2 s, and time-in-target was calculated as [values in range] / [total number

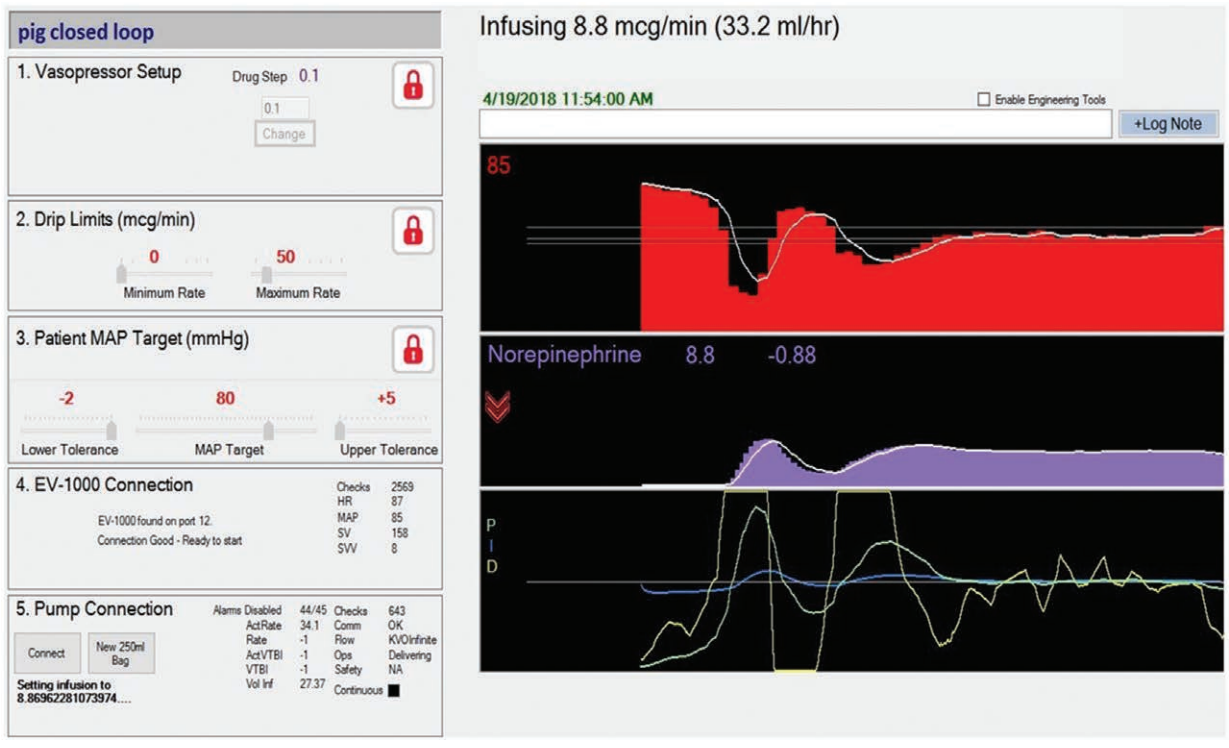

Fig. 2. Closed-loop controller interface. MAP, mean arterial pressure.

observations]. Five other performance parameters were quantified using the Varvel method.[21] These included: *performance error* (PE), as the percent difference between measured (m) and target (t) MAP (PE= [(MAPm-MAPt)/(MAPt)] × 100); *wobble,* as the intrapig variability in PE (which is directly related to the ability of the closed-loop controller to achieve MAP stability); *bias,* as median PE calculated as median (PE_j,j=1,…,N); *inaccuracy* (which is the median absolute PE calculated as median[$|PE_j|$, j=1,…,N]); and *divergence* (defined as "the slope of the linear regression equation of absolute values of PE against time"). Optimal performance is characterized by low median absolute PE and wobble values combined with a high percentage of protocol time of MAP within 5 mmHg of the target.

Data are expressed as mean ± SD. Mean and SD for each case were calculated across the entirety of the collected data for that case. Overall values for the groups are calculated as the mean of the seven observations for the group. Normality of data was checked with the Shapiro–Wilk test. Group comparison for time-in-target was performed with a test of proportions. Varvel criteria were calculated with Microsoft Excel (Microsoft Corp.) and R version 3.3.3.[22] Groups were compared with Student's *t* test. Varvel criteria were further individually assessed for performance error, median performance error, and median absolute performance error using a linear mixed-model approach with the individual animal as a random factor and time of observation as independent factor (*wobble* and *divergence* are calculated as an individual value for each animal and are thus not amenable to calculation by modeling in this manner). Statistical tests were run with R and all comparisons made with two-tailed tests. A P value of <0.05 was considered statistically significant.

