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Precision Automated Critical Care Management: Closed-loop critical care for the treatment of distributive shock in a swine model of ischemia-reperfusion

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BACKGROUND: Goal-directed blood pressure management in the intensive care unit can improve trauma outcomes but is labor-intensive. Automated critical care systems can deliver scaled interventions to avoid excessive fluid or vasopressor administration. We compared a first-generation automated drug and fluid delivery platform, Precision Automated Critical Care Management (PACC-MAN), to a more refined algorithm, incorporating additional physiologic inputs and therapeutics. We hypothesized that the enhanced algorithm would achieve equivalent resuscitation endpoints with less crystalloid utilization in the setting of distributive shock.

METHODS: Twelve swine underwent 30% hemorrhage and 30 minutes of aortic occlusion to induce an ischemia-reperfusion injury and distributive shock state. Next, animals were transfused to euvolemia and randomized into a standardized critical care (SCC) of PACC-MAN or an enhanced version (SCC+) for 4.25 hours. SCC+ incorporated lactate and urine output to assess global response to resuscitation and added vasopressin as an adjunct to norepinephrine at certain thresholds. Primary and secondary outcomes were decreased crystalloid administration and time at goal blood pressure, respectively.

RESULTS: Weight-based fluid bolus volume was lower in SCC+ compared with SCC (26.9 mL/kg vs. 67.5 mL/kg, $p = 0.02$). Cumulative norepinephrine dose required was not significantly different (SCC+: 26.9 μg/kg vs. SCC: 13.76 μg/kg, $p = 0.24$). Three of 6 animals (50%) in SCC+ triggered vasopressin as an adjunct. Percent time spent between 60 mm Hg and 70 mm Hg, terminal creatinine and lactate, and weight-adjusted cumulative urine output were equivalent.

CONCLUSION: Refinement of the PACC-MAN algorithm decreased crystalloid administration without sacrificing time in normotension, reducing urine output, increasing vasopressor support, or elevating biomarkers of organ damage. Iterative improvements in automated critical care systems to achieve target hemodynamics in a distributive-shock model are feasible. (*J Trauma Acute Care Surg.* 2023;95: 490–496.

KEY WORDS: Critical care; resuscitation; trauma; shock; swine.

Submitted: August 2, 2022, Revised: May 1, 2023, Accepted: May 2, 2023, Published online: June 14, 2023.

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This study was presented at the 81st annual meeting of the AAST, September, 21, 2022, in Chicago, IL.

Supplemental digital content is available for this article. Direct URL citations appear in the printed text, and links to the digital files are provided in the HTML text of this article on the journal's Web site (www.jtrauma.com).

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DOI: 10.1097/TA.0000000000004054

The treatment of severe circulatory shock often requires intensive care unit (ICU) admission and invasive monitoring devices.[1,2] Regardless of the shock etiology, the resulting systemic inflammatory response leads to end-organ dysfunction which is marked by tissue ischemia.[3] Optimizing macrovascular oxygen delivery is the primary objective for improving shock mortality.[4] Crystalloid and vasopressor use as multimodal adjuncts to support hemodynamics were initially described in 1969 and have remained mainstays of resuscitation for hemorrhagic, neurogenic, cardiogenic, and septic shock.[1,5,6–8]

This treatment strategy of maintaining tissue perfusion after initial restoration of intravascular volume and/or source control has been studied in patients with differing shock types with a clear emphasis on maintaining normotension and has been associated with improved outcomes.[9–11] However, the goal of driving toward and maintaining systemic normotension in an effort to promote oxygen delivery carries the well described risks associated with excessive fluid administration and/or vasopressor usage.[12] To date, there are ongoing efforts to strike the balance between providing therapies to achieve sufficient end-organ perfusion while minimizing unwanted crystalloid and vasopressor consequences.[13]

The burden of providing precision volume resuscitation and vasopressor titration in addition to numerous tasks bedside physicians provide for multiple patients (e.g., gastrointestinal prophylaxis, ventilator management, antibiotics administration, frequent laboratories) can jeopardize patient outcomes.[14] These effects have become apparent during the COVID-19 pandemic, with ICUs stretched to their capacities and provider job dissatisfaction becoming more commonplace.[15] Automation may offer a solution. Although closed-loop systems for ventilation and anesthesia have been studied for the past 45 years, their clinical translation to patient care has remained just out of reach. Past prototypes of closed-loop systems focused on single therapeutic interventions but never a cohesive platform modulating interventions in parallel.[16,17] With both health care and market forces leveraging big data and automated systems throughout the hospital, the environment for innovative provider-in-the-loop automated systems is improving.

