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Establishing goals of volume management in critically ill patients with renal failure

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Abstract

Background: **Volume management remains a challenging component of caring for the critically ill. Renal failure complicates fluid management. We sought to identify relationships between delta blood volume and physiology-based targets for both the adequacy of left ventricular filling (stroke volume index [SVI]) and preload dependency (stroke volume variability [SVV]) in patients undergoing dialysis in the intensive care unit.**

Methods: **Patients undergoing dialysis with an arterial line in place were eligible. Delta blood volume was measured during dialysis along with simultaneous SVI and SVV via an arterial pressure cardiac output monitor. Patients were dichotomized as "negative" fluid strategy if fluid was removed, or "positive" fluid strategy if fluid was added during renal replacement therapy. Delta blood volume's association with SVI and SVV was examined separately by fluid strategy group.**

Results: **A total of 26 patients (11 continuous and 15 intermittent dialysis) were investigated. Compared with that in patients with negative fluid strategy, SVV was significantly higher at baseline in patients with positive fluid strategy, while baseline SVI was significantly lower. Fluid removal was associated with significant increases to SVV in both strategy groups. Fluid removal was associated with significant decreases to SVI, and this effect was similar regardless of fluid strategy.**

Conclusion: **Physiologic variables assessing cardiac performance (SVI) and preload responsiveness (SVV) provide simple yet meaningful targets when one is determining the best approach for volume management in critically ill patients undergoing dialysis.**

Key words: *Delta blood volume, Fluid management, Fluid overload, Stroke volume, Stroke volume variability*

Introduction

Appropriate management of intravascular volume in the critically ill improves outcome, yet achieving optimal volume status remains challenging. Recent guidelines support the use of aggressive resuscitation in the early phases of critical illness (1, 2); however, an excessively positive fluid balance independently impacts patient outcomes, including mortality and length of stay (3-9).

In patients with acute kidney injury (AKI), volume management becomes even more complex. Renal replacement therapy (RRT) allows precise titration of intravascular volume by prescribing various amounts of ultrafiltration (10). One goal is to remove excess extracellular fluid and simultaneously avoid detrimental reductions in intravascular volume (11). Dialysis-associated hypotension is common (12-14), and targeting delta blood volume (DBV) during RRT to avoid large fluid shifts is a common strategy to address this issue. DBV is calculated as a percentage change in circulating blood volume based upon the degree of hemodilution (+DBV) or hemoconcentration (–DBV) achieved during an RRT session.

Evaluation of cardiac performance utilizing stroke volume index (SVI) and preload responsiveness with stroke volume variability (SVV) determined from the arterial waveform is increasingly being utilized for volume management of the critically ill. The arterial pressure cardiac output (APCO) monitor is an evolving technology providing physiologic data to determine appropriate interventions using improved cardiac performance as a goal (15). SVV is a sensitive predictor of volume or preload responsiveness and is a primary output in the data display of the commercially available APCO technologies (16-18).

The best approach for managing volume in critically ill dialysis patients is unknown. Positive fluid balance in patients with

acute renal failure is a risk factor for 60-day mortality (4, 7). Patients with acute respiratory distress syndrome demonstrated decreased number of days on mechanical ventilation and length-of-stay when managed with aggressive volume removal (3). Optimal fluid management in patients with renal failure may ultimately improve mortality and morbidity and is always a goal of RRT. Specifically, volume therapy is prescribed during RRT often based on fluid balance and/or weight gain. Current strategies for optimal volume management recognize the potential deleterious effects of both volume overload and hypovolemia (2-9). Using physiologic targets allows precise titration of the volume prescription for the critically ill.

The purpose of our study was to examine the relationship of DBV to SVI and SVV over 3 hours in critically ill patients with renal failure undergoing dialysis.

Materials and methods

Study subjects

After institutional review board approval, we completed this protocol in the adult intensive care unit (ICU) of Baystate Medical Center, Springfield, Massachusetts. Each patient or patient surrogate provided informed consent for this prospective, observational study. Eligible patients received RRT with simultaneous volume-controlled mechanical ventilation along with the presence of an indwelling arterial catheter. Exclusion criteria included aortic valve regurgitation, the presence of an intra-aortic balloon pump and weight of less than 40 kg. Also excluded were patients with pronounced cardiac dysrhythmias, including atrial fibrillation, atrial flutter and bigeminy, due to their impact on the hemodynamic data, specifically the utility of SVV as a measure of volume responsiveness.

