Journal of Clinical Monitoring and Computing (2019) 33:549–556
https://doi.org/10.1007/s10877-018-0179-3

ORIGINAL RESEARCH

Can variable practice habits and injection port dead-volume put patients at risk?

Michael T. Kuntz[1] · Roman Dudaryk[1] · Richard R. McNeer[1]

Received: 2 April 2018 / Accepted: 28 June 2018 / Published online: 10 July 2018

Abstract
Injection ports used to administer medications and draw blood samples have inherent dead-volume. This volume can potentially lead to inadvertent drug administration, contribute to erroneous laboratory values by dilution of blood samples, and increase the risk of vascular air embolism. We sought to characterize provider practice in management of intravenous (IV) and arterial lines and measure dead-volumes of various injection ports. A survey was circulated to anesthesiology physicians and nurses to determine practice habits when administering medications and drawing blood samples. Dead-volume of one and four-way injection ports was determined by injecting methylene blue to simulate medication administration or blood sample aspiration and using absorption spectroscopy to measure sample concentration. Among the 65 survey respondents, most (64.52%) increase mainstream flow rate to flush medication given by a 1-way injection port. When using 4-way stopcocks, 56.45% flush through the same injection site. To obtain a sample from an arterial line, 67.74% draw back blood and collect the sample from the same 4-way stopcock; 32.26% use a different stopcock. Mean (SD) dead-volume in microliters ranged from 0.1 (0.0) to 5.6 (1.0) in 1-way injection ports and from 54.1 (2.8) to 126.5 (8.3) in 4-way injection ports. The practices of our providers when giving medications and drawing blood samples are variable. The dead-volume associated with injection ports used at our institution may be clinically significant, increasing errors in medication delivery and laboratory analysis.

Keywords Administration, intravenous · Blood specimen collection · Embolism, air · Medication error · Vascular access device

1 Introduction

Drug delivery can be significantly affected by the manner medications are administered through intravenous (IV) lines [1, 2]. Intravenous fluid and drug delivery systems have inherent volumes that can serve as reservoirs for medications, fluids, or air, variably referred to as dead-space or dead-volume. The interaction of dead-volume with carrier fluid flow rates can lead to medication delivery errors [3, 4]. Furthermore, adjustments of infusion rates may be significantly delayed reaching patients due to system dead-volume [5]. Injection ports used to administer medications or draw blood samples for laboratory analysis contain some amount of dead-volume [1]. Consequences of this dead-volume have been previously studied, including the infectious risk posed by residual propofol [6]. Air contained in this dead-volume has also been attributed to fatal outcomes [7]. Furthermore, the inherent inaccuracy in small volume measurement [8, 9] may exacerbate these inconsistencies with the precision of medication delivery.

Recently, we observed two types of outcome for which root causes could not be identified and for which dead-volumes may have played a role: (i) Two surgical patients appearing to have re-onset of muscle paralysis in the perioperative period even though unintentional administration of a neuromuscular blocker had been ruled out; (ii) Serial measurement of arterial hematocrit in ICU patients yielding low values subsequently determined to be erroneous. To investigate the potential role of dead-volume in these scenarios, we first sought to characterize the practices of

✉ Richard R. McNeer
McNeer@miami.edu

Michael T. Kuntz
Michael.Kuntz@jhsmiami.org

Roman Dudaryk
RDudaryk@med.miami.edu

[1] Department of Anesthesiology, Jackson Memorial Hospital, University of Miami, 1611 NW 12th Ave, SW 303, Miami, FL 33136, USA

medical providers when administering medications and drawing blood samples. Next, using a laboratory model, we measured the amount of dead-volume in the injection ports and 4-way stopcock side-ports currently used in IV and arterial-line systems at our institution.

2 Materials and methods

2.1 Conceptualization of problem

2.1.1 One-way injection port medication administration

One-way injection ports (Fig. 1a, i.) are commonly used to bolus medications (ii.). It is possible for residual medications to be retained in the dead-volume of the injection port after flushing of mainstream tubing (iii.). Introduction of dead-volume content into mainstream flow during subsequent use of the injection port (iv.) is one potential consequence of not recognizing this dead-volume.

2.1.2 Four-way stopcock medication administration

Stopcocks (Fig. 1b, i.) can be used to bolus medications (ii.). After mainstream flushing, medication could remain in the dead-volume comprised of the stopcock injection port neck and valve conduit (iii.). If this dead-volume is not cleared, subsequent administration of any fluid through the injection port could result in unintended medication administration (iv.).