Closed-loop automated critical care (ACC) systems for vasopressor titration and crystalloid management can achieve goal-directed resuscitation endpoints with smaller, more frequent interventions while avoiding delays in interventions that are commonplace in conventional critical care.[18,19] These strategies seek to minimize undesired consequences from the resuscitation itself and provide a more targeted approach to re-establishing homeostasis. Currently, little research is dedicated to closed-loop ACC systems that automate multiple therapeutic components in parallel. The feasibility of ACC has been proposed by some,[20,21] while others have focused on computational modeling of ACC systems[22–25] with the majority focusing on single therapeutic interventions and not parallel interventions.[26,27] To that end, we refined our first-generation closed-loop heuristic-based critical care algorithm by incorporating multiple physiologic parameters vital to targeted resuscitation strategies. The first- and second-generation algorithms were implemented with our automated fluid and drug delivery platform, Precision Automated Critical Care Management (PACC-MAN), in a highly reproducible distributive shock model. We hypothesized that an enhanced critical care algorithm with additional physiologic inputs would reduce crystalloid and vasopressor administration while achieving equivalent resuscitation endpoints when compared with our first-generation algorithm in a swine distributive shock model.

METHODS

Overview

The Institutional Animal Care and Use Committee approved this study. Animal care and use were in strict compliance with the Guide for the Care and Use of Laboratory Animals in a facility accredited by AAALAC and adhered to ARRIVE guidelines (Supplemental Digital Content, Figure 1, http://links.lww.com/TA/D127).

Animal Preparation

Naive healthy adult, castrated male and non-pregnant female Yorkshire-cross swine, were fasted, then premedicated with 5 mg/kg to 7 mg/kg intramuscular tiletamine/zolazepam (Supplemental Digital Content, Figure 1, http://links.lww.com/TA/D127). After endotracheal intubation, animals were maintained with ~2% isoflurane and mechanically ventilated to maintain end-tidal CO_2 at 35 mm Hg to 45 mm Hg in our operative suite. Animals received a 1-L bolus of Plasma-Lyte A, followed by maintenance intravenous fluids (mIVF) at 10 $mL \cdot kg^{-1} \cdot h^{-1}$. To offset the vasodilatory effects of isoflurane, a low dose norepineprhine (NE) infusion (0.02–0.06 mcg/kg/min) was titrated before experimentation to maintain a mean arterial pressure (MAP) greater than 60 mm Hg. An underbody warmer maintained core body temperature between 37°C and 39°C.

Instrumentation

The bilateral common femoral arteries and left femoral vein were surgically exposed for arterial sheath and venous dual lumen hemorrhage and resuscitation catheter placement. The left external jugular vein was cannulated with a triple lumen catheter for mIVF, vasoactive medication administration, and central venous pressure (CVP) measurements. The left axillary artery was surgically exposed and cannulated for proximal blood pressure (BP) measurements. The right brachial artery was exposed and cannulated with a micropuncture sheath for laboratory draws. After a laparotomy and cystostomy tube placement, a splenectomy was performed to minimize hemodynamic variation from autotransfusion. Perivascular flow probes (Transonic, Ithaca, NY) were placed around the supraceliac aorta, renal artery, and carotid artery. A 7-Fr custom compliant aortic balloon catheter was introduced through the left femoral arterial sheath and positioned just distal to the aortic flow probe in the distal descending thoracic aorta, with placement confirmed by manual palpation. The abdomen was closed with cable ties and a plastic sheet to minimize insensible losses. The mIVF rate was then decreased to 5 $mL \cdot kg^{-1} \cdot h^{-1}$. Intravenous heparin (50 units/kg bolus plus 10 $units \cdot kg^{-1} \cdot h^{-1}$) was administered to offset hypercoagulability (Supplemental Digital Content, Figure 1, http://links.lww.com/TA/D127).

Data Collection

Physiologic measurements (proximal and distal arterial BP, CVP, and aortic flow) were collected in real time with a multichannel data acquisition system at a rate of 1000 Hz (Powerlab, AD Instruments, Colorado Springs, CO). Plasma and urine neutrophil gelatinase-associated lipocalin (N-GAL) concentrations were quantified (Abcam, Waltham, MA) to calculate the plasma-to-urine N-GAL ratio and before euthanasia (Supplemental Digital Content, Figure 1, http://links.lww.com/TA/D127).[27]