Design

We prospectively measured several parameters in patients undergoing intermittent RRT (IRRT) or continuous RRT (CRRT). These included DBV and hematocrit (HCT) measured via the Crit-Line III (Hemametrics, Kaysville, UT, USA), a portable fluid management tool incorporating photo-optical technology attached to the dialysis circuitry (http://www.hemametrics.com). Cardiovascular parameters obtained simultaneously included cardiac index (CI; l/min/m^2), SVI (ml/beat/m^2) and SVV (%) measured with the FloTrac Vigileo system (Edwards Life Sciences, Irvine, CA, USA; http://www.edwards.com).

Data collection and statistical analysis

Data were collected continuously while patients underwent RRT (either continuous or intermittent) and analyzed at 5-minute intervals, up to a maximum of 36 time points (3 hours). The change in blood volume, DBV, calculated as the percentage change (+ or –) from baseline at each interval, was the primary predictor of interest. Patients were grouped into negative or positive DBV based on each individual's slope of DBV over time. Patients were classified as "negative" fluid strategy if fluid was removed during RRT, or "positive" fluid strategy if fluid was added during RRT. For each outcome, intraclass correlation coefficients (ICCs) were calculated using large 1-way analysis of variance (ANOVA). The ANOVA-estimated ICC ranges from 0 to 1; higher values suggest between-patient variability is large relative to within-patient variability (19). Substantial ICCs suggest appropriate repeated-measures analyses should be used to ensure accurate estimation of standard errors and p values. Random effects linear models were built to quantify the DBVs' association with SVV and SVI. Interaction terms were included in the linear models to examine whether the impact on cardiac parameters differed significantly by fluid strategy group. The main effects coefficients represent the average change in each cardiac measure for every percentage change of DBV (20). Alpha was specified at ≤0.05 for all tests of significance. Analyses were conducted in Stata/MP 11.2 for Windows (2009; StataCorp LP, College Station, TX, USA).

Results

A total of 26 patients (11 CRRT, 15 IRRT) were enrolled in the study. Patient characteristics are shown in Table I. The average patient age was 51.7 years, most were male (73%); and 58% were on IRRT. All were mechanically ventilated.

Delta blood volume

Over the 3-hour analysis interval, the average patient's DBV was –2.5% ± 3.9%. DBV became more negative over time in 18 of 26 patients (β=–0.19%, 95% confidence interval [95% CI], –0.12% to –0.25%), whereas it was more positive over time in 8 of 26 patients (β=0.09%, 95% CI, 0.04% to 0.13%).

DBV association with cardiac measures

Means, standard deviations and ICCs of all cardiac measures are presented by DBV in Table II.

TABLE I
BASELINE PATIENT CHARACTERISTICS (n=26)

Age, years	51.7 ± 13.9
Female	7 (26.9%)
Pressors	9 (34.6%)
Mortality	9 (34.6%)
ALI/ARDS	14 (53.8%)
Mechanical ventilation	26 (100%)
Intermittent renal replacement therapy	15 (57.7%)
Acute renal failure	22 (84.6%)
Baseline hemodynamics	
SVV (%)	10.6 ± 5.8
SVI (ml/beat/m^2)	38.3 ± 7.1
CI (l/min/m^2)	3.7 ± 1.0

Values are means ± SD, or number (percentage), as indicated. ALI/ARDS = acute lung injury / acute respiratory distress syndrome; CI = cardiac index; SVI = stroke volume index; SVV = stroke volume variability.

Stroke volume variability

Baseline SVV was significantly higher in patients with positive DBV (Tab. III). For patients with negative DBV strategy, each unit of fluid removed increased SVV by 0.12% (95% CI, 0.02% to 0.22%). For patients with positive DBV strategy, each unit of fluid removed increased SVV by 0.43% (95% CI, 0.24% to 0.63%). The difference in response between groups (0.31%) was statistically significant (p=0.006), and was apparent in the divergence of slopes in Figure 1.