2.1.3 Four-way stopcock blood sampling

Four-way stopcocks associated with arterial or central line systems can be used to sample blood (Fig. 2a). After collecting a sample (i.), the side-stream port neck can be cleared of blood by flushing from an upstream source (ii.) and blood in the tubing and arterial catheter can then be cleared by mainstream flushing (iii.). In preparing to obtain a subsequent sample, if blood is aspirated from an upstream stopcock to clear crystalloid (iv.), unintended dilution or contamination of the sample could ensue due to crystalloid contained in the sampling stopcock dead-volume (v.).

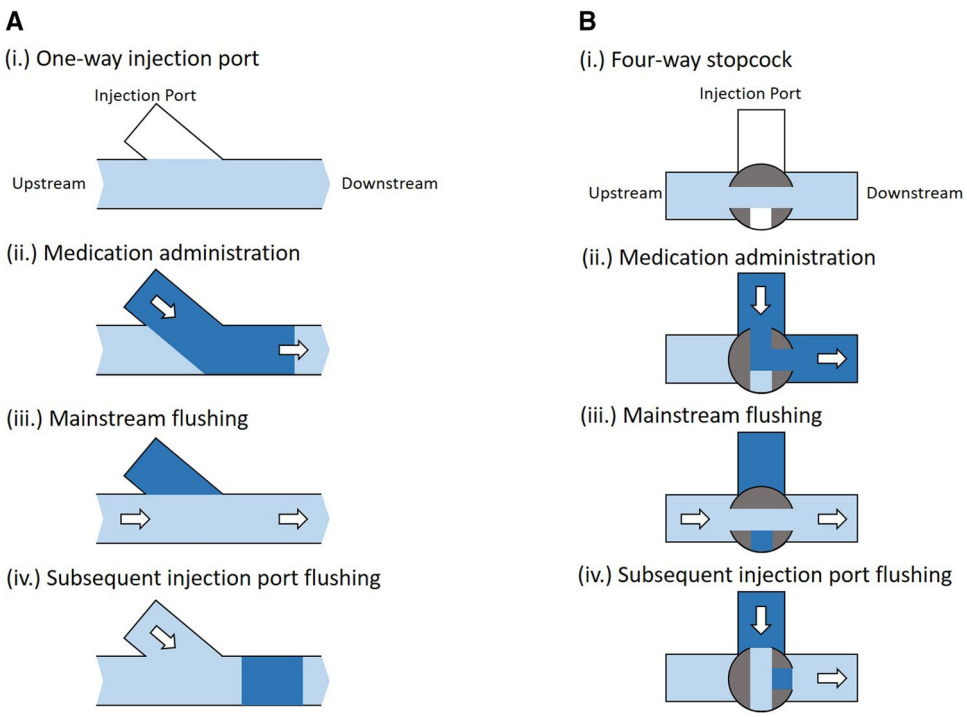

Fig. 1 Conceptualization of dead-volume in injection ports during medication administration. Dead-volume is present in the 1-way injection port neck (**a**) which is shown here to initially contain air (i.). After medication administration (ii.) and mainstream flushing, medication can occupy the dead-volume (iii.). If this dead-volume is not cleared, subsequent administration of any fluid can lead to unintended medication administration (iv.). Dead-volume is present in the 4-way injection port neck and valve conduit (**b**) which is shown here to initially contain air (i.). After medication administration (ii.) and mainstream flushing, medication can occupy the dead-volume (iii.). If this dead-volume is not cleared, subsequent administration of any fluid can lead to unintended medication administration (iv.). To simulate medication administration via 1-way injection ports (**a**) and 4-way stopcocks (**b**), methylene blue was used as a surrogate for the medication

