

Infusion System Architecture Impacts the Ability of Intensive Care Nurses to Maintain Hemodynamic Stability in a Living Swine Simulator

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ABSTRACT

Background: The authors have previously shown that drug infusion systems with large common volumes exhibit long delays in reaching steady-state drug delivery and pharmacodynamic effects compared with smaller common-volume systems. The authors hypothesized that such delays can impede the pharmacologic restoration of hemodynamic stability.

Methods: The authors created a living swine simulator of hemodynamic instability in which occlusion balloons in the aorta and inferior vena cava (IVC) were used to manipulate blood pressure. Experienced intensive care unit nurses blinded to the use of small or large common-volume infusion systems were instructed to maintain mean arterial blood pressure between 70 and 90 mmHg using only sodium nitroprusside and norepinephrine infusions. Four conditions (IVC or aortic occlusions and small or large common volume) were tested 12 times in eight animals.

Results: After aortic occlusion, the time to restore mean arterial pressure to range (t_1 : 2.4 ± 1.4 vs. 5.0 ± 2.3 min, $P = 0.003$, average \pm SD), time-out-of-range (t_{OR} : 6.2 ± 3.5 vs. 9.5 ± 3.4 min, $P = 0.028$), and area-out-of-range (pressure–time integral: 84 ± 47 vs. 170 ± 100 mmHg·min, $P = 0.018$) were all lower with smaller common volumes. After IVC occlusion, t_1 (3.7 ± 2.2 vs. 7.1 ± 2.6 min, $P = 0.002$), t_{OR} (6.3 ± 3.5 vs. 11 ± 3.0 min, $P = 0.007$), and area-out-of-range (110 ± 93 vs. 270 ± 140 mmHg·min, $P = 0.003$) were all lower with smaller common volumes. Common-volume size did not impact the total amount infused of either drug.

Conclusions: Nurses did not respond as effectively to hemodynamic instability when drugs flowed through large common-volume infusion systems. These findings suggest that drug infusion system common volume may have clinical impact, should be minimized to the greatest extent possible, and warrants clinical investigations. (**ANESTHESIOLOGY 2016; 124:1077-85**)

CRITICALLY ill patients in intensive care units (ICUs) often require infusions of potent vasoactive and inotropic compounds. Careful titration is necessary to maintain hemodynamic stability. We and others have shown in a series of *in vitro* experiments how drug delivery rate does not always match intended dose.¹⁻⁷ By implication, infused drugs that enter into a manifold to be combined with an inert drug carrier flow would then require an interval of time to traverse the common volume (also known as the dead volume) before entering the patient's blood. Common volume is defined as the volume between the point where the drug and carrier streams meet and the patient's blood.¹ Under circumstances of large common-volume infusion system or slow overall fluid flow, intended changes in the rate of drug delivery may lag significantly behind the changes made at drug infusion pumps. Others maintain that delays caused by drug and carrier interactions within the common volume can lead to patient morbidity.^{8,9} We have demonstrated that these transient lags in drug delivery result in delays in pharmacologic response *in vivo*.^{5,10,11}

What We Already Know about This Topic

- The time taken to reach steady-state drug delivery and desired pharmacologic effect may be longer with larger volume infusion systems, but it is not clear if this impacts restoration of hemodynamic stability.

What This Article Tells Us That Is New

- In a live swine model of hemodynamic instability, experienced intensive care unit nurses responded less effectively when drugs flowed through large common-volume infusion systems. Thus, the infusion system common volume may have clinical impact and should be minimized.

We established a living simulator model for unstable hemodynamics in anesthetized swine. In this living simulator, blood pressure instability was modeled through inflation of occluding balloons either in the descending aorta or in the inferior vena cava (IVC). We then asked experienced ICU registered nurses (RNs) to maintain mean arterial pressure

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(MAP) within narrow limits using only norepinephrine and sodium nitroprusside (SNP) infusions. The two drugs were delivered to the animal *via* either a small or a large common-volume manifold. The nurses were blinded as to when each manifold was used. We hypothesized that the use of drug infusion systems with smaller common volumes would allow the vigilance and skill of experienced ICU nurses to better respond to hemodynamic instability than drug infusion systems with larger common volumes.

Materials and Methods

An anesthetized healthy swine model was used to define the role common-volume infusion system plays in the ability of experienced ICU RNs to maintain stable MAP using only norepinephrine and nitroprusside infusions through either a large- or a small-volume infusion manifold plus catheter combination. To model hemodynamic instability, the blood pressure was surreptitiously manipulated either upward by inflating an occlusion balloon in the aorta or downward with an occlusion balloon in the IVC. MAP signals were recorded along with every change in medication made by the RN.

Infusion Systems

Separate, dedicated infusion pumps (Cardinal Health Alaris PC, USA) were used to control the infusion rates of

norepinephrine (8 mg/250 ml; PharMEDium Services LLC, USA) and SNP (50 mg/250 ml; Marathon Pharmaceuticals LLC, USA). A third infusion pump infused a Ringer’s lactate solution (B. Braun Medical Inc., USA) as an inert drug carrier at a fixed flow rate of 10 ml/h. Infusion lines (Codan Corporation, USA) connected each channel to stopcocks, which were used to divert flow to either a large or a small common-volume infusion system. The large-volume infusion system consisted of a preconnected bank of four stopcocks (Codan Corporation, W20041) attached to the sidearm of a 9-French introducer sheath (I505BF9; Edwards Lifesciences, USA). The carrier infusion was connected to the upstream-most stopcock (fig. 1). The norepinephrine infusion flowed into the downstream-most stopcock, and the SNP flowed into the one upstream to it. Each stopcock adds 0.3 ml to the common volume. Norepinephrine entered the fluid path halfway through the stopcock and thus the manifold contribution to the common volume was 0.15 ml. SNP entered halfway through its stopcock and then through the norepinephrine stopcock, thus adding 0.45 ml to the common volume. The introducer sheath volume was 3.30 ml resulting in a total common volume of 3.45 ml for norepinephrine infusion and 3.75 ml for SNP infusion (fig. 1). The small-volume infusion system consisted of an Edelvaiss Mutiline® drug infusion manifold (#D2006140; Doran