Stroke volume index

As shown in Table IV and Figure 2, baseline SVI was significantly higher in patients with negative DBV strategy than in those with positive DBV strategy. Nevertheless, the association of DBV with SVI was similar regardless of fluid strategy, with SVI decreasing modestly when fluid was removed in either group.

Cardiac index

Baseline CI was modestly but significantly higher in patients with negative DBV strategy (3.89 l/min/m^2 vs. 3.12 l/min/m^2; p=0.02). Negative DBV produced a nonsignificant reduction

TABLE II
CARDIAC MEASURES BY DELTA BLOOD VOLUME

		Negative	Positive
DBV (%)	Mean	-4.14 (-5.79, -2.49)	+0.19 (-2.29, 2.67)
	ICC	0.53 (0.35, 0.70)	0.64 (0.39, 0.89)
CI (l/min/m^2)	Mean	3.88 (3.50, 4.26)	3.12 (2.53, 3.71)
	ICC	0.78 (0.66, 0.90)	0.55 (0.26, 0.84)
SVI (ml/beat/m^2)	Mean	39.71 (36.53, 42.89)	32.47 (27.52, 37.42)
	ICC	0.69 (0.53, 0.84)	0.77 (0.56, 0.97)
SVV (%)	Mean	11.93 (8.33, 15.54)	18.40 (12.77, 24.02)
	ICC	0.70 (0.55, 0.85)	0.82 (0.66, 0.99)

Values are means (95% confidence interval) and ICCs (95% confidence interval).
CI = cardiac index; DBV = delta blood volume; ICC = intraclass correlation coefficient, proportion of between-subject variability relative to total variability (within-subject plus between-subject); SVI = stroke volume index; SVV = stroke volume variability.

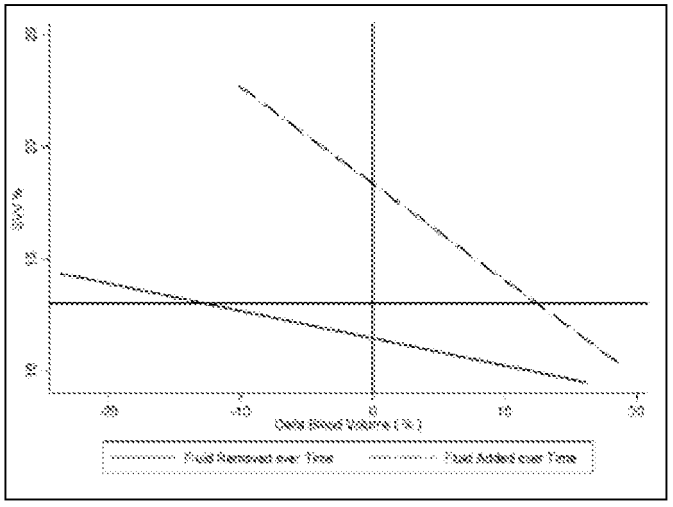

Fig. 1 - Average stroke volume variability (SVV) among patients with positive fluid strategy (n=8) was 6.9 units (%) higher than in patients with negative fluid strategy (n=18) when delta blood volume (DBV) was 0. A significant difference in slopes suggests a stronger response to fluid change among patients with a positive fluid strategy.

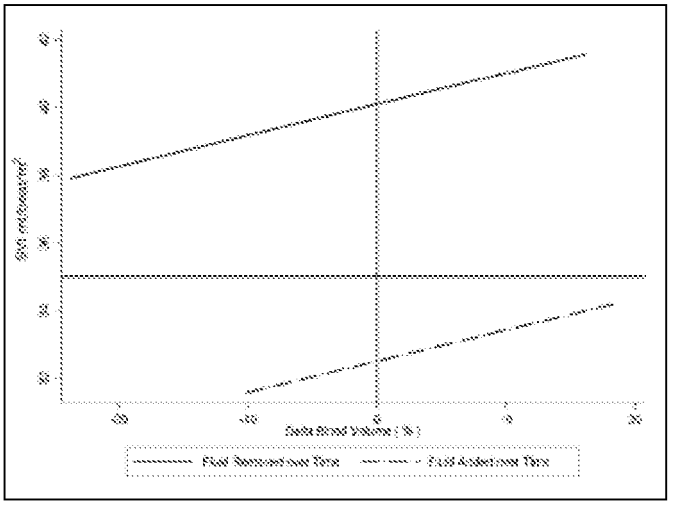

Fig. 2 - Average stroke volume index (SVI) among patients with positive fluid strategy (n=8) was 7.6 units (ml/beat/m²) lower than patients with negative fluid strategy (n=18) when delta blood volume (DBV) was 0. Despite differences in baseline, the common slope suggests that SVI of patients in both strategies responds similarly to alterations in DBV.