Creation of Distributive Shock Condition

To create a reproducible shock state where swine are consistently fluid avid and hypotensive with consistent peak lactate levels, an autonomously controlled model incorporating hypovolemic shock exacerbated by ischemia-reperfusion injury was used.[18] Following instrumentation, the animals underwent a 30% total body blood volume (0.3 × 60 mL/kg × body weight in kg) controlled hemorrhage over 30 minutes (T0–T30). Shed blood was collected in citrated bags and stored at 39°C. After hemorrhage, the prepositioned aortic occlusion balloon was autonomously inflated to complete occlusion, as measured by the absence of distal aortic flow, for 30 minutes (T30–T60). At T45 (during occlusion phase), 200 mg of calcium gluconate was infused over 20 minutes to counteract the citrated blood transfusion chelation effect. At T55, the animals were transfused back to 95% of their total blood volume over 18 minutes. Starting at T60, the aortic balloon was autonomously weaned over 15 minutes during transfusion, provided central aortic pressure was maintained above 65 mm Hg, minimizing hemodynamic decompensation

during reperfusion. At T75, the balloon catheter was removed and each animal was randomized to standardized critical care (SCC) or standardized critical care plus (SCC+) (Supplemental Digital Content, Figure 1, http://links.lww.com/TA/D127). A sealed-envelope system was used to randomly assign treatment groups at T0, ensuring no knowledge of the animal's eventual group assignment would have an impact on animal instrumentation prior to start of computer-automated protocolized injury. The critical care phase (CCP) lasted for 255 minutes (T75-T330) and was entirely autonomously controlled. The only direct input from lab personnel was to ensure anesthesia maintenance, sufficient crystalloid fluid and medication infusion supplies, and blood and urine collection (Supplemental Digital Content, Figure 1, http://links.lww.com/TA/D127).

Automated Care Platform

A custom-built automation platform (PACC-MAN) and data acquisition system was used to continuously monitor analog physiology data from the animal as previously described.[18] Analog data was collated by a microcontroller and converted to a digital signal, which was passed to the PACC-MAN platform with graphical user interface running on a separate computer. This software facilitated experimental workflow scripting to enable high reproducibility. PACC-MAN runs rules-based critical care algorithms to actuate three peripheral devices (crystalloid bolus infusion pump, mIVF and drug infusion pump, and endovascular balloon syringe pump) via BluetoothLE wireless communication (Supplemental Digital Content, Figure 1, http://links.lww.com/TA/D127).

Standardized Critical Care

Our custom rules-based algorithm incorporates proximal MAP and CVP as inputs (Supplemental Digital Content, Figure 2, http://links.lww.com/TA/D121). The algorithm's branching logic constantly assesses the animal's hemodynamic state (normotension, hypertension, hypotension, severe hypotension). Those that are hypertensive (MAP >70 mm Hg) and receiving NE will proceed with scaled decrease in NE. Animals that fall in the normotension pathway (MAP 60–70 mm Hg) will remain in steady state, unless the current NE dose is greater than a threshold value and the CVP is less than a threshold value, which will trigger normotensive fluid bolusing in an attempt to reduce the NE dose (Supplemental Digital Content, Figure 1, http://links.lww.com/TA/D127 and Supplemental Digital Content, Figure 2, http://links.lww.com/TA/D121).

The algorithm's core focuses on the hypotensive state (MAP 50–59 mm Hg) and determining fluid responsiveness state (delta MAP of 5 mm Hg) based on response to test boluses which then dictates intensity of fluid bolus administration. Animals deemed fluid responsive undergo fluid boluses until either a max number of boluses are administered, at which point NE is increased, or normotension is achieved. For animals deemed "fluid non-responsive", there is an immediate NE increase. Norepinephrine dosing is titrated based on current dose level, hypotension depth, and fluid responsive state. The fluid responsive state was reset 1 hour from the last test bolus or after five interventions in a particular state (Supplemental Digital Content, Figure 1, http://links.lww.com/TA/D127 and Supplemental Digital Content, Figure 2, http://links.lww.com/TA/D121).

Certain circumstances will trigger two subalgorithms, "CVP-Based Fluid Bolus" and "Vasopressor Resistance" pathways, built to incorporate fluid therapy in fluid non-responsive animals that persistently fail to reach targeted MAP goals (Supplemental Digital Content, Figure 1, http://links.lww.com/TA/D127 and Supplemental Digital Content, Figure 2, http://links.lww.com/TA/D121).