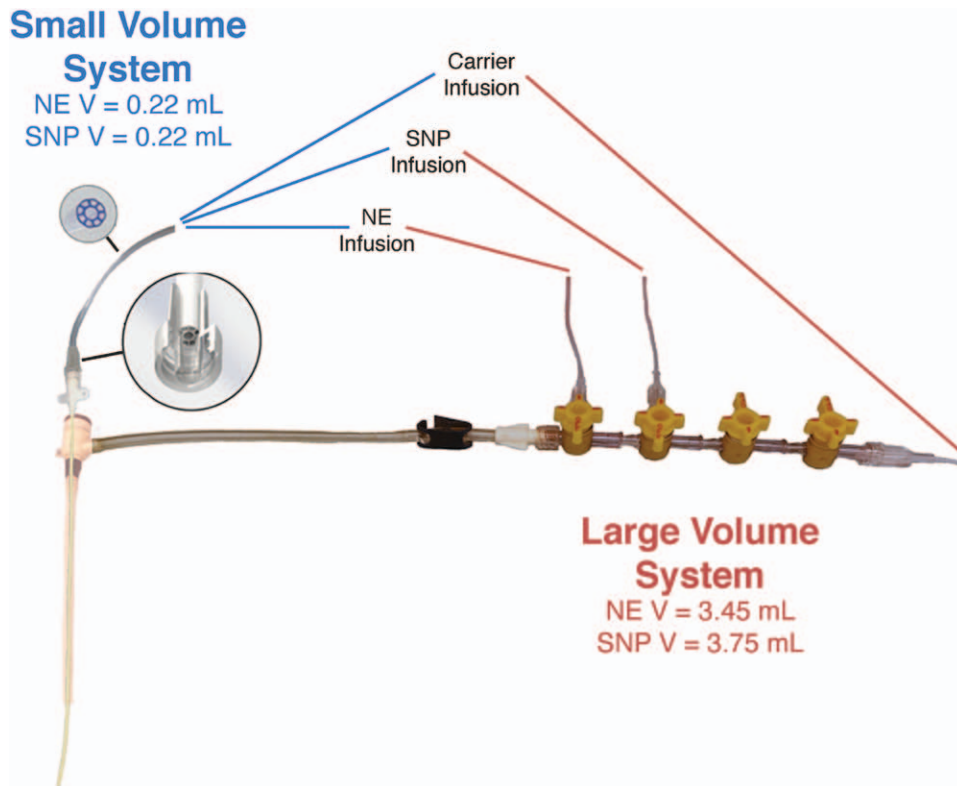


Fig. 1. Sodium nitroprusside (SNP) and norepinephrine (NE) infusions were administered through either a small or large common-volume (V) infusion system. The manifold for the small common-volume infusion system had a single 150-cm infusion line with eight separate parallel channels that do not meet until the distal luer connector. This manifold was connected to a 16-gauge, single-lumen catheter, which was then passed through the lumen of a 9-French introducer sheath. The large common-volume infusion system consisted of preconnected bank of four stopcocks, which were attached to the sidearm of the same 9-French introducer sheath.

International, France) connected to a 16-gauge single-lumen catheter (#CS-04300; ArrowMedical, USA), which was passed through the lumen of the same 9-French sheath. The small-volume manifold has ports for eight infusions that run through separate channels contained within a flexible plastic tube. Since fluids from the individual channels do not meet until they exit this manifold's tip, this device adds no extra common volume to the 0.22 ml of the single-lumen catheter (fig. 1). Norepinephrine, SNP, and carrier infusions were connected to adjacent ports on the low-volume manifold. All infusion lines were primed, and the carrier infusion was allowed to flow for 15 min before experimentation.

Animal Preparation

All surgical procedures were approved by the Steward St. Elizabeth's Medical Center Institutional Animal Care and Use Committee (Boston, Massachusetts). Eight adolescent Yorkshire swine (36 to 41 kg) were sedated with an intramuscular injection of telazol (2.5 ml), xylazine (125 mg), and ketamine (125 mg). Each animal was then intubated with a 7.0-mm endotracheal tube (Covidien Mallinckrodt, USA) and ventilated (Ohmeda Excel 110 Anesthesia Machine, USA). Anesthesia was maintained with 2% isoflurane. The large-volume drug delivery catheter (9 French) was placed in a femoral vein. Twelve-French introducer sheaths (Cook Medical, USA) were placed in the other femoral vein and in a femoral artery. Balloon occlusion catheters (Cordis Endovascular, USA) were passed through these sheaths into the IVC and the aorta. A pressure transducer (Kent Scientific, USA) was connected to the lumen of the arterial balloon occlusion catheter for arterial blood pressure monitoring (Hewlett Packard m1094b, USA) and digital storage (LabChart 7; ADInstruments, USA). Before experimentation, the balloons were positioned and inflated with saline such that systolic blood pressure (SBP) would increase or decrease by at least 20 mmHg. The inflation volume of the IVC balloon was between 10 and 15 ml. The inflating volume of the aortic balloon was between 4 and 7 ml. A 9-French catheter (I505BF9; Edwards Lifesciences) was placed in the right internal jugular vein, the sidearm of which was used for crystalloid, anesthetic, and antiarrhythmic infusions. A Swan-Ganz catheter (746HF8; Edwards Lifesciences) was passed through this introducer for pulmonary artery and central venous pressure monitoring. After cannulation, lidocaine