TABLE III
STROKE VOLUME VARIABILITY

Intercepts	Point estimates*	95% CI
Positive DBV	18.36%	13.22% to 23.51%
Negative DBV	11.46%	8.12% to 14.79%
Slopes	Point estimates†	
Positive DBV	-0.43%	-0.24% to -0.63%
Negative DBV	-0.12%	-0.02% to -0.22%

For every 1 unit of fluid removed, stroke volume variability (SVV) increased by 0.12% in patients with negative delta blood volume (DBV) and by 0.43% in patients with positive DBV. This response profile differs significantly by DBV (difference in slopes of 0.31%, p=0.006). When DBV and time were zero, represented by the model intercept (point estimates), patients in the negative DBV group had significantly lower SVV. This supports the concept that lower SVV indicates adequate preload and the ability to tolerate volume removal.
95% CI = 95% confidence interval.
*Intercepts differ significantly at p=0.027.
†Slopes differ significantly at p=0.006.

TABLE IV
EFFECT OF FLUID REMOVAL ON STROKE VOLUME INDEX

Intercepts	Point estimate*	95% CI
Positive DBV, ml/beat/m²	32.51	27.80-37.22
Negative DBV, ml/beat/m²	40.10	37.05-43.14
Slope	Point estimate†	95% CI
Slope, ml/beat/m²	0.09	0.003-0.18

When delta blood volume (DBV) and time were zero, represented by the model intercept (point estimates), patients in the negative DBV group had significantly higher stroke volume index (SVI) than those in the positive DBV group. Every unit of fluid removed was associated with a decrease in SVI of 0.09 ml/beat per m² (or, conversely, increase if fluid was added). Unlike stroke volume variability (SVV), fluid change affected SVI similarly, regardless of overall fluid strategy.
*Intercepts differ significantly at p=0.008.
†Common slope for positive and negative DBV.

in CI (–0.01%, 95% CI, 0.0% to 0.01%); the magnitude of this effect was similar in both negative and positive DBV strategy groups (p=0.35).

Discussion

Physiologic variables assessing cardiac performance (i.e., SVI) and preload responsiveness (i.e., SVV) provide simple targets to aid volume management in critically ill patients undergoing dialysis. Our study examined the effects of DBV on these measures. When dialysis groups were dichotomized based upon positive or negative DBV, patients with a negative DBV strategy started with both a higher SVI and a lower SVV. This was the expected result, as SVI is a measure of cardiac performance, and higher values indicate adequate preload. Volume removal in these patients can be managed using hemodynamic physiology that depends on adequate preload to maintain optimal flow.

SVV also correlated well with volume strategy. This was expected, as SVV predicts preload responsiveness. Patients with low SVV are on the preload-independent part of the Frank-Starling curve, and volume removal is not expected to negatively influence cardiac performance. An SVV of less than 13% is an accepted cutoff to indicate that a patient falls into this category (21-23). CI was not a good predictor for tolerance of DBV. Stroke volume (SV) is a better measure of the impact of changes in preload on cardiac performance eliminating the effect of heart rate (HR) on CI.

The change in SVV induced by volume removal independent of overall DBV strategy was also expected. Our data were continuous, and the primary end points were volume removal or addition over the time intervals studied; however, even in patients whose overall DBV was negative, there would be time intervals when DBV was increasing – similarly, for those patients whose overall DBV was positive, there would be time intervals when DBV was decreasing. The slope of the lines reflecting these intervals can be thought of as the slope of the Frank-Starling curve at a specific point in time (Fig. 3). Patients who required volume during their dialysis session are on the steep portion of the Frank-Starling curve (Fig. 3, section A) and thus have greater slope (or change in volume per unit of fluid removed). Those undergoing volume removal during their dialysis treatment and operating on the preload-independent, flat portion of the Frank-Starling curve (Fig. 3, section B) would be expected to see less change in SVV for each unit of fluid removed.