Study size was based on budgetary considerations and discussion with the institutional animal care and use committee on the minimum sample appropriate for preclinical testing. This sample size is consistent with previous publications in closed-loop systems.[23,24]

Results

Fourteen pigs (11 males and 3 females, weight 42 ± 6 kg) were randomized into the two groups (7 into control group and 7 into closed-loop group) and studied between March 1 and April 19, 2018. All fourteen pigs were included in analysis, and there were no periods of missing or lost data. The total protocol length varied slightly from 130 min to 145 min due to surgical preparation differences.

The closed-loop controller maintained MAP in the target range of 80 ± 5 mmHg for 98 ± 1.4% of the study protocol *versus* the control group, where the MAP was 80 ± 5 mmHg for 14.0 ± 2.8% of the time ($P < 0.0001$). The MAP in the closed-loop group was above target range for 1.2 ± 1.2% and below it for 0.5 ± 0.9% of the time.

The MAP in the closed-loop group never reached the predetermined maximum norepinephrine rate of 50 mcg/min, and as a result, the principal investigator (A.J.) never needed to intervene with the system. Table 1 shows mean performance and time in target for each animal. Figure 3 shows the MAP values for each animal during the whole protocol. All of the animals survived the protocol.

Table 1. Mean Performance and Time in Target for Each Animal

		MAP (mmHg)		Time in Range (%)						
	Total Samples	Mean	SD	< 50	< 60	< 70	< 75	75–85	> 85	> 90
Control 1	407	58.7	7.0	6.7	46	86	88	12	0	0
Control 2	416	58.1	4.9	0.0	82	83	90	10	0	0
Control 3	394	55.3	3.6	3.2	79	84	84	16	0	0
Control 4	396	55.8	5.2	3.9	80	83	88	12	0	0
Control 5	402	57.4	6.6	4.6	68	85	86	12	1.8	0.7
Control 6	400	55.3	7.4	14	77	82	82	18	0	0
Control 7	406	54.1	7.5	21	77	82	83	17	0	0
Closed-loop 1	400	79.4	2.3	0	0	0	2.3	98	0.2	0
Closed-loop 2	435	80.1	1.8	0	0	0	0	98	2.1	0
Closed-loop 3	411	80.2	1.5	0	0	0	0	100	0	0
Closed-loop 4	389	80.6	2.4	0	0	0	0.9	98	0.9	0
Closed-loop 5	416	80.7	2.3	0	0	0	0.2	97	2.8	0
Closed-loop 6	419	80.7	2.7	0	0	0	0	98	2.1	0
Closed-loop 7	405	81.0	3.1	0	0	0	0	100	0	0
Control (overall)		56.4	6.0	7.5	73	84	86	14	0.3	0.1
Closed-loop (overall)		80.4	2.3	0	0	0	0.5	98	1.2	0

Values are expressed as percentage of case time in the different ranges. Mean and SD for each case are calculated across the entirety of the collected data for that case. Overall values for the groups are calculated as the mean of the 7 observations for the group in the table. Total Samples indicate the number of observations made during the case; there are small variations due to differences in time to complete the preparation of the animal and the protocol.

MAP, mean arterial pressure.