(2 mg · kg⁻¹ · h⁻¹), amiodarone (1 mg · kg⁻¹ · h⁻¹), ketamine (5 mg · kg⁻¹ · h⁻¹), and fentanyl (10 µg · kg⁻¹ · h⁻¹) were infused through ports on the internal jugular vein introducer, and isoflurane was reduced to 1%.

Experimental Protocol

This protocol was approved by the Steward St. Elizabeth's Medical Center Institutional Review Board (Boston, Massachusetts), which did not require informed consent from the ICU RN volunteers. One RN volunteer was used per animal. Examples of the large- and small-volume manifolds were shown and described *ex vivo* to each RN volunteer; however, nurses were blinded to which device was being used at any given time during experimental trials. The RN was then presented with a clinical scenario that demanded tight blood pressure control with the added constraint to minimize overall fluid administration (appendix). The RN was instructed to titrate norepinephrine and nitroprusside infusions to keep the MAP between 70 and 90 mmHg while maintaining the carrier fluid flow rate at 10 ml/h. The RN was free to infuse drugs at his/her discretion at any time during the 3 h of simulation. Blankets covered the animal and blinded the RN to the stopcocks that determined which drug infusion device was being used, the catheters, and the syringes controlling the occlusion balloons.

Before experimentation, the carrier was allowed to flow through either the large- or small-volume infusion system for 15 min. Each manipulation consisted of inflating either the IVC or the aortic balloon for 5 min, followed by 15 min of data recording while the RN attempted to stabilize the blood pressure. The manipulations were paired so that each balloon would be inflated once before the infusion catheter was switched. The animal was allowed to stabilize for 10 min after switching from one drug infusion pathway to the other.

Four distinct sequences were used to mitigate any effects caused by the order of manipulations and infusion system changes. The four sequences ensured that both large- and small-volume infusion systems were the initial system four times and both the aortic and IVC occlusions were the initial manipulation four times (table 1). Each of the four sequences was repeated twice in a total of eight animals. Because the animals were prone to tachyphylaxis to both drugs, RNs were restricted to maximum doses of norepinephrine (0.5 µg · kg⁻¹ · min⁻¹) and SNP (3 µg · kg⁻¹ · min⁻¹).

Table 1. Experimental Sequences

	Sequence A	Sequence B	Sequence C	Sequence D
First manipulation	Small common-volume aorta	Large common-volume aorta	Small common-volume IVC	Large common-volume IVC
Second manipulation	Small common-volume IVC	Large common-volume IVC	Small common-volume aorta	Large common-volume aorta
Third manipulation	Large common-volume aorta	Small common-volume aorta	Large common-volume IVC	Small common-volume IVC
Fourth manipulation	Large common-volume IVC	Small common-volume IVC	Large common-volume aorta	Small common-volume aorta
Fifth manipulation	Small common-volume aorta	Large common-volume aorta	Small common-volume IVC	Large common-volume IVC
Sixth manipulation	Small common-volume IVC	Large common-volume IVC	Small common-volume aorta	Large common-volume aorta

Four distinct experimental sequences were repeated twice in eight animals for a total of 12 repetitions of each experimental condition. These sequences ensured that both infusion systems were the initial system and that both the aortic and inferior vena cava (IVC) manipulations were the first manipulation four times.

Preliminary experimentation showed that animals did not survive severe hypotension. Therefore, if the SBP fell below 60 mmHg during an IVC occlusion, the balloon was transiently partially deflated to keep the SBP above this limit. Similarly, if SBP rose above 220 mmHg during an aortic occlusion, the balloon was transiently partially deflated until SBP recovered. Thus, we imposed a floor and ceiling for SBP of 60 and 220 mm Hg, respectively.

Statistical Analyses

Prior data from our laboratory suggested that the time to achieve 50% of maximal pharmacodynamic response to norepinephrine infusion was approximately 40% lower with a small-volume infusion system over a larger one.⁵ Power analyses assumed that this decreased response time would translate to better hemodynamic control by the nurse volunteer and thus 40% lower outcome indices. The analysis assumed two independent normally distributed groups indicating that 8 and 12 data points in each group would be needed to power the current study to 90 and 99%, respectively, with less than 5% chance of a type I error ($P < 0.05$). We were able to reliably perform six occlusion maneuvers per animal in the 3 h volunteered by the RNs. We used eight animals and collected 12 data points for each maneuver, thus powering the study to 99%. In each animal, four manipulations were performed for one infusion system and two manipulations for the other (table 1).

Outcome variables included the time needed to return MAP to the target range after the release of the aorta or IVC occlusion and subsequent drop or rise, respectively, in MAP (t_1 , shown in fig. 2A) and the total amount of time MAP was above 90 mmHg or below 70 mmHg during the 15 min after release of occlusion balloon (t_{OR}). Also calculated were the area-out-of-range (AOR: time integral of MAP above 90 mmHg or below 70 mmHg over time) for both the 20-min experiment (AOR₂₀) and for just the 15-min data collection period (AOR₁₅). In addition, the amounts of drug delivered during and after the release of the occluding balloon were tracked.