Utilization of vital signs to ascertain volume status is common. Static pressure measures, central venous pressure and pulmonary artery occlusion pressure are sometimes employed but are poor measures of volume status and fluid responsiveness (24-26). Additionally pressure measurements by themselves do not provide any information regarding cardiac performance (4, 7).

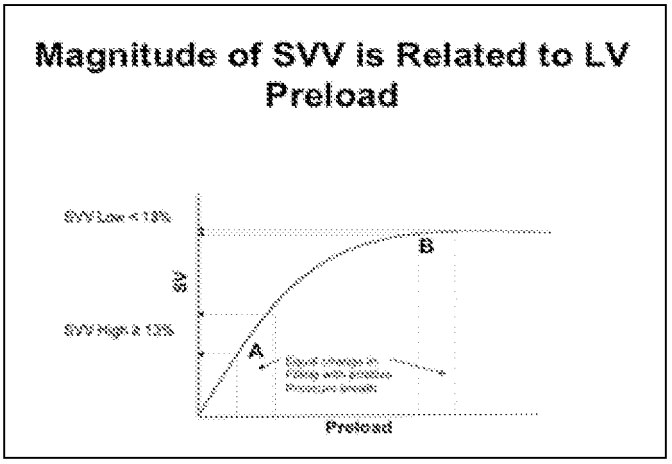

Fig. 3 - Sections A and B represent different locations on the Frank-Starling curve. The change in preload induced by the ventilator is identical. The impact on stroke volume (SV) is not. The change in SV induced by 1 positive pressure breath is proportional to stroke volume variability (SVV). In the critically ill, these patients often require and receive volume. SVV determines the magnitude of preload dependency. Patients with higher SVV are more volume responsive (A – preload dependent) functioning on the steeper portion of the Frank-Starling curve. SVV decreases as preload dependent LV function is optimized (B – preload independent). In these patients (section B), volume can be safely removed, as cardiac performance is not influenced by changes in preload. SVV/SVI pairs allow individual discrimination of a patient's Frank-Starling curve that can determine when volume is required to improve cardiac performance and conversely when volume can be safely removed.

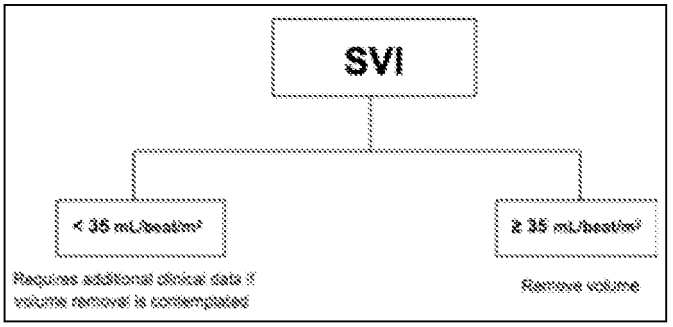

Fig. 4 - Proposed algorithm for fluid management of critically ill patients. Fluid removal is expected to be well tolerated provided stroke volume index (SVI) >35 ml/beat per m². When SVI <35 ml/beat per m², stroke volume variability (SVV) <13% may provide guidance, fluid removal is possible. However, if SVV is increasing rapidly or SVI is decreasing, this would indicate the patient is functioning on the steep portion of the Frank-Starling curve and will not tolerate fluid removal. In fact, many of these patients will require volume expansion.

SVV allows recognition of optimal preload by identifying and individualizing the Frank-Starling relationship (Fig. 3) (23). Utilizing a cardiac function target (i.e., SVI) while being guided by a number (i.e., SVV) provides important physiologic assurance that hemodynamic performance is not compromised during volume manipulation with RRT (23). Regardless of dialysis technique, baseline SVV provided excellent discrimination of those patients from whom volume could be safely removed. An SVI of at least 35 ml/beat/m^2 (27), provides further assurance that volume removal during RRT will not negatively impact hemodynamic status.

Figure 4 is a proposal for applied physiologic volume management during RRT that requires validation.