Standardized Critical Care Plus

To build nuance into the SCC algorithm, two key refinements were made (Supplemental Digital Content, Figure 3, http://links.lww.com/TA/D122). First, our analysis from prior studies demonstrated excessive crystalloid volume administration. To address this, we incorporated smaller and more modular fluid-based interventions. Boluses that previously delivered over a 2-minute period were now divided into one-minute boluses. The benefit of this partitioning was to minimize large fluctuations in hemodynamics in response to administered boluses while simultaneously avoiding overresuscitation. In addition, total volume administration during a single hypotensive event was capped (Supplemental Digital Content, Figure 1, http://links.lww.com/TA/D127 and Supplemental Digital Content, Figure 3, http://links.lww.com/TA/D122).

A more fundamental enhancement to the algorithm involved reframing the fluid responsiveness concept. Instead of considering the hemodynamic response to a fluid bolus as simply a binary outcome, we expanded into three state conditions after fluid test bolus based on MAP response: nonresponsive (MAP increase <3 mm Hg), partially responsive (MAP increase 3–5 mm Hg), fully responsive (MAP increase >5 mm Hg). The normotensive subalgorithm was also restructured and expanded to include additional inputs, lactate and urine output (UOP), to provide additional triggers for interventions, and to balance fluid and vasopressor administration. Vasopressin (0.04 units/minute) was added as a NE adjunct to lessen the catecholamine-based vasopressor effects when NE doses exceeded 0.3 μg/kg/min and stopped when NE dose fell below 0.2 μg/kg/min. Lastly, the NE titration scaling factors were adjusted to be more granular and reduce significant fluctuations in NE dosing and subsequent effects on systemic hemodynamics (Supplemental Digital Content, Figure 1, http://links.lww.com/TA/D127 and Supplemental Digital Content, Figure 3, http://links.lww.com/TA/D122).

Data Analysis

Data analysis was performed with Python Version 3.7 (Python Software Foundation, Wilmington, Delaware), R statistical software (R Foundation for Statistical Computing, Vienna, Austria), and STATA (StataCorp, College Station, Texas). Continuous variables are presented as medians with interquartile ranges (IQR) and statistical differences were tested with the Mann-Whitney U-test. Dichotomous and categorical variables were analyzed by χ^2 statistics. Statistical significance was set at $p < 0.05$ (Supplemental Digital Content, Figure 1, http://links.lww.com/TA/D127).

A priori exclusion criteria included a pre-procedure white blood cell count >25 × 10^9/L, fulfillment of death criteria prior to end of study (proximal MAP <20 mm Hg for 5 minutes), or significant technical deviations from the established protocol. In addition, animals were excluded if a NE dose rate of greater than 0.1 μg/kg/min was required to maintain normotension for more than 10 minutes prior to experimentation, or if the NE dose rate to maintain normotension immediately prior to the experiment start was greater than 0.06 μg/kg/min, signifying abnormal

TABLE 1. Baseline Characteristics

Median With IQR	SCC	SCC+	*p*
Included animals	6	6	
Excluded animals	0	0	1.0
Weight (kg)	70.40 (68.70–72.40)	73.30 (70.78–73.88)	0.52
Baseline proximal BP (mm Hg)	78.1 (69.6–82.3)	73.05 (70.8–81.9)	0.82
Proximal BP at end of hemorrhage (mm Hg)	33.56 (27.6–38.0)	34.4 (31.1–40.5)	0.70
Baseline creatinine (mg/dL)	1.6 (1.5–1.6)	1.9 (1.7–1.9)	0.11
Baseline lactate (mmol/L)	2.1 (2.0–2.3)	2.31 (2.0–2.7)	0.52
Lactate at randomization (T75) (mmol/L)	9.1 (9.0–9.2)	9.4 (8.9–9.5)	0.47

baseline hemodynamics (Supplemental Digital Content, Figure 1, http://links.lww.com/TA/D127).

Based on prior studies, the primary outcome was a difference in crystalloid volume between the two algorithms (SCC and SCC+) using Mann-Whitney *U* test. The prior group had an average of 100 mL/kg (20 mL/kg standard deviation) with the same injury model. With our changes to the SCC+ algorithm, we were expecting a 40% decrease in crystalloid volume with an alpha of 0.05 and power of 80%. This would require 12 animals total with 6 animals per group (Supplemental Digital Content, Figure 1, http://links.lww.com/TA/D127).

Secondary outcomes between the two algorithms included NE requirements, time spent in target MAP zone (60–70 mm Hg), cumulative weight-based UOP, terminal creatinine and lactate, and plasma:urine N-GAL (Supplemental Digital Content, Figure 1, http://links.lww.com/TA/D127).