RN practice styles were characterized using the following parameters measured during a single 20-min experiment: the time elapsed between balloon inflation in either the aorta or the IVC and the RN's first change in drug delivery (t_{rxn}), MAP at t_{rxn} (MAP_{rxn}), the time until the first use of a maximum dose of either drug (t_{to-max}), and the total time that the maximum dose of either drug was delivered (t_{at-max}). Also calculated were the number of total changes in drug delivery (N_{Δ}), the number of times an RN switched from one drug to another ($N_{switches}$), and the number of times a drug was turned off or on ($N_{on/off}$).

A D'Agostino-Pearson omnibus test was applied to all data sets to test for normality (Prism 5.0; GraphPad Software, Inc., USA). Outcome variables for small and large common volume were compared using a t test with Welch correction assuming unequal variance if both data sets were normally distributed (Prism 5.0). If either one of the data sets was not normally distributed, comparisons were made using a nonparametric

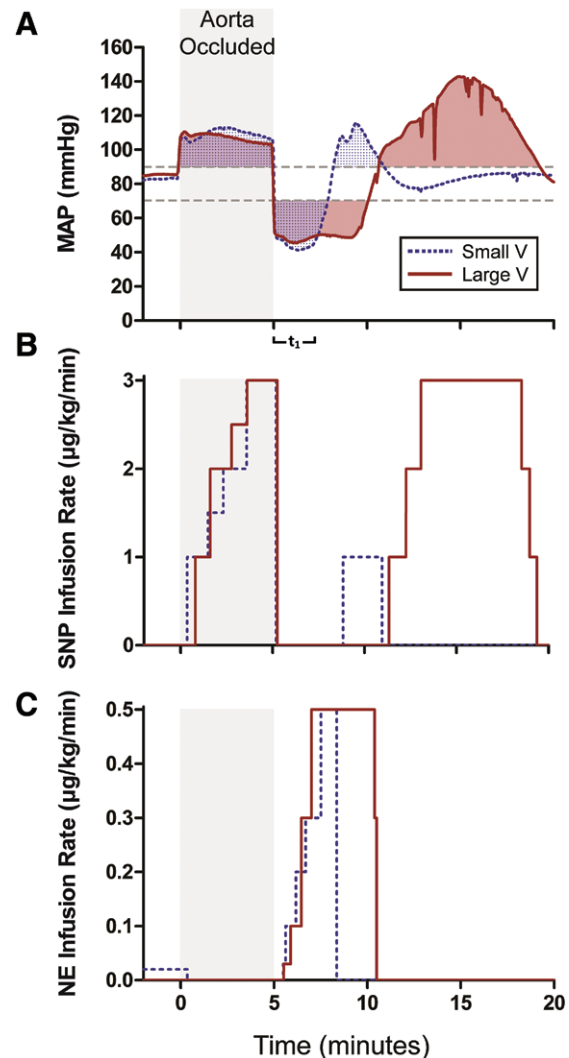


Fig. 2. A representative example of the aortic occlusion experiment. Mean arterial pressure (MAP) is elevated for the duration of the 5-min occlusion (A), prompting the registered nurse (RN) to infuse sodium nitroprusside (SNP) at the maximum dose of $3 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ with both infusion systems (B). Once the aortic occlusion is released, the MAP falls (A), prompting the RN to turn off the SNP infusion (B) and begin norepinephrine (NE) infusion, eventually reaching the maximum dose of $0.5 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ in both conditions (C). Approximately 5 min postocclusion, MAP is stabilized within the target range with the small common-volume (V) system (A), and all drug infusion is stopped shortly thereafter (B and C). In this example, MAP is never stabilized within range using the large common-volume system (A), and the RN again infuses SNP at the maximum dose in response to another rise in MAP (B). The time required for the RN to bring MAP back within the target range after occlusion release (t_1) for the small common-volume infusion system is shown as an example for clarity.

Mann–Whitney test (Prism 5.0). Data were considered distinct when the P value was less than 0.05. Spearman correlations were performed on all outcome data (Prism 5.0) to verify that the order in which a manipulation was performed in each animal did not correlate with each outcome variable.

Results

Aorta Occlusion and Release

With aortic occlusion, MAP instantaneously increased in every experiment. There was variability in timing and extent of the RNs' pharmacologic response and subsequent MAP as the experiment continued. A representative example is shown (fig. 2) that illustrates the trends observed in the other trials. Aortic occlusion caused MAP to increase above the 90-mmHg threshold regardless of the infusion system (fig. 2A). Nurses responded by infusing SNP and, in the representative example, opted to infuse at the maximum dose of $3 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ with both the large and small common volumes (fig. 2B). After release of the aortic occlusion, MAP always dropped below the 70-mmHg lower threshold in both infusion systems, prompting the RNs to stop SNP delivery and begin infusing norepinephrine (fig. 2C). MAP increased back within target range more quickly using the small-volume infusion system than with the large-volume infusion system (t_1 ; table 2). MAP often increased over 90 mmHg again before falling back within the target range (fig. 2A); however, the MAP with the large common volume ultimately spent more time-out-of-range than with small common volume (t_{OR} ; table 2). Additionally, the AOR_{15} and AOR_{20} for experiments with large-volume infusion systems were 170 ± 100 and 330 ± 120 mmHg·min, respectively, compared with 84 ± 47 and 200 ± 87 mmHg·min with small common volume (table 2).