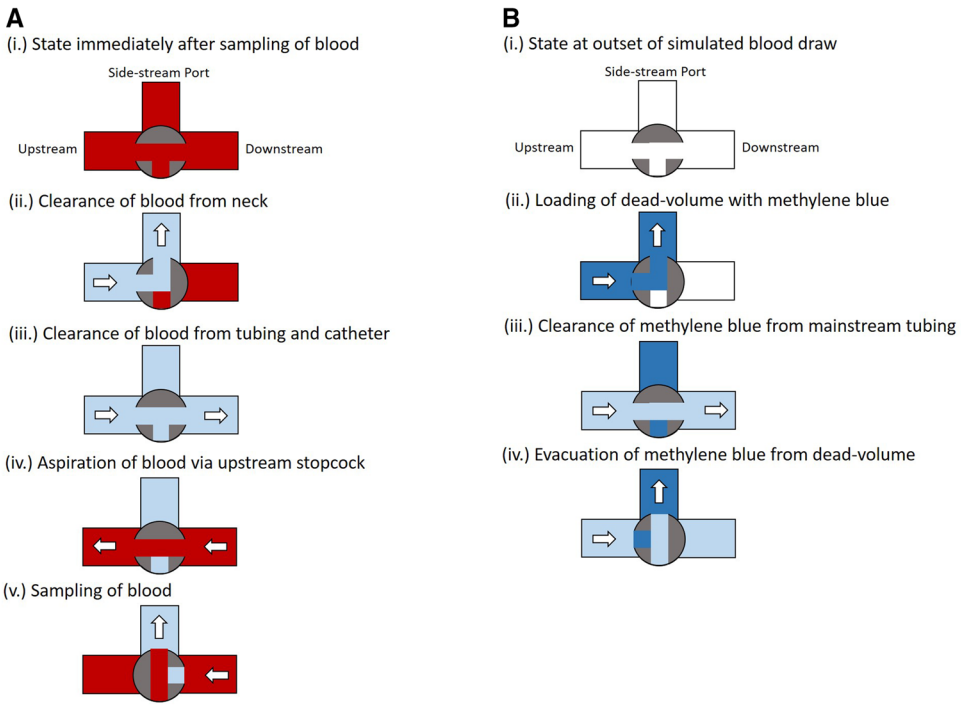

Fig. 2 Conceptualization of dead-volume in 4-way stopcocks during blood sampling. The stopcock (**a**) is shown in a state immediately after blood has been sampled (i) It is not uncommon for blood to be cleared from the side-stream port neck by flushing crystalloid from upstream (ii) and then flushing the mainstream tubing to catheter tip (iii). If in preparing to obtain another sample, blood is first aspirated via an upstream stopcock to clear tubing of crystalloid (iv.), blood aspirated from the sampling stopcock can become diluted and contaminated (v., upstream stopcock not shown). To simulated blood sampling via stopcock side-stream port (**b**), methylene blue was used as a surrogate for crystalloid

2.2 Materials

Injection ports, IV lines, syringes, and Plasmalyte-A were collected from materials opened for use in the operating room which had subsequently expired and were to be discarded. Methylene blue, Eppendorf tubes, 96 well plates, and pipette tips were purchased by the authors' Department of Anesthesiology. Specific stopcocks and injection ports studied include the low flow 4-way stopcock included with arterial lines (ICU Medical, Ref 46053-14), the individually packaged high flow 4-way stopcock (ICU Medical, Ref B4018), the 4-way stopcock included with Y-type blood tubing (Braun, Ref 490422), the 1-way injection port included in Y-type blood tubing (Braun, Ref 490422), and the 1-way injection port included in Outlook Infusion System tubing (Braun, Ref 354213).

2.3 Provider survey

Given the nature of the study, no formal Institutional Review Board approval was necessary, and a waiver stating this was obtained. A survey (Appendix 1) regarding provider practices when administering medications through IV lines and drawing blood samples from 4-way stopcocks was distributed to attending, fellow, and resident anesthesiologists, as well as nursing staff at the multiple institutions affiliated with the authors' Department of Anesthesiology. Participation was invited by an initial e-mail and a follow-up reminder. There was no incentive offered for participation in the survey and results were kept anonymous. In order to prevent incomplete responses, all items in the survey required a response.

2.4 Spectrometric measurements

Methylene blue was used as a surrogate for medication or crystalloid in simulation experiments as it is commercially available and the concentration may be easily determined by spectrometric measurement. Absorption spectrometric measurements were conducted using a Clariostar Multimode micro plate reader (BMG Labtech). Preliminary spectrum analysis of our stock methylene blue revealed three main absorption peaks at 608, 664, and 668 nm; 608 nm was chosen because it had the largest extinction coefficient.

2.5 Simulated medication administration through 1-way injection port

The 1-way injection ports included in Y-type blood tubing and Outlook Infusion System tubing were studied in this simulation. Methylene blue was used to represent medication and Plasmalyte-A was used as crystalloid during mainstream and injection port flushing (Fig. 1a). Each 1-way injection port was primed with Plasmalyte-A (i.). Methylene blue (1 mL) was administered using a luer lock syringe to simulate medication administration (ii.). Plasmalyte-A (20 mL) was then used to flush the line from above to ensure only methylene blue in the injection port dead-volume remained (iii.). The dead-volume was evacuated by flushing the injection port with two successive 5 mL aliquots of Plasmalyte-A

(iv.); these aliquots were collected downstream and used to calculate the dead-volume (Appendix 2). This procedure (Fig. 1a, i–iv) was performed on three individual 1-way injection ports of each type.