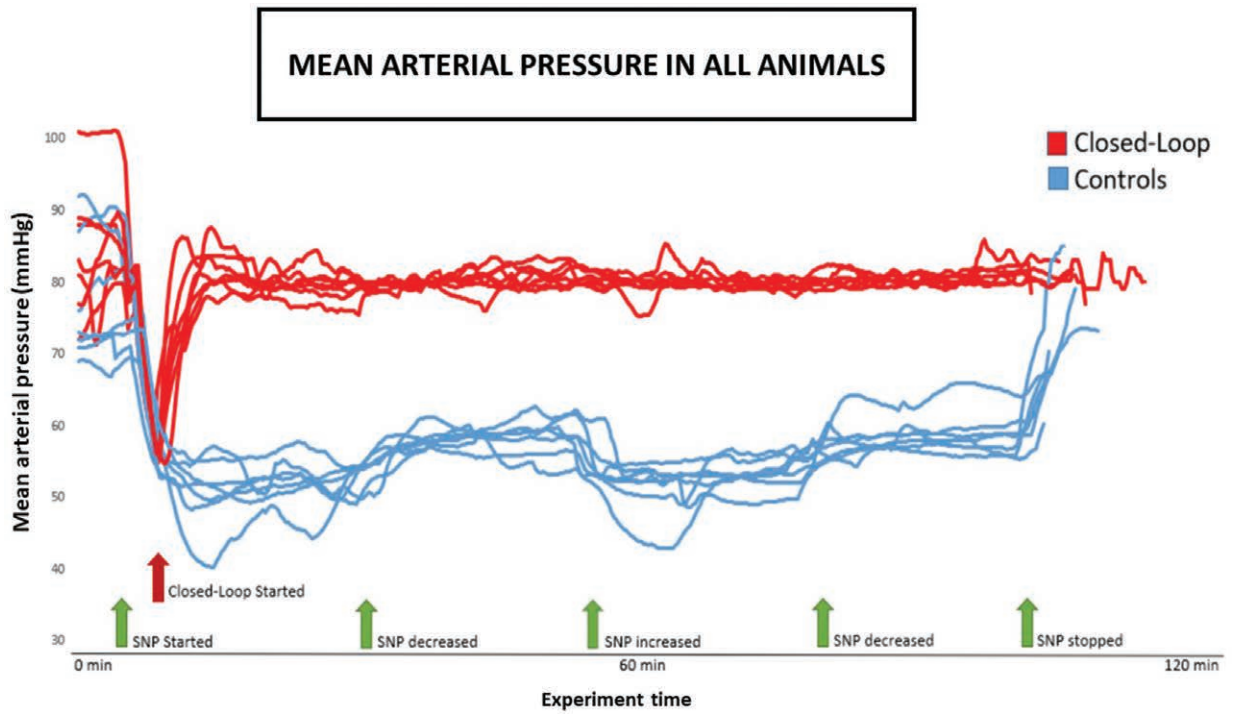

Fig. 3. Mean arterial pressure in all animals during the 2-hr study protocol. SNP, sodium nitroprusside.

Table 2. Varvel Performance Values for Closed-loop Controller

Experiment	Performance Error (%)	Median Absolute Performance Error (%)	Median Prediction Error (Bias, %)	Wobble (%)	Divergence (%)/m
Closed-loop 1	–1.3	2.5	–1.3	0.1	–9.2
Closed-loop 2	–0.3	1.3	0	0	–12
Closed-loop 3	0.4	1.3	0	0	–19
Closed-loop 4	1	2.5	1.3	0.1	–10
Closed-loop 5	1	2.5	1.3	0.1	–17
Closed-loop 6	0.7	1.3	0	0	–9
Closed-loop 7	0.3	1.3	0	0	–17
Mean (SD)*	0.3 (0.8)	1.8 (0.6)	0.2 (0.9)	0.0 (0.1)	–13 (4)
Model†	0.1	2.5	0.3	‡	‡

*Calculated as the mean and SD of the individual animal experiments; corresponds to the approximate location and spread that may be expected from any individual run with the controller in this setting. †Calculated as the intercept of a mixed-effects linear model incorporating the times of the observations, plus the individual animal as a random effect, on the measure; corresponds to the global performance of the controller. ‡Wobble and divergence are calculated as a single value per experiment and are therefore not amenable to calculation by mixed-effects modeling.

Across all closed-loop animals, the performance error was 0.3 ± 0.8%, median absolute performance error was 1.8 ± 0.6%, median performance error was 0.2 ± 0.9%, wobble was 0.0 ± 0.1%, and divergence was −13 ± 4%/m. Table 2 shows the Varvel performance values for each closed-loop animal. Using a mixed-model approach to analysis of these criteria yielded similar results (table 2).

There were no manual adjustments of the norepinephrine infusion made at any time; all adjustments were made by the system. The mean ± SD of norepinephrine adjustments per closed-loop case was 225 ± 80. Regarding the actual norepinephrine used, the median (25th–75th quartiles) was 1,152 μg/ml (752–1,248), and the mean ± SD was 1,008 ± 320 μg/ml.

All fluid prompts by the assisted fluid management system were followed with a bolus. In the control group, the median (25th–75th quartiles) of fluid administration was 500 (300–500) ml (minimum, 200 ml; maximum, 1,000 ml). In

the closed-loop group, the median (25th–75th quartiles) was 400 (100 to 500) ml (minimum, 0 ml; maximum, 700 ml).

Discussion

During hypotensive challenges induced by sodium nitroprusside, the closed-loop controller maintained MAP at the predefined target level for 98 ± 1% of the study time by continuously adjusting norepinephrine infusion rates. The other calculated performance metrics were also optimal.

The time-in-target performance and all the Varvel performance metrics were comparable with recent observations by Marques *et al.*,[23] who used a similar protocol using phenylephrine as a vasopressor and a different closed-loop controller.