Our study has several limitations. It is based on a heterogeneous but small (n=26) sample; therefore, we were unable to examine whether associations varied by sex, age or dialysis type. Studies in larger numbers of patients should be undertaken to support our preliminary findings and test their generalizability. Our findings should be interpreted as hypothesis-generating and should not be used to inform treatment strategies. Nevertheless, the relationship between SVV and SVI is well described and is used routinely to optimize the Starling relationship (22, 24, 28).

Pulse contour analysis of the arterial waveform provides an estimate of SV that is significantly influenced by both pathophysiology and therapy which influence vasomotor tone. In our study, lack of detailed assessment of pathophysiology and therapy (vasoactive drugs) that impact vascular tone is a major limitation potentially limiting generalizability of these findings (29). Furthermore, the utility of SVV as a measure of volume responsiveness without description of both tidal volume (V_t) and lung compliance further limits comprehensive understanding of these data (30, 31). However, despite these significant limitations, we still find SVI and SVV to be highly correlated to fluid strategy.

Our study is unique in looking at cardiac performance and volume responsiveness for critically ill patients undergoing RRT. More research is needed to better define protocols for volume management in critically ill patients undergoing RRT. Physiology-based volume removal in the critically ill patient with renal failure may simplify what is often a challenging and largely arbitrary decision. As we learn more about how to DE-resuscitate VOLume oVErloaded patients (letting them Devolve Mailloux/McGee 2009), it is possible we will see a concurrent improvement in their outcomes as other data support this (3-9).

Conclusions

SVI and SVV targets, providing assurance volume management based on DBV as measured with the Crit-Line, have a physiologic basis. Physiologic goals have the potential to facilitate volume management in critically ill patients undergoing RRT.

Institutional Review Board (IRB) approval was obtained, and the study adhered to the Declaration of Helsinki.

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Conflict of interest statement: William McGee, MD, is on a speakers' panel for Edwards Lifesciences.

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References

1. Rivers E, Nguyen B, Havstad S, et al; Early Goal-Directed Therapy Collaborative Group. Early goal-directed therapy in the treatment of severe sepsis and septic shock. N Engl J Med. 2001;345(19):1368-1377.
2. Gan TJ, Soppitt A, Maroof M, et al. Goal-directed intraoperative fluid administration reduces length of hospital stay after major surgery. Anesthesiology. 2002;97(4):820-826.
3. Wiedemann HP, Wheeler AP, Bernard GR, et al; National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome (ARDS) Clinical Trials Network. Comparison of two fluid-management strategies in acute lung injury. N Engl