2.6 Simulated medication administration through a 4-way stopcock

The 4-way stopcocks included in our arterial line system, Y-type blood tubing, and the individually packaged high-flow type were studied in this experiment. Methylene blue was used to represent medication, and Plasmalyte-A was used as crystalloid during mainstream and injection port flushing (Fig. 1b). The primed stopcock (i.) was turned with the off position to upstream flow and methylene blue (1 mL) was administered using a luer lock syringe (ii.). Next, with the stopcock turned off to the injection port (iii.), 20 mL of Plasmalyte-A was flushed (mainstream) to ensure that only methylene blue remained in the injection port neck and valve conduit. The stopcock was then opened to the injection port (iv.) and two successive 5 mL aliquots of Plasmalyte-A were administered with a luer lock syringe, collected at the downstream end, and used to calculate dead-volume. This procedure (Fig. 1b, i–iv.) was performed on 3 individual 4-way stopcock of each type.

2.7 Simulated blood sampling through a 4-way stopcock

The 4-way stopcocks studied in this experiment were those included in the arterial line tubing and the individually packaged high-flow type. Methylene blue was used to represent crystalloid or blood retained in dead-volume, and Plasmalyte-A was used to represent crystalloid during mainstream flushing (Fig. 2b). Stopcocks were primed with Plasmalyte-A. To fill the dead-volume with methylene blue, a luer locked syringe was attached to the upstream port, and methylene blue (1 mL) was injected and allowed to flow out of the side-stream port neck (ii.). With the stopcock position off to the side-stream port, the mainstream conduit was flushed with 20 mL of Plasmalyte-A to ensure that only methylene blue remained in the side-stream port neck and valve conduit (iii.). Then 10 mL of Plasmalyte-A was used to evacuate the side-stream port using a luer lock syringe in the same flow direction as initial methylene blue administration (iv.); this aliquot was collected and used to calculate dead-volume. This procedure (Fig. 2b, i–iv) was performed on three individual 4-way stopcocks of each type.

2.8 Statistical analysis

Standard calibration curves were set-up by serially diluting methylene blue 10 times by a factor of 2 with Plasmalyte-A. Each standard sample was aliquoted on the spectrometric well plates to generate three replicates for analysis at 608 nm. The three absorption measurements for the given dilution were averaged and the dilution factors were plotted as a function of measured absorption. The linear portion of the curve was used to determine a line of best fit. Each experimental procedure was performed three times on each stopcock or injection port. The absorption of experimental samples was subsequently determined by aliquoting each sample to generate three replicates for analysis at 608 nm. These three replicates were then averaged to give an average absorption for the single experimental run. These absorption results from the three experimental runs per stopcock or injection port were then averaged to produce a final average absorption value. This final average absorption and the standard calibration curve were used to determine dead-volume (Appendix 2). Calculated dead-volume for each injection port type is reported as mean ± standard deviation.

3 Results

3.1 Provider survey

Sixty-five individuals who completed the survey were represented by attending, fellow and resident physicians, nurse anesthetists, and critical care nurses. Areas of practice included cardiothoracic, neuro, obstetric, pediatric and general anesthesiology, as well as regional/acute pain, chronic pain, and critical care. When administering a medication through a 1-way injection port, 35.48% flush through the same injection port as the medication was given through, while 64.52% simply increase the mainstream flowrate. When administering medication through the side-port of a 4-way stopcock, 56.45% flush medication in using the same injection site, while 43.55% use a different injection site or increase mainstream flowrate. When obtaining a sample of blood from an arterial line, 67.74% draw back blood (clearing dead-volume) and collect the sample from the same 4-way stopcock, while 32.26% use two different stopcocks. A majority (85.48%) flush residual blood out of the side-stream port after obtaining the sample. Regarding medication administration, 66.13% remain committed to using a single injection port throughout a case.

3.2 Dead-volume measurements

Calculated dead-volumes obtained during simulated medication administration were generally higher in 4-way stopcocks compared to 1-way injection ports. Dead-volume associated with the infusion tubing injection port was negligible while dead-volume associated with the Y-tubing injection port was comparably larger but about an order of magnitude

smaller than dead-volumes measured in stopcocks (Table 1). Depending on the injection port type, between 0.1 and 1.2% of total dead-volume was measured in the second sequential 5 mL sample collected (not considering the Horizon Infusion system injection port which had negligible dead-volume). Among the 4-way stopcocks, the largest dead-volume was measured in the high-flow stopcock, and the smallest was measured in the arterial-line stopcock. In the setting of simulated blood sampling, higher dead-volumes were measured in these 2 stopcocks relative those obtained during simulated medication administration (Table 1).