In the operating room setting, numerous large retrospective studies have shown that perioperative hypotension is a risk factor for increased occurrence of stroke,[7] acute kidney injury,[5] myocardial injury,[3] and overall mortality.[25–27] Futier *et al.* recently demonstrated in a prospective randomized controlled trial that individualized blood pressure management targeting a systolic blood pressure close to the patient's baseline resulted in less postoperative organ dysfunction than with standard blood pressure management in high-risk patients undergoing major surgery.[9] There are a variety of reasons why a patient may become hypotensive in the perioperative or intensive care setting (*e.g.*, sepsis, severe heart failure, blood loss, and changes in anesthesia level, among others). Clearly, vasopressors are not appropriate treatments for all of these etiologies. If a vasopressor infusion is indicated, however, it is still largely titrated manually at the bedside, which can result in suboptimal control, perhaps especially in the operating room or intensive care unit, where anesthesia providers and intensive care nurses work in distracting environments and are often managing multiple other tasks simultaneously.

This potential problem is also relevant in the management of critically ill patients with sepsis who require optimal MAP control.[28–30] Use of protocols to control MAP in these patients has consistently resulted in maintenance of MAP levels well above target ranges.[31–33] Alternatively, when higher MAP levels are targeted, patients are routinely found to have MAP values at least 10 to 15 mmHg below goal.[28,34,35] Importantly, these results occurred in studies where *strict* blood pressure management was a predefined goal, and one can assume that even greater variation may occur outside the clinical trial context. In our own institution, when vasopressors were used with traditional MAP goals, 10% of patients were undertreated (MAP less than 60 mmHg), and 30% overtreated (MAP greater than 80 mmHg).[11] The reasons for these shortcomings are likely multifactorial.[28,36]

We anticipate that clinical use of closed loop systems for multiple processes, including blood pressure control, will continue to expand as technology develops.[20,37] An important design consideration with all such systems will be to ensure that (1) clinicians are kept "aware" of what the system is doing and remain in control of the targets and treatments; and (2) anticipation and mitigation of possible causes of failure (including measurement error, communication failure, and intervention disruption or futility) are built into the device.

Our study has several limitations. First, no animal model is perfectly representative of human physiology under surgical or critical care conditions. It is possible that subtle performance differences may appear if the closed-loop controller is used in different clinical models moving forward. Second, this model of hypotension was induced with a sodium nitroprusside infusion (a direct vasodilator). It is possible that other causes of hypotension (*e.g.*, cardiogenic shock) may respond differently, and therefore exhibit different performance characteristics in clinical practice, particularly if the cause of hypotension is not directly attributable to vasoplegia. Our goal with this system was to improve the current "state of the art" of vasopressor infusions. In the future, multidrug systems and/or systems that incorporate other aspects of perfusion monitoring will likely be appropriate.

As previously described, the current system is an isolated vasopressor controller. At present, the current controller will respond to other interventions (*e.g.*, fluid loading, addition of an inotrope) only in regards to how these interventions affect MAP. If the interventions improve MAP above the target, the controller will accordingly decrease the infusion rate, and *vice versa*. Ideally, closed-loop systems could be built to work together to control multiple aspects of patient care simultaneously. For example, anesthetic drugs, fluid management, and hemodynamics all interact during anesthesia, and having a controller that understands the present state of all three could perform more holistically than individual controllers working independently. This is a long-term goal, however, and individual steps like those taken in the present work are going to be essential building blocks toward such a potential future state.

Conclusion

In this experimental model of induced normovolemic hypotensive episodes in healthy pigs, the automated closed-loop system titrated norepinephrine infusion to correct hypotension and keep MAP within ±5 mmHg of target for 98% of management time. This system may represent a powerful new tool for controlling hypotension in perioperative and intensive care patients.

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Research Support

This work was supported solely by departmental sources.

Competing Interests

Drs. Cannesson, Joosten, and Rinehart are consultants for Edwards Lifesciences (Irvine, California). Drs. Cannesson and Rinehart have ownership interest in Sironis (Newport Beach, California), and Sironis has developed a fluid closed-loop system that has been licensed to Edwards Lifesciences. The present closed-loop system in this study is new, not owned or supported by Edwards Lifesciences, Sironis, or any other commercial entity, and is the sole creation of the coauthors. Edwards Lifesciences, Sironis, and any other commercial entity have not provided any funding, directly or indirectly, in support of the current work, to the individual authors or any of their respective departments. A provisional patent has been submitted through the University of California, Irvine, Orange, California, by Drs. Rinehart and Cannesson covering aspects of closed-loop vasopressor administration, but does not cover any of the processes discussed in the current manuscript. Closed-loop vasopressor administration itself was first patented in 1978. Dr. Vincent is Editor-in-Chief of *Critical Care*. He has no other conflicts related to this article. The other authors declare no competing interests.