RESULTS

Baseline Characteristics

There were 12 animals in all analyses, n = 6 animals per group, with no excluded animals. The median animal weight between groups was equivalent (SCC: 70.4 kg vs. SCC+: 73.3 kg, $p = 0.52$). Blood pressure was similar between groups at baseline and end of hemorrhage ($p = 0.82$ and $p = 0.70$, respectively). Likewise, at the start of critical care (T75), lactate levels were equivalent ($p = 0.47$) (Supplemental Digital Content, Figure 1, http://links.lww.com/TA/D127 and Supplemental Digital Content, Table 1, http://links.lww.com/TA/D123) (Table 1).

Resuscitation Requirements and Hemodynamics

The difference in median weight-adjusted volume of crystalloid required during the CCP was significant at 67.5 mL/kg (IQR, 56.3–75.0 mL/kg) and 37.5 mL/kg (IQR, 10.8–54.2 mL/kg), $p = 0.02$, for SCC and SCC+, respectively. There was no difference in cumulative NE requirement during the CCP between the two groups (SCC: 13.76 μg/kg vs. SCC+: 26.9 μg/kg, $p = 0.24$). Fifty percent of the SCC+ animals triggered vasopressin infusion (Table 2).

During the CCP, the median proportion of time spent with MAP between 60 mm Hg and 70 mm Hg for SCC was 79% (IQR, 76–79%) compared with SCC+: 80% (IQR, 80–81%), $p = 0.09$. The proportion of time with MAP less than 60 mm Hg and MAP greater than 70 mm Hg was similar between SCC and SCC+, $p = 1.0$ and $p = 0.24$, respectively (Table 2).

Crystalloid Bolus Hemodynamics

During the CCP, there were 20 test boluses (fluid responsive: 95.0%, fluid nonresponsive: 5.0%) in the SCC (5 mL/kg) group, and 21 test boluses (fluid responsive: 95.2%, fluid partially responsive: 4.8%, fluid nonresponsive: 0%) in the SCC+ (3 mL/kg) group.

During the CCP, there were 43 (5 mL/kg) intervention boluses in the SCC group and 47 (1.5 mL/kg) intervention boluses in the SCC+ group. Intervention boluses were defined as a bolus in response to hypotension during a known fluid responsiveness state at the time of bolus (Fig. 1). The time from onset of hypotension to return to normotension (≥ MAP 60 mm Hg) was similar between SCC (1.5 seconds) and SCC+ (2 seconds), $p = 0.10$. The maximum BP during the intervention bolus for SCC was 76 mm Hg compared with SCC+ was 72 mm Hg, $p = <0.01$. The time from maximum BP to return to normotension (MAP ≤ 70 mm Hg) for SCC was 89.5 seconds compared with SCC+, which was 1.0 second, $p \leq 0.01$ (Table 3).

Renal Function

There was no difference between weight-adjusted cumulative UOP at all measured time points. Of note, the cumulative weight-adjusted UOP after hemorrhage (T30) was 0.0 mL/kg (IQR, 0.0–0.23) for SCC and 0.31 mL/kg (IQR, 0.25–0.42) for SCC+, $p = 0.06$. UOP at the end of occlusion and ICU phase start (T75) was 0.35 mL/kg (IQR, 0.19–0.50) for SCC and 0.35 mL/kg (IQR, 0.26–0.91) for SCC+, $p = 0.59$. At the end of study (T330), UOP was 9.24 mL/kg (IQR, 6.04–10.71) for SCC and 7.12 mL/kg (IQR, 5.12–8.24) for SCC+, $p = 0.18$. Figure 2 displays the cumulative weight-adjusted UOP graphical representation (Supplemental Digital Content, Table 2, http://links.lww.com/TA/D124).

Biomarkers of Injury

There was no difference in creatinine or lactate during the injury phase (T0-T75) or during the CCP (T75-T330). The plasma:urine ratio of N-GAL at the start of the experiment was 15% (IQR, 9%–17%) for SCC and 20% (IQR, 19%–21%) for

TABLE 2. Resuscitation Requirements and Hemodynamics

Median With IQR	SCC	SCC+	*p*
Crystalloid volume (mL/kg)	67.5 (56.25–75)	37.5 (33.75–46.875)	0.02
Cumulative norepinephrine dose (μg/kg)	13.76 (8.2–14.4)	26.9 (10.8–54.2)	0.24
Proportion of use of vasopressin (%)	Not applicable	50%	Not applicable
Proportion of time with MAP at 60–70 mm Hg	79% (76%–79%)	80% (80%–81%)	0.09
Proportion of time with MAP <60 mm Hg	4% (2%–6%)	4% (3%–5%)	1.0
Proportion of time with MAP >70 mm Hg	18% (15%–20%)	16% (15%–17%)	0.24

TABLE 3. Intervention Bolus Statistics.