4 Discussion

A system approach to safety involves layering defenses, barriers, and safeguards between hazards and patients [10]. Holes in these layers can be classified as either active failures (e.g. unsafe acts) or latent factors (which can include inherent and often unknown properties of equipment), and when a combination of these holes line up, opportunity (accident trajectory) for patient harm exists (referred to as the "Swiss cheese model"). The impetus for the current study was the anecdotal reporting of odd and unexpected observations relating to apparent re-onset of muscle paralysis and erroneous blood test measurements. We identified two factors at our institution that could explain these outcomes: variable/inappropriate practice related to injection port and stopcock use (active failure) and the presence of potentially clinically significant levels of dead-volume in injection ports and stopcocks (latent factor). We conclude based on our findings that it is plausible that a combination of these factors could lead to scenarios of inadvertent drug administration and inaccurate blood sampling with subsequent unwarranted transfusion.

Table 1 Dead-volumes (in microliters) observed during simulated medication administration and blood sampling

	Medication administration		Blood sampling
	Mean (SD)	%[a]	Mean (SD)
One-way injection port			
Y-tubing	5.6 (1.0)	1.1	–
Infusion pump tubing	0.1 (0.0)	2.6	–
Four-way stopcock			
Arterial line	54.1 (2.8)	0.1	84.1 (4.4)
High flow	82.3 (1.5)	0.5	126.5 (8.3)
Y-tubing	67.9 (6.1)	1.2	–

SD standard deviation

[a]Percentage of dead-volume present in the second 5 mL used to evacuate

Although medical supplier product catalogues typically include the priming volume for IV line products, this volume is distinct from the functional dead-volume of injection ports which we sought to characterize. One prior study examined the functional dead-volume of various injection ports [1]. Their study demonstrated generally higher amounts of dead-volume, with results varying from 0.10 to 0.43 mL, while our study demonstrated volumes varying from negligible for the Outlook Infusion System tubing injection port to almost 0.13 mL for the high flow 4-way stopcock. This difference may reflect the fact that our study simulated the administration of medications and blood draws and reproduced the manner by which dead-volume content may be subsequently released. However, it is also possible that product design has improved since the prior study. Indeed, there is an unexpectedly large difference between the dead-volumes measured in the two 1-way injection ports we studied. Clearly, it is possible to design a 1-way injection port with little or no inherent dead-volume as in the Outlook Infusion System tubing injection port. However, it is less clear how dead-volume could be eliminated in 4-way stopcocks. The results of this study help emphasize this engineering and design gap. Additionally, preferential purchase by hospitals of system tubing with minimal or no dead-volume over those with larger volumes should help mitigate associated risk.

Almost half of survey respondents at our institution report flushing through a different injection site or increasing mainstream flowrate when administering medications through a 4-way stopcock which can have almost one-tenth of a milliliter of dead-volume as measured during simulated medication administration. Table 2 shows predicted amounts of common medications that could be inadvertently administered in this scenario. Although this dead-volume might not seem immediately relevant in an adult setting, it certainly bears consideration in pediatrics, where volumes less than one milliliter may commonly be used. Casella, et al. measured the accuracy of pediatric nursing staff attempting to deliver small volumes of insulin [9]. They found that, particularly when attempting to deliver smaller volumes, dose delivery could be both inaccurate and imprecise. When attempting to deliver 0.5 units of insulin, the average delivered amount was nearly twice the intended dose. Muffly, et al. measured the accuracy of both pediatric anesthesiologists and pediatric nurses in measuring small volumes [8]. Their experimental design was similar to ours in that it involved the measurement of a fluorescent dye and determination of medication delivery by measurement of sample fluorescence. Their results show that attempted measurement of volumes less than or equal to 0.5 mL resulted in significant variation, with increasing variability for diminishing volumes. When considered in the context of our results, where some 4-way injection ports contain over a tenth of a milliliter of dead-volume, drug delivery may be highly inaccurate