IVC Occlusion and Release

With IVC occlusion, MAP instantaneously decreased in every experiment. There was variability in timing and extent of the RNs' pharmacologic response and subsequent MAP as the experiment continued. A representative example is shown (fig. 3) that illustrates the trends observed in the other trials. After occlusion of the IVC, MAP dropped below the 70-mmHg threshold, prompting nurses to begin norepinephrine infusion (fig. 3C). Nurses increased the norepinephrine dose up to, or very near, the maximum dose of $0.5 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ in each trial regardless of infusion

system. This caused MAP to increase above the 90-mmHg threshold after cessation of IVC occlusion, prompting discontinuation of norepinephrine and initiation of SNP infusion in both groups (fig. 3A); however, MAP with small common volume fell back within the target range more quickly than with large common volume (t_1 ; table 3). MAP was outside of the target range for less time (t_{OR}) with small common volume. AOR_{15} and AOR_{20} were only 110 ± 93 and 170 ± 81 mmHg·min, respectively, with the small common-volume system compared with 270 ± 140 and 340 ± 140 mmHg·min with the large common-volume system (table 3).

Drug Delivery

During aortic occlusion and subsequent increase in MAP, averaged over all trials, there was no discernible difference in the amount of SNP delivered by the nurses between the two infusion systems (table 4). Also averaged over all trials, after releasing occlusion of the aorta with subsequent decrease in MAP, nurses gave $83 \pm 46 \mu\text{g}$ of norepinephrine through the large-volume system compared with $54 \pm 43 \mu\text{g}$ through the small-volume system, showing an insignificant difference (table 4). During IVC occlusion, there was no difference in norepinephrine delivered by the nurses between the two infusion systems (table 5). After releasing the IVC occlusion with abrupt increase in MAP, nurses gave $450 \pm 250 \mu\text{g}$ of SNP through the large-volume manifold compared with $270 \pm 380 \mu\text{g}$ through the small-volume manifold, an insignificant difference (table 5). The only significant difference in drug delivery was observed after release of IVC occlusion, where more norepinephrine was given during the 15-min data collection with the large-volume infusion system ($78 \pm 55 \mu\text{g}$) than the small-volume one ($41 \pm 51 \mu\text{g}$).

RN Technique

Registered nurse technique in attempting to maintain a stable MAP was highly variable as evidenced by large SDs in t_{rxn} , MAP_{rxn} , $t_{\text{to-max}}$, $t_{\text{at-max}}$, N_{Δ} , N_{switches} , and $N_{\text{on/off}}$ and none of these indices were impacted by the common volume used (table 6).

Table 2. Aortic Occlusions: Hemodynamic Indices

	t_1 (min)	t_{OR} (min)	AOR_{15} (mmHg·min)	AOR_{20} (mmHg·min)
Large volume	5.0 ± 2.3	9.5 ± 3.4	170 ± 100	330 ± 120
Small volume	2.4 ± 1.4	6.2 ± 3.5	84 ± 47	200 ± 87
<i>P</i> value	0.003	0.028	0.018	0.002
Large volume				
Spearman <i>R</i> (<i>P</i> value)	0.25 (0.66)	-0.54 (0.29)	-0.086 (0.92)	0.14 (0.80)
Small volume				
Spearman <i>R</i> (<i>P</i> value)	-0.086 (0.92)	0.25 (0.66)	0.14 (0.80)	0.25 (0.66)

Four variables were measured and compared: the time required for the registered nurse to bring mean arterial pressure (MAP) back within the target range after aortic occlusion release (t_1), the total time elapsed where MAP was above 90 mmHg or below 70 mmHg during the 15 min after occlusion release (t_{OR}), and the sum of the areas in MAP tracing above 90 mmHg and below 70 mmHg during the 15 min after occlusion release (AOR_{15}) and for the entire 20-min experiment (AOR_{20}). Spearman correlation coefficient of each index with the order performed within each animal is also shown with associated *P* values. Each data point was repeated 12 times (average \pm SD). *P* values generated from nonparametric Mann-Whitney tests.