Median With IQR	SCC n = 43	SCC+ n = 47	*p*
Minimum BP (mm Hg)	58.5 (57.8–59.0)	58.0 (57.0–59.0)	0.10
Maximum BP (mm Hg)	76.0 (73.0–81.0)	72.0 (69.0–75.0)	<0.01
From trigger of bolus to normotension (seconds)	1.5 (1–2.75)	2 (1–7)	0.10
Time for return to normotension from max pressure (seconds)	89.5 (32.0–155.3)	1.0 (1–52)	<0.01

SCC+, $p = 0.03$. This ratio at the experiment end was 11% (IQR, 8%–16%) for SCC and 22% (IQR, 10–70%) for SCC+, $p = 0.18$. Figure 3 displays graphical representation of lactate, creatinine, and plasma:urine N-GAL ratio during the experiment (Supplemental Digital Content, Table 1, http://links.lww.com/TA/D123).

Impact of Physiologic Inputs

Creating subalgorithms that incorporated UOP and lactate levels into the enhanced SCC+ algorithm were designed to assist with specific scenarios that its predecessor algorithm, SCC, could not address or anticipate such as impending clinical decline. This was implemented to be anticipatory and predictive rather than reactive. The first subalgorithm (marked as 'Stage 12' in Supplemental Digital Content, Figure 3, http://links.lww.com/TA/D122) involves the condition of the animal maintaining MAPs between 60 and 70 but requiring even low-dose vasopressor(s) with uptrending lactate levels with concomitant downtrending UOP from the previous hour. This represents a unique scenario where the animal shows signs of physiologic decline based on physiologic indicators but may not yet demonstrate hemodynamic compromise. As a result, this subalgorithm triggered micro boluses in an effort to improve UOP, support hemodynamics, and lessen vasopressor requirements. The second subalgorithm (marked by "Stage 13" in Supplemental Digital Content, Figure 3, http://links.lww.com/TA/D122) addressed the condition in which the animal has reached MAPs in the higher end of the normotensive range (MAP 65–70 mm Hg) with downtrending lactate levels and higher-than-necessary UOP (>1 $mL \cdot kg^{-1} \cdot h^{-1}$) in an attempt to decrease vasopressor requirements. Three of six animals in the SCC+ group (50%) triggered Stage 12. Cumulatively, this was triggered five times between the three animals (7% of all 72 cumulative stages triggered by the 3 animals). Zero animals in the SCC+ group triggered stage 13. See Supplemental Digital Content, Table 3 for more information, http://links.lww.com/TA/D200.

DISCUSSION

This study demonstrates automated resuscitation in the face of a severe ischemia-reperfusion injury model is possible. Moreover, these observations represent an incremental advance in the refinement of a standardized critical care algorithm that incorporates additional physiologic inputs and resuscitation adjuncts. Most notably, these refinements decreased crystalloid utilization without adversely impacting the resuscitation endpoints.

Specifically, the modified standard critical care algorithm (SCC+) provided an overall decreased crystalloid volume (~45%) during the CCP while simultaneously maintaining similar hemodynamics compared with our previous algorithm (SCC). This is a significant finding as increased crystalloid utilization can exacerbate coagulopathy, inflammatory response, hypothermia, acidosis, and lead to mortality.[29,30] Furthermore, SCC+ demonstrated improved performance with more precise hemodynamic control by delivering more nuanced volume resuscitation (smaller bolus volumes and lower bolus truncation thresholds) during hypotension states, limiting overshot MAPs above the predetermined target range. Importantly, this reduced reliance on crystalloid in the SCC+ group did not come at the expense of significantly increased vasopressor requirements suggesting that our improved algorithm is able to strike an improved balance between volume resuscitation and vasopressor utilization in this model. That being said, three of six animals (50%) in SCC+ group did require vasopressin infusion. However, this was a desired outcome, as vasopressin use as a NE adjunct is a standard clinical practice with the purpose of reducing the detrimental impact of high-dose NE on splanchnic circulation. There is evidence in translational models that vasopressin is associated with reduced morbidity and mortality in the context of catecholamine-refractory hemorrhagic shock due to endogenous vasopressin store depletion.[31] Ultimately, there were no differences in cumulative weight-adjusted UOP, end-organ perfusion markers (creatinine and lactate), and end-of-study plasma:urine N-GAL, a renal injury marker.