Table 2 Unintended dose of selected medications as a function of dead-volume

Medication	Concentration	Calculated unintended dose	
		Y-tubing stopcock	High flow stopcock
Rocuronium	10 mg/mL	0.7 mg	0.8 mg
Epinephrine	100 mcg/mL	6.8 mcg	8.2 mcg
	10 mcg/mL	0.7 mcg	0.8 mcg
Ephedrine	5 mg/mL	0.3 mg	0.4 mg
Phenylephrine	100 mcg/mL	6.8 mcg	8.2 mcg
Nicardipine	250 mcg/mL	17.0 mcg	21.0 mcg
	100 mcg/mL	6.8 mcg	8.2 mcg
Esmolol	10 mg/mL	0.7 mg	0.8 mg
Heparin	20,000 units/mL	1358 units	1646 units
	10,000 units/mL	679 units	823 units
	5000 units/mL	340 units	412 units
	2000 units/mL	136 units	165 units
	1000 units/mL	68 units	82 units
Insulin	500 units/mL	34 units	41 units
	100 units/mL	7 units	8 units

Table 3 Effect of dead-volume (dead-volume (=84.1 µL) measured from arterial line system 4-way stopcock) on selected measurements of drawn blood

	Collected sample volume (mL)				
	0.3	0.5	1.0	2.0	3.0
Hematocrit (%)					
20	15.0	17.1	18.4	19.2	19.5
30	22.4	25.7	27.7	28.8	29.2
40	29.9	34.2	36.9	38.4	38.9
PaO_2 (mmHg)					
60	44.9	51.4	55.3	57.6	58.4
120	89.8	102.7	110.7	115.2	116.7
250	187.0	214.0	230.6	239.9	243.2
600	448.9	513.6	553.4	575.8	583.6
$PaCO_2$ (mmHg)					
30	22.4	25.7	27.7	28.8	29.2
40	29.9	34.2	36.9	38.4	38.9
50	37.4	42.8	46.1	48.0	48.6

if providers do not account for injection port dead-volume when administering medications. Considering neuromuscular blockade, a maintenance dose of rocuronium (0.1 mg/kg) could be inadvertently administered to a 7 kg pediatric patient if the dead-volume (almost 70 mcL) measured in our IV tubing 4-way stopcock contained 10 mg/mL of rocuronium. Under similar circumstances, 6.8 mcg of epinephrine could be inadvertently administered (see Table 2). The risk of air entrained within dead-volume is also of higher consequence in pediatric patients, as highlighted by one report of air embolism suspected during medication administration [7]. For smaller patients such as full-term and premature neonates who often weigh between 2 and 4 kg, the risk of adverse outcomes is obviously higher.

One-third of respondents at our institution reported using two different stopcocks when drawing blood samples and a majority flush residual blood out of the injection port after obtaining the sample. Blood tests such as arterial blood gases, resuscitation panels, and i-STAT assays can be performed with sample volumes of 0.5 mL. Concern over iatrogenic anemia [11, 12] has helped foster the adoption of blood conservation strategies which encourage minimizing blood sample volume associated with lab tests [12, 13]. Manufacturers of point-of-care laboratory systems such as i-STAT do not give specific guidance as to the suggested volume of sampling (http://www.pointofcare.abbott/us/en/offerings/support/technical-documentation/user-guides). In this situation, the dead-volume observed in our arterial line system stopcocks would represent 16–26% of the total blood sample drawn, and commonly measured parameters would be underestimated accordingly. The magnitude of underestimation would obviously be decreased at higher sampling volumes (Table 3), however, universal use of one stopcock is an attainable change in practice that would obviate risk of sample dilution and allow for blood conservation strategies.

Intravenous and arterial tubing must be primed in order to remove air. Incomplete priming may leave residual air in injector port dead-volume (Figs. 1a, i; b, i and 2a, i) which can subsequently be introduced into patients. Vascular air embolism is an underappreciated and yet potentially serious complication usually associated with large administered air volumes [14]. However, volumes as low as 20 mcL associated with syringe injection may have contributed to the death of a small neonate [7]. We measured dead-volume more than three times this size in the stopcock that comes with our IV tubing. In patients with atrial septal defects including adults, small volumes can occlude coronary vessels (paradoxical air embolism) [15]. Manual flushing of arterial lines can cause retrograde blood flow which can deliver vascular air emboli to the brain [16, 17]. Attempts to minimize variability of practice among providers in favor of practices that effectively account for dead-volume when managing arterial line systems should help decrease risk of vascular air embolism.