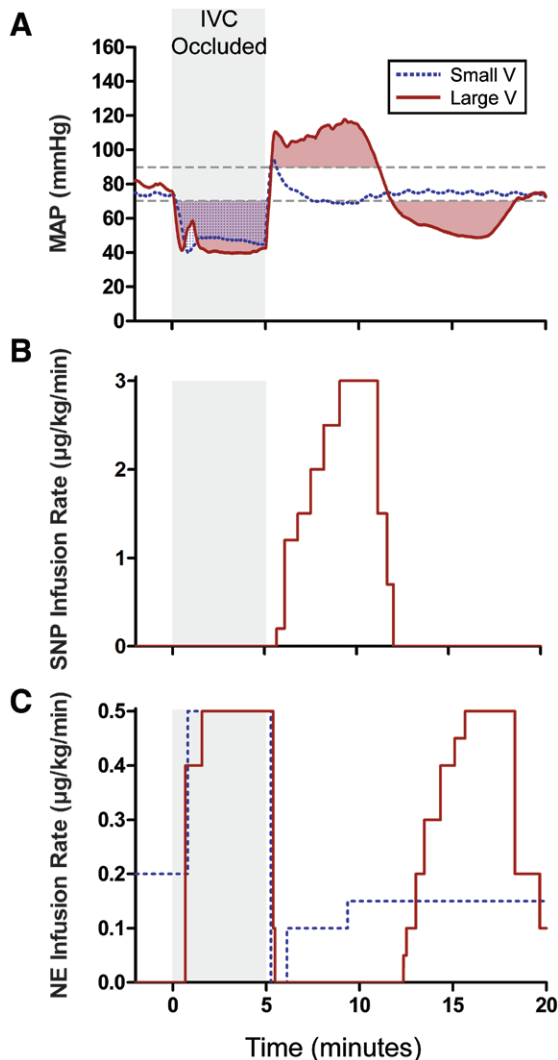


Fig. 3. A representative example of the inferior vena cava (IVC) occlusion experiment. Mean arterial pressure (MAP) is depressed for the duration of the 5-min occlusion (A), prompting the registered nurse (RN) to infuse norepinephrine (NE) at the maximum dose of $0.5 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ with both infusion systems (C). Once the IVC occlusion is released, the MAP rises above the target range (A), prompting the RN to turn off the norepinephrine infusion (C). While MAP is stabilized within the target range with the small common-volume (V) system with a norepinephrine infusion (C), MAP remains elevated with the large common-volume system, prompting the RN to infuse sodium nitroprusside (SNP) at the maximum dose of $3 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ (B). MAP then drops below the threshold (A), prompting the RN to switch to norepinephrine infusion at the maximum dose (C).

Discussion

We created a living simulator of hemodynamic instability where we mechanically manipulated the blood pressure of swine through occlusion of the IVC or aorta and used this model to test the impact of common-volume infusion system on the restoration of hemodynamic stability by experienced ICU RNs. The data clearly demonstrate that infusion system

architecture can influence the return to hemodynamic stability in this model (tables 2 and 3). All MAP-derived outcome metrics were significantly different for the two common volumes studied. Immediately after release of the occluding balloon, the time for MAP to first enter the target range (t_1) was shorter for the small common volume. Likewise, the time-out-of-range (t_{OR}) was greater for the large common volume. The AORs were also smaller for the small common-volume infusion system, regardless of whether the analysis included the balloon occlusion or only the 15-min follow-up period. Thus, the architecture of the infusion system impacts the ability of experienced bedside clinicians to return the animal to desired hemodynamics.

Similar amounts of both norepinephrine and SNP were infused with either drug infusion system (tables 4 and 5). While this may seem counterintuitive, the SDs of some of these data are large relative to the measurements, perhaps reflecting the wide variety of practice styles of the ICU RNs volunteering for the study. Some RNs appeared to intuit the consequences of each change in drug infusion, anticipated well, and brought the MAP within target range within minutes, while others did not. Some RNs quickly adjusted the infusions after balloon occlusion (t_{rxn}), while others did not (table 6). Some RNs made adjustments when MAP was only slightly out of range (MAP_{rxn}). Some quickly used the maximum drug dosing (t_{to-max}) and spent much time at maximum dose rate (t_{ar-max}). Some made frequent small adjustments, while others made less frequent changes (N_{Δ}). Some switched between norepinephrine and SNP multiple times ($N_{switches}$) in the short 20-min experiment. Given the wide variation in practice styles, it is not surprising that the total amount of each drug infused is not impacted by the common volume. Despite this diversity in practice styles, the data consistently showed tighter blood pressure control with smaller common volume (tables 2 and 3). Thus, we can conclude the superiority of infusion systems with smaller common volumes, even in experienced hands.

We were interested in testing the effects of the infusion system hardware and not the human volunteer and therefore recruited ICU RNs with greater than 3-yr experience. Having a single volunteer might have made the data more consistent; however, we recognized that over time, any volunteer might adapt their practice to the simulation. To make the results widely applicable, we wanted to capture a range of practice styles and therefore used eight experienced ICU RNs.

Each RN treated one animal only in terminal experiments where multiple vascular occlusions were performed in each swine (table 1). It is possible that the animal might have been altered in some way after multiple occlusions, or that the RN volunteer might adapt to the simulation over time. Our protocol was designed to minimize RN adaption, by not showing them which infusion system was being used and not explaining the etiology of the hemodynamic perturbations they were attempting to treat. No outcome metric correlated with order in which the manipulation was performed (Spearman R ; tables 2–5). In

Table 3. IVC Occlusion: Hemodynamic Indices

	t_1 (min)	t_{OR} (min)	AOR ₁₅ (mmHg·min)	AOR ₂₀ (mmHg·min)
Large volume	7.1 ± 2.6	11 ± 3*	270 ± 140	340 ± 140
Small volume	3.7 ± 2.1	6.3 ± 3.5	110 ± 93	170 ± 81
<i>P</i> value	0.002	0.007	0.003	0.002
Large volume				
Spearman <i>R</i> (<i>P</i> value)	−0.54 (0.30)	−0.26 (0.66)	−0.6 (0.24)	−0.26 (0.66)
Small volume				
Spearman <i>R</i> (<i>P</i> value)	−0.03 (1)	−0.6 (0.24)	−0.49 (0.36)	−0.49 (0.36)

Four variables were measured and compared: the time required for the nurse to bring mean arterial pressure (MAP) back within the target range after inferior vena cava (IVC) occlusion release (t_1), the total time elapsed where MAP was above 90 mmHg or below 70 mmHg during the 15 min after occlusion release (t_{OR}), and the sum of the areas in MAP tracing above 90 mmHg and below 70 mmHg during the 15 min after occlusion release (AOR₁₅) and for the entire 20-min experiment (AOR₂₀). Spearman correlation coefficient of each index with the order performed within each animal is also shown with associated *P* values. Each data point was repeated 12 times (average ± SD). *P* values generated from nonparametric Mann–Whitney tests.