ACC systems have the potential to reduce the clinician's workload while maintaining a high standard of care. This duality is growing in importance as the demands to closely monitor and titrate medication treatments in the critical care setting coincide with decreasing provider bandwidth. Currently, there is paucity of research involving closed-loop ACC systems for the

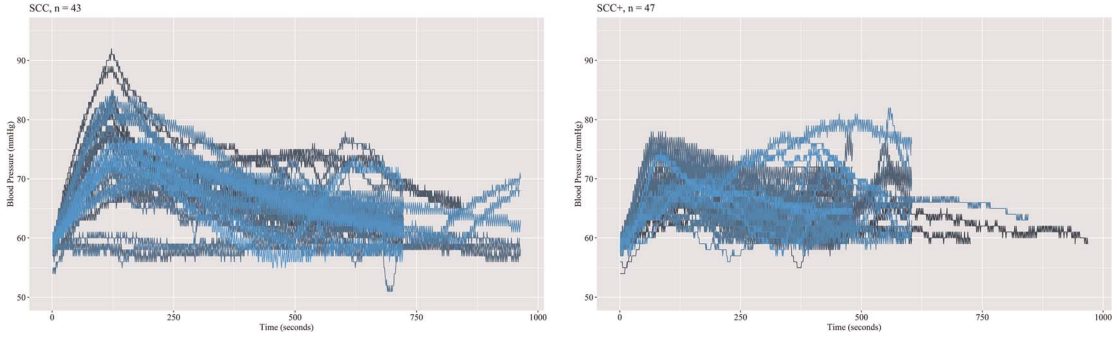

Figure 1. The intervention boluses in response to hypotension graphed from start of bolus to 4 minutes after end of bolus sequence. Bolus duration varied by BP response.

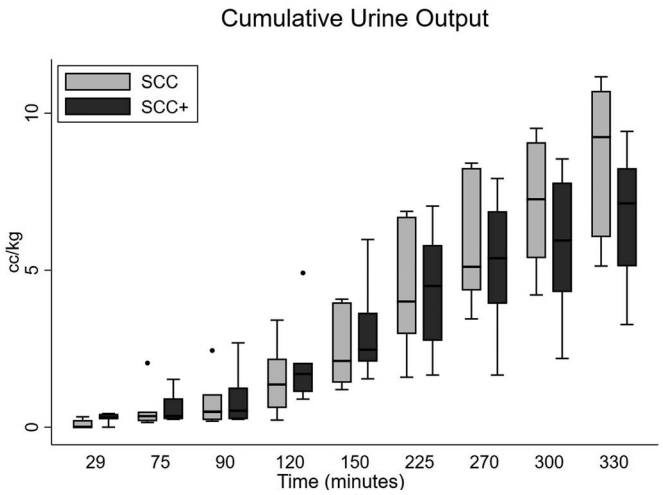

Figure 2. Urine output represented as cumulative urine output over study time (mL/kg).

management of critically-ill patients, particularly automating multiple therapeutic components in parallel. Difficulty arises from the complex nature of layering multiple algorithms cohesively to manage multiple interventions.[20] Despite this, several research groups have studied and theoretically proposed the feasibility of ACC.[20,21] In contrast, other groups have focused efforts on the computational modeling aspects[22] of ACC systems and have leveraged applied animals.[23–25] Given the complexity of this nascent field, limited human research in this area has largely focused on only a single intervention at a time.[26,27]

Our initial algorithm, SCC, focused on two specific therapies, fluid resuscitation and vasopressor titration via NE infusion. These therapies were modulated based on MAP response to crystalloid administration. Our refined algorithm, SCC+, improved upon its predecessor by layering additional physiologic inputs to closely approximate clinical inputs that are commonly used to guide resuscitation, as well as the addition of vasopressin to augment NE titration. Moreover, this additional complexity is a departure from existing ACC systems described in literature. The present study demonstrates that an algorithm capable of multiple therapeutic interventions can work in unison while simultaneously taking into consideration physiologic end points.