J Med. 2006;354(24):2564-2575.
4. Payen D, de Pont AC, Sakr Y, Spies C, Reinhart K, Vincent JL; Sepsis Occurrence in Acutely Ill Patients (SOAP) Investigators. A positive fluid balance is associated with a worse outcome in patients with acute renal failure. Crit Care. 2008;12(3):R74.
5. Brandstrup B, Tønnesen H, Beier-Holgersen R, et al; Danish Study Group on Perioperative Fluid Therapy. Effects of intravenous fluid restriction on postoperative complications: comparison of two perioperative fluid regimens: a randomized assessor-blinded multicenter trial. Ann Surg. 2003;238(5):641-648.
6. Gillespie RS, Seidel K, Symons JM. Effect of fluid overload and dose of replacement fluid on survival in hemofiltration. Pediatr Nephrol. 2004;19(12):1394-1399.
7. Bouchard J, Soroko SB, Chertow GM, et al; Program to Improve Care in Acute Renal Disease (PICARD) Study Group. Fluid accumulation, survival and recovery of kidney function in critically ill patients with acute kidney injury. Kidney Int. 2009;76(4):422-427.
8. Bagshaw SM, Brophy PD, Cruz D, Ronco C. Fluid balance as a biomarker: impact of fluid overload on outcome in critically ill patients with acute kidney injury. Crit Care. 2008;12(4):169.
9. Van Biesen W, Yegenaga I, Vanholder R, et al. Relationship between fluid status and its management on acute renal failure (ARF) in intensive care unit (ICU) patients with sepsis: a prospective analysis. J Nephrol. 2005;18(1):54-60
10. Bouchard J, Mehta RL. Volume management in continuous renal replacement therapy. Semin Dial. 2009;22(2):146-150.
11. Pinsky MR, Brophy P, Padilla J, Paganini E, Pannu N. Fluid and volume monitoring. Int J Artif Organs. 2008;31(2):111-126.
12. Ronco C, Brendolan A, Bellomo R. Online monitoring in continuous renal replacement therapies. Kidney Int Suppl. 1999;(72):S8-14.
13. Santoro A, Mancini E, Paolini F, Cavicchioli G, Bosetto A, Zucchelli P. Blood volume regulation during hemodialysis. Am J Kidney Dis. 1998;32(5):739-748.
14. Basile C. Should relative blood volume changes be routinely measured during the dialysis session? Nephrol Dial Transplant. 2001;16(1):10-12.
15. McGee WT. A simple physiologic algorithm for managing hemodynamics using stroke volume and stroke volume variation: physiologic optimization program. J Intensive Care Med. 2009;24(6):352-360.
16. LiDCO Cardiac Sensor Systems. Continuous, real-time cardiovascular monitoring [website home page]. Available at: http://www.lidco.com/. Accessed July 28, 2011.
17. Phillips. PiCCO: continuous cardiac output monitoring [website page]. Available at: http://www.healthcare.philips.com/main/products/patient_monitoring/products/picco/index.wpd. Accessed July 28, 2011.
18. Edwards Lifesciences. Flo Trac Sensor [website page]. Available at: http://www.edwards.com/products/mininvasive/pages/flotracsensor.aspx. Accessed July 28, 2011.
19. Verbeke G. Linear mixed models for longitudinal data. New York, NY: Springer Verlag, LLC; 2009:25.
20. Vittinghoff E. Regression methods in biostatistics: linear, logistic, survival and repeated measures models. New York, NY: Springer Science+ Business Media;2005:276-278.
21. Michard F, Teboul JL. Predicting fluid responsiveness in ICU patients: a critical analysis of the evidence. Chest. 2002;121 (6):2000-2008.
22. Marik PE, Cavallazzi R, Vasu T, Hirani A. Dynamic changes in arterial waveform derived variables and fluid responsiveness in mechanically ventilated patients: a systematic review of the literature. Crit Care Med. 2009;37(9):2642-2647.
23. Michard F. Stroke volume variation: from applied physiology to improved outcomes. Crit Care Med. 2001;39(2):402-403.
24. Osman D, Ridel C, Ray P, et al. Cardiac filling pressures are not appropriate to predict hemodynamic response to volume challenge. Crit Care Med. 2007;35(1):64-68.
25. Marik PE, Baram M, Vahid B. Does central venous pressure predict fluid responsiveness? A systematic review of the literature and the tale of seven mares. Chest. 2008;134(1): 172-178.
26. Michard F, Boussat S, Chemla D, et al. Relation between respiratory changes in arterial pulse pressure and fluid responsiveness in septic patients with acute circulatory failure. Am J Respir Crit Care Med. 2000;162(1):134-138.
27. Moran SE, Pei KY, Yu M. Hemodynamic monitoring: arterial and pulmonary artery catheters. In: Gabrielli A, Layon AJ, Yu M, eds. Critical care. 4th ed. Philadelphia, PA: Wolters Kluwer/Lippincott Williams & Wilkins; 2009:171-191.
28. McGee WT, Horswell JL, Hatib FS, et al. Relationship of SVV to SV: beyond Frank-Starling using arterial pressure-based technology. Crit Care Med. 2006;34(12)(Suppl):A60.
29. Pinsky MR. Probing the limits of arterial pulse contour analysis to predict preload responsiveness. Anesth Analg. 2003;96(5):1245-1247.
30. De Backer D, Heenen S, Piagnerelli M, Koch M, Vincent JL. Pulse pressure variations to predict fluid responsiveness: influence of tidal volume. Intensive Care Med. 2005;31(4): 517-523.
31. Mesquida J, Kim HK, Pinsky MR. Effect of tidal volume, intrathoracic pressure, and cardiac contractility on variations in pulse pressure, stroke volume, and intrathoracic blood volume. Intensive Care Med. 2011;37(10):1672-1679.

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