As a result of this study, the following changes to practice will be promoted in our department:

1. All IV and arterial systems will be primed by flushing mainstream tubing and injection ports before use with patients. This will evacuate air from the injection port dead-volume.
2. After administering medication through an injection port, at least 5 mL volume of crystalloid will be adminis-

tered as a chaser to clear the injection port dead-volume of medication. The provider may use more volume as needed for medication to reach the patient.
3. Blood sampling from arterial and central venous systems will be performed using a single stopcock to avoid dilution or contamination of sample.

Our study was limited in that it only included equipment used specifically at our institution and only surveyed practitioners from one department. Other providers may therefore have difficulty when considering how to modify their practices when approaching the equipment available at their own institution. In addition, practice habits of practitioners in our department may not necessarily represent that of practitioners in other departments. Our data does still demonstrate that many stopcocks and injection ports contain a relevant amount of dead-volume, and any medical provider administering medications should be aware of the potential impact of this on medication delivery. In addition, our study assumes that methylene blue responds identically within IV equipment as other commonly used medications. This may not be the case, and methylene blue may have a different affinity to adhere to the inside of tubing relative to other medications. It is also worth mentioning that we obtained slightly different values for the dead-volume of the side-stream ports of the 4-way stopcocks in the medication administration and blood sample aspiration experiments (Table 1). This is likely due to the different manner fluid fills the side-stream port during injection into the flow stream versus flush from the flow stream.

This study demonstrates that injection ports and stopcocks can contain clinically relevant amounts of dead-volume. Although it is unlikely the dead-volume of an injection port contains sufficient neuromuscular blocking drug to result in re-onset of neuromuscular blockade in an adult patient, this is a valid concern in pediatric patients. In addition, depending on sampling practices, the dead-volume of sampling ports may certainly contribute to erroneously low hemoglobin levels. Clinical practice that does not account for the presence (known or unknown) of dead-volume can potentially lead to errors in medication delivery and laboratory analysis.

Acknowledgements The authors acknowledge Emre Dikici, PhD of the University of Miami Department of Biochemistry and Molecular Biology, Miami, FL, USA, for allowing use of his laboratory's spectrophotometer for absorption measurements.

Funding Equipment for this study was purchased using RM's departmental discretionary funds.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval Given the nature of the survey in this study, no formal Institutional Review Board approval was necessary. A waiver stating this was obtained. All procedures were in accordance with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Appendix 1

Provider survey

Question 1. When administering a medication through a one-way injection port on an IV line, do you typically flush the medication in:

By flushing through the same injection port as the medication was given through?
By increasing the flow rate of the IV line?

Question 2. When administering a medication through the side-port of a 4-way stopcock, do you typically flush the medication in by flushing through:

The same injection site as the medication was given?
A different injection site or increasing the flow rate of the IV line?

Question 3. When you draw a blood sample from an arterial line, do you typically draw back on the line and remove the blood sample from:

The same 4-way stopcock?
A different 4-way stopcock (e.g., one closer to the patient)?

Question 4. After drawing a blood sample from an arterial line, do you flush out and remove the residual blood from the side port from where you drew the sample? (Yes or No)

Question 5. Do you remain committed to using a single injection port to administer all medications throughout a case? (Yes or No)

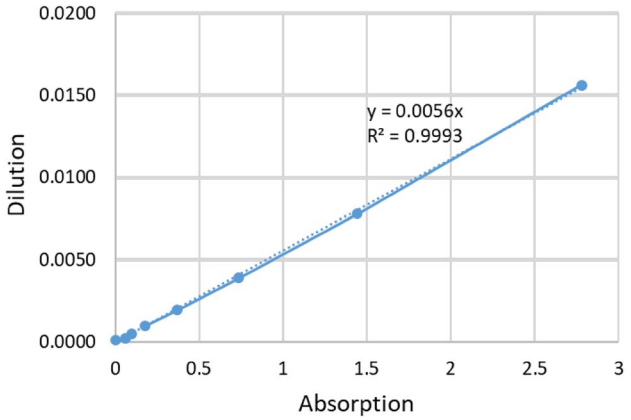

Fig. 3 Example of calibration curve used to calculate dead-volume

Appendix 2: calibration curves and calculation of dead-volume

Calibration curve set-up

On the day of experiments, calibration curves were set-up by serially diluting stock methylene blue 10 times by a factor of 2 with Plasmalyte-A. Each standard sample dilution was aliquoted on the spectrometric well plates to generate three replicates for spectrometric analysis at a wavelength of 608 nm. The three measures were averaged to determine standard sample absorption. The calculated dilution factors were plotted as a function of measured absorptions. The linear portion of the curve was used to calculate the equation of a line of best fit (Fig. 3).