*Did not pass D’Agostino–Pearson omnibus test for normality (Prism 5.0; GraphPad Software, Inc.).

Table 4. Aortic Occlusions: Drug Delivered

	Norepinephrine		SNP	
	Occluded (μg)	Released (μg)	Occluded (μg)	Released (μg)
Large volume	4.8 ± 10*	83 ± 46	260 ± 170	200 ± 250
Small volume	8.9 ± 15*	54 ± 43	190 ± 180	150 ± 260*
<i>P</i> value	0.54	0.132	0.369	0.67
Large volume				
Spearman <i>R</i> (<i>P</i> value)	−0.086 (0.92)	0.37 (0.50)	0.60 (0.24)	−0.086 (0.92)
Small volume				
Spearman <i>R</i> (<i>P</i> value)	0.37 (0.50)	0.43 (0.42)	−0.60 (0.24)	−0.086 (0.92)

Total drug delivered during each manipulation was analyzed for norepinephrine and sodium nitroprusside (SNP) both during and after aortic occlusion. Spearman correlation coefficient of each index with the order performed within each animal is also shown with associated *P* values. Each data point was repeated 12 times (average ± SD). *P* values generated from nonparametric Mann–Whitney tests.

*Did not pass D’Agostino–Pearson omnibus test for normality (Prism 5.0; GraphPad Software, Inc.).

Table 5. IVC Occlusion: Drug Delivered

	Norepinephrine		SNP	
	Occluded (μg)	Released (μg)	Occluded (μg)	Released (μg)
Large volume	51 ± 18*	78 ± 55*	4.0 ± 11.0*	450 ± 250
Small volume	53 ± 14	41 ± 51*	2.4 ± 7.1*	270 ± 380*
<i>P</i> value	0.84	0.033	0.727	0.172
Large volume				
Spearman <i>R</i> (<i>P</i> value)	0.77 (0.10)	0.66 (0.18)	−0.54 (0.27)	−0.26 (0.66)
Small volume				
Spearman <i>R</i> (<i>P</i> value)	0.26 (0.66)	0.14 (0.80)	−0.34 (0.53)	−0.49 (0.36)

Total drug delivered during each manipulation was analyzed for norepinephrine and sodium nitroprusside (SNP) both during and after inferior vena cava (IVC) occlusion. Spearman correlation coefficient of each index with the order performed within each animal is also shown with associated *P* values. Each data point was repeated 12 times (average ± SD). *P* values generated from nonparametric Mann–Whitney tests.

*Did not pass D’Agostino–Pearson omnibus test for normality (Prism 5.0; GraphPad Software, Inc.).

addition, we analyzed seven metrics of RN “behavior” under four conditions each (table 6). Two of the 28 measured indices (t_{rxn} after IVC occlusion in a large common volume and t_{to-max} after IVC occlusion in a small common volume) correlated with the order in which it was acquired in each animal. The other 26 indices did not correlate with the order in which it was acquired. Thus, the data generally suggest that the animals were not altered by transient occlusion of their vessels and the RNs did not seem to significantly adapt to the simulation.

Implications

It has been suggested that long lag times between changes at the infusion pump and actual drug delivery may tempt clinicians to overtreat patients, leading to unintended hemodynamic fluctuation.² The natural reaction of bedside clinicians to the lack of immediate pharmacologic response caused by these delays is to increase dosing, possibly to supratherapeutic levels. If supratherapeutic levels are used for several minutes, the exaggerated effect will tempt clinicians to drastically lower

Table 6. RN Practice Styles

	Aortic Occlusion		IVC Occlusion	
	Large Common Volume	Small Common Volume	Large Common Volume	Small Common Volume
t_{rxn} (min)	0.35 ± 0.28 (0.03–0.80)	0.32 ± 0.18 (0.01–0.50)	0.62 ± 0.29 (0.06–1.07)	0.96 ± 0.60 (0.36–1.9)
		$P = 0.76$		$P = 0.10$
MAP _{rxn} (mmHg)	110 ± 16 (71–130)	110 ± 22 (67–140)	58 ± 11 (43–73)	59 ± 12 (42–74)
		$P = 0.91$		$P = 0.87$
t_{to-max} (min)	4.0 ± 3.9* (1.3–14), N = 10	2.4 ± 2.2* (0.3–5.9), N = 7	4.5 ± 5.3 (0.6–16), N = 12	4.0 ± 2.8 (0.8–8.9), N = 11
		$P = 0.35$		$P = 0.75$
t_{at-max} (min)	7.0 ± 5.1 (0–13)	4.7 ± 3.9 (0–11)	7.6 ± 3.7 (1.3–11)	6.0 ± 5.3 (0–15)
		$P = 0.24$		$P = 0.40$
N_{Δ}	16 ± 5 (6–25)	16 ± 10* (3–28)	18 ± 8 (2–31)	16 ± 8 (4–30)
		$P = 0.30$		$P = 0.67$
$N_{switches}$	2.0 ± 1.0 (0–3)	2.5 ± 2.6* (0–9)	2.3 ± 1.0* (0–3)	2.6 ± 2.3* (0–9)
		$P = 0.82$		$P = 0.85$
$N_{on/off}$	5.6 ± 2.3 (2–10)	6.1 ± 5.6* (2–21)	4.7 ± 2.1* (0–6)	5.9 ± 5.1* (0–20)
		$P = 0.41$		$P = 0.99$

The following data were used to characterize registered nurse (RN) practice style with the use of large and small common-volume infusion systems during aortic and inferior vena cava (IVC) occlusion experiments. Values shown are average ± SD (minimum–maximum). Number of repetitions (N) is 12 for all experiments unless otherwise shown. *P* values generated from nonparametric Mann–Whitney tests.