There are multiple study limitations. First, the physiologic state of this model limits generalizability across all resuscitation scenarios. Thus, our autonomous resuscitation algorithm (SCC+) may not perform sufficiently in other pathologic states like neurogenic shock. Nonetheless, the proposed methodology can be expanded to include additional physiologic inputs and interventions targeting specific disease states. Second, both study groups consisted of young healthy animals that were nearly always deemed "fluid responsive". This was evidenced by their robust BP increases in response to fluid boluses with concomitant increase in aortic flow, suggesting a consistent augmentation in cardiac output (CO) in response to fluid challenges. This observation suggests that our simplified approach to assessing the need for fluid administration requires more data than simply analyzing the MAP response to a fluid challenge. In addition, our observations may reflect intrinsic characteristics of juvenile swine cardiovascular systems, which would limit clinical applicability of this approach. However, it also may indicate that when vasopressor titration is finely tuned, the cardiovascular system is more capable of using those bolus volumes to augment BP and aortic flow. While our definition of fluid responsiveness was created *a priori*, it is not consistent with the conventional definition of a greater than 15% increase in CO in response to a fluid bolus.[32] It should be noted that this accepted standard itself is somewhat arbitrary.[33] Moreover, the clinical definition of fluid responsiveness was created using CO requiring routine use of Swan Ganz catheters, which are rarely used in clinical practice. Therefore, we defined CO augmentation using BP as a surrogate, which is ubiquitous in ICU environments. It is also unclear if a positive response to fluid administration in terms of either BP or CO augmentation equates to the need for fluid administration. We observed in this model that animals will continue to augment these metrics even when they are clearly euvolemic or hypervolemic. Third, this was a non-survival study and was not designed to observe potential differences between the algorithms that would naturally manifest far beyond the 6.5 hour study time. Lastly, while there was no statistical difference in the biomarkers of injury, there was notable increased variance in the SCC+ cohort when examining the data in graphical form. It is worth noting that two outlier animals were observed. One of which had complete small bowel ischemia from a mesenteric volvulus seen at necropsy. The second animal was extremely vasoplegic and much sicker than its counterparts. Both animals remained fluid avid and required both vasopressin and high norepinephrine doses. Had the first animal not developed small bowel ischemia and if the second had a similar physiologic response to its counterparts, resuscitation requirements for the SCC+ cohort likely would have been even lower than reported and therefore less likely to skew the presently reported data.

Further studies are planned to compare PACC-MAN and SCC+ to manual, provider-driven critical care based on current best clinical practice. Moreover, testing different methods for determining fluid responsiveness will include machine learning algorithms and other measures (continuous oximetry, continuous thermistor, near-infrared spectroscopy, esophageal Doppler, etc.).

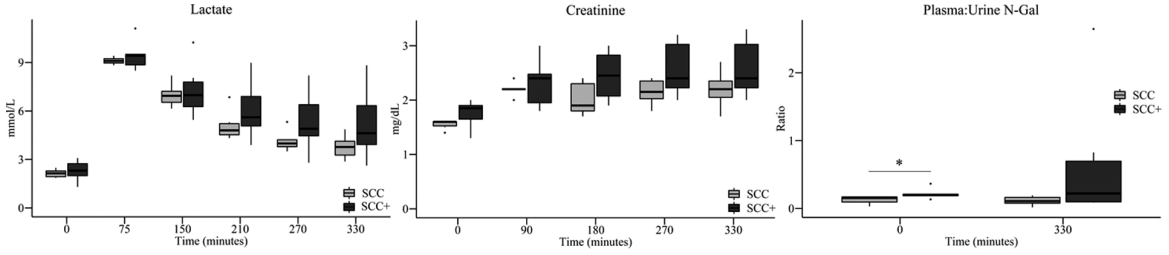

Figure 3. Laboratory markers of injury. *p Value 0.03.

The ultimate goal of ACC systems like PACC-MAN is to relieve the provider's cognitive burden while providing precise and targeted interventions. Our closed-loop ACC platform (PACC-MAN) running enhanced algorithms demonstrated decreased crystalloid fluid utilization without differences in terminal biomarkers of injury or time spent outside of the target BP range. This study demonstrates feasibility of automated critical care to achieve target hemodynamics, while concurrently optimizing multi-modal resuscitation. PACC-MAN may serve as a foundational precursor to what will become an essential tool in a clinician's armamentarium.

AUTHORSHIP

All authors contributed to both the study design and the literature search. A.S.G., N.T.P.P., M.R.L., A.P.W., J.E.J., L.P.N., and T.K.W. collected the data. A.S.G., N.T.P.P., M.A.J., J.Y.A., L.P.N., and T.K.W. performed the data analysis and interpretation. A.S.G., N.T.P.P., L.P.N., T.K.W., and M.A.J. wrote the article. All authors critically revised the manuscript.

DISCLOSURE

L.P.N., T.K.W., M.A.J., and J.Y.A. are co-founders of Certus Critical Care, Incorporated. N.T.P.P. is a paid consultant for Certus Critical Care, Incorporated. The remaining authors have disclosed that they do not have any conflicts of interest.

Funding for this study was provided by the US Army Medical Research and Development Command. Award: W81XWH-18-2-0072.

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