Reproducible Science

Full protocol available at: Alexandre.Joosten@erasme.ulb.ac.be. Raw data available at: Alexandre.Joosten@erasme.ulb.ac.be.

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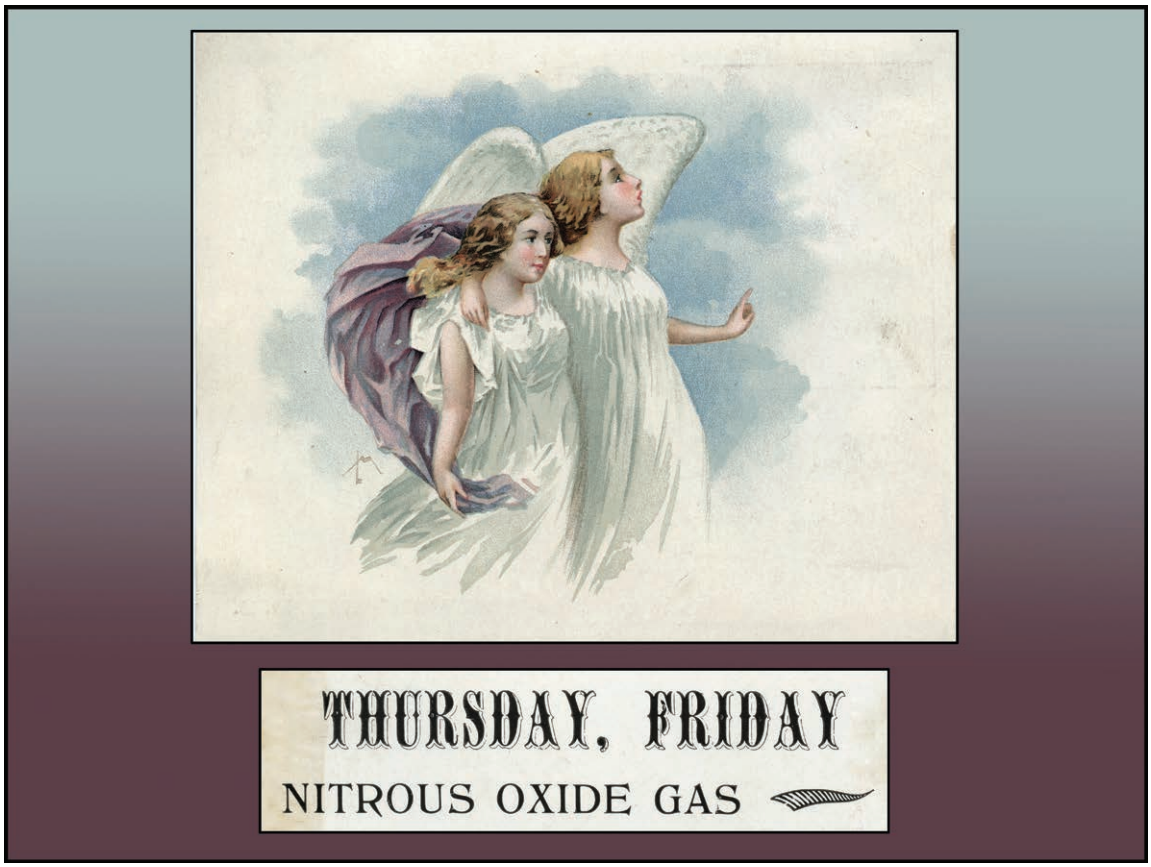
ANESTHESIOLOGY REFLECTIONS FROM THE WOOD LIBRARY-MUSEUM

Joining the Angels: Laughing-gas Advertising Divined by Dr. G. W. Chamberlain



An angel guides a young woman skyward (*upper image*) in this image from the obverse of a trade card from the Ben Z. Swanson Collection of the Wood Library-Museum. On the card's reverse, one box (*lower*) cites two of the weekdays that dental and "nitrous oxide gas" services would be provided at New Egypt, New Jersey, by George Whitehill Chamberlain, D.D.S. (1855 to 1905). In the early 1900s, understandably, most American physicians and dentists shied away from advertising death, dying, or the heavenly hereafter in any connection with their anesthetics. Could this 50-yr-old dentist have possibly been divining his own future? While "merry-making" at his church's Fourth of July celebration in 1905, Dr. Chamberlain collapsed in front of 800 of his fellow parishioners and presumably joined the angels…. (Copyright © the American Society of Anesthesiologists' Wood Library-Museum of Anesthesiology.)

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