*Did not pass D’Agostino–Pearson omnibus test for normality (Prism 5.0; GraphPad Software, Inc.).

MAP = mean arterial pressure; MAP_{rxn} = MAP at t_{rxn} ; N_{Δ} = the number of changes made by RNs in drug delivery; $N_{on/off}$ = the number of times either drug was turned on or off; $N_{switches}$ = the number of times RNs switched infusions from one drug to another; t_{at-max} = the total time a maximum dose of either drug was delivered; t_{to-max} = the time until the first use of a maximum dose for either drug; experiments where RNs never reached a maximum dose were excluded and thus $N < 12$; t_{rxn} = the time elapsed between aortic or IVC occlusion and the first change in drug infusion made by the RN.

drug infusion rates possibly leading to another period of sub-therapeutic treatment and repetition of this cycle. Thus, the interaction between clinician and infusion system delays can result in slower restoration of hemodynamic stability that can take significant time and skill to dampen. Indeed, these phenomena were observed in this study. In one experiment, the infused drug was switched between norepinephrine and SNP nine times during the 20-min experiment, confirming the potential for frequent and large swings in blood pressure.

Limitations

The interpretation of these data needs to be tempered by the conditions in which our living simulator lacked complete authenticity. These swine were healthy adolescents, lacked comorbidities, and thus were not necessarily typical of critically ill patients requiring vasoactive infusions. After the simulation, many RNs commented how the simulator itself might have hindered their ability to gain control of the MAP. For example, the RNs did not have access to the “patient” and could not perform a physical examination or inspect the infusion devices. Furthermore, several RNs commented that in their practice, they would have requested orders for single-time medications such as β -blockers, Ca^{2+} channel blockers, or α -agonists. Some sought to transiently increase the carrier rate as might be their practice but needed to be reminded that the “patient” required strict fluid restriction. (Note that minimizing fluid administration with drugs and carriers can be a critical therapeutic goal in patients with cardiac, renal, or neurologic pathologies as well as in pediatric and neonatal populations.)

Had the nurses been allowed to increase the carrier flow rate, the drug propagation delays in the infusion system common volume would have been reduced and the impact of common volume might be less evident, but this would be at the expense of greater fluid administration. In addition, the maximum infusion rates of norepinephrine and SNP we permitted were lower than some RNs were used to. These limits were needed to prevent rapid tachyphylaxis and loss of simulator responsiveness to medications. Finally, some RNs commented that they would have put the norepinephrine and SNP in different ports or catheters, but the simulation did not allow for this. Our study aimed to isolate the effect of common volume on restoration of desired hemodynamics. Thus, while our data strongly suggest the relationship between infusion system architecture and blood pressure stability, other clinical techniques under some circumstances may allow RNs to compensate to achieve their clinical goals. Despite the imperfections of our living swine simulator, the data suggest that minimization of common volume will allow better titration of the optimal dose of medication to restore hemodynamic stability.

Conclusions

A living swine simulator of hemodynamic perturbation was used to assess the impact of infusion system architecture on the restoration of hemodynamic stability by ICU RNs. The data support our hypothesis that configuring the infusion system with small common volume would result in more reliable return to hemodynamic stability despite very different practice styles and infusion techniques by experienced ICU nurses. Whether this improved hemodynamic control might result in superior patient outcomes requires further investigation.

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Competing Interests

The authors declare no competing interests.

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Appendix. Clinical Scenario Presented to Each Intensive Care Unit Nurse

The patient was a 55-yr-old male with a medical history remarkable for an uncorrected infrarenal abdominal aortic aneurysm, coronary artery disease (80% occlusion of the left anterior descending artery and 80% occlusion of the left circumflex artery), severe aortic stenosis, insulin-dependent diabetes mellitus, and chronic renal failure. The patient was scheduled for a combined coronary artery bypass graft/aortic valve replacement surgery, to be followed a few weeks later by an endovascular repair of his abdominal aortic aneurysm. Before these procedures could be performed, he suffered a motor vehicle accident with a closed head injury. He underwent emergent intracranial clot evacuation. It is now postoperative day 2 and his intracranial pressure remains elevated. In the last 24 h, his renal function has deteriorated with increased serum creatinine and potassium, and he is awaiting continuous veno-veno hemodialysis (CVVH).

He is currently on the neurosurgical service with input from a consulting cardiologist and a consulting nephrologist. CVVH will start pending equipment availability, which is expected within 3 h.

Allergies: No known drug allergies

Medications: Dilantin

Metoprolol

Esomeprazole

Laboratories: Hematocrit, 30%; platelets, 220,000/mcl; leukocytes, 8,000/mcl; serum creatinine, 3.4 meq/l; serum potassium, 5.4 meq/l; pH, 7.30; partial pressure of carbon dioxide in arterial blood, 37 mmHg; and partial pressure of oxygen in arterial blood 212 mmHg.

Plan over the next 3 h:

1. Maintain current ventilator settings
2. Awaiting CVVH
3. Strict fluid restriction
4. Keep mean arterial pressure between 70 and 90 mmHg using norepinephrine and sodium nitroprusside infusions.