Calculation of dead-volume

Each collected experimental sample was plated to generate three replicates and the three absorption measurements were averaged to yield the absorption for the given experimental sample. The three experimental runs for each stopcock or injection port were then averaged to yield a final absorption value. Dead-volume was calculated by determining an experimental sample's dilution based on the calibration's equation of a line. The sample's dilution was then multiplied by the volume of the collected sample to yield the calculated dead-volume. Using this approach, it was not necessary to determine the concentration of stock methylene blue. In the simulations of drug administration (Fig. 1), two sequential 5 mL samples were collected when evacuating methylene blue. In this case, dead-volumes were calculated separately for the sequential samples and then added to calculate the total dead-volume.

References

1. Smart NG. The functional deadspace of needle-free injection ports. Anaesth Intensive Care. 1991;19(3):429–33.
2. Gould T, Roberts RJ. Therapeutic problems arising from the use of the intravenous route for drug administration. J Pediatr. 1979;95(3):465–71.
3. Lovich MA, Doles J, Peterfreund RA. The impact of carrier flow rate and infusion set dead-volume on the dynamics of intravenous drug delivery. Anesth Analg. 2005;100(4):1048–55.
4. Lovich MA, Kinnealley ME, Sims NM, Peterfreund RA. The delivery of drugs to patients by continuous intravenous infusion: modeling predicts potential dose fluctuations depending on flow rates and infusion system dead volume. Anesth Analg. 2006;102(4):1147–53.
5. Bartels K, Moss DR, Peterfreund RA. An analysis of drug delivery dynamics via a pediatric central venous infusion system: quantification of delays in achieving intended doses. Anesth Analg. 2009;109(4):1156–61. https://doi.org/10.1213/ane.0b013e3181b220c9.
6. Cole DC, Baslanti TO, Gravenstein NL, Gravenstein N. Leaving more than your fingerprint on the intravenous line: a prospective study on propofol anesthesia and implications of stopcock contamination. Anesth Analg. 2015;120(4):861–7. https://doi.org/10.1213/ANE.0b013e318292ed45.
7. Wald M, Kirchner L, Lawrenz K, Amann G. Fatal air embolism in an extremely low birth weight infant: can it be caused by intravenous injections during resuscitation? Intensive Care Med. 2003;29(4):630–3. https://doi.org/10.1007/s00134-003-1681-7.
8. Muffly MK, Chen MI, Claure RE, et al. Small-volume injections: evaluation of volume administration deviation from intended injection volumes. Anesth Analg. 2017;125(4):1192–9. https://doi.org/10.1213/ANE.0000000000001976.
9. Casella SJ, Mongilio MK, Plotnick LP, Hesterberg MP, Long CA. Accuracy and precision of low-dose insulin administration. Pediatrics. 1993;91(6):1155–7.
10. Reason J. Human error: models and management. BMJ. 2000;320(7237):768–70.
11. Stefanini M. Iatrogenic anemia (can it be prevented?). J Thromb Haemost. 2014;12(10):1591. https://doi.org/10.1111/jth.12642.
12. Steffen K, Doctor A, Hoerr J, et al (2017) Controlling phlebotomy volume diminishes PICU transfusion: implementation processes and impact. Pediatrics. https://doi.org/10.1542/peds.2016-2480.
13. Fowler RA, Berenson M. Blood conservation in the intensive care unit. Crit Care Med. 2003;31(12 Suppl):715-20. https://doi.org/10.1097/01.CCM.0000099350.50651.46.
14. Brull SJ, Prielipp RC. Vascular air embolism: a silent hazard to patient safety. J Crit Care. 2017;42:255–63.
15. Kumar D, Gadhinglajkar SV, Moorthy K, Bhandari D. Paradoxical air embolism to left anterior descending artery during induction of anesthesia in a patient with an atrial septal defect. A A Case Rep. 2014;2(6):66–9. https://doi.org/10.1213/XAA.0000000000000007.
16. Dube L, Soltner C, Daenen S, Lemariee J, Asfar P, Alquier P. Gas embolism: an exceptional complication of radial arterial catheterization. Acta Anaesthesiol Scand. 2004;48(9):1208–10. https://doi.org/10.1111/j.1399-6576.2004.00476.x.
17. Murphy GS, Szokol JW, Marymont JH, Avram MJ, Vender JS, Kubasiak J. Retrograde blood flow in the brachial and axillary arteries during routine radial arterial catheter flushing. Anesthesiology. 2006;105(3):492–7.