

Mini-fluid Challenge of 100 ml of Crystalloid Predicts Fluid Responsiveness in the Operating Room

Matthieu Biais, M.D., Ph.D., Hugues de Courson, M.D., Romain Lanchon, M.D., Bruno Pereira, Ph.D., Guillaume Bardonneau, M.D., Marion Griton, M.D., Musa Sesay, M.D., Karine Nouette-Gaulain, M.D., Ph.D.

ABSTRACT

Background: Mini-fluid challenge of 100 ml colloids is thought to predict the effects of larger amounts of fluid (500 ml) in intensive care units. This study sought to determine whether a low quantity of crystalloid (50 and 100 ml) could predict the effects of 250 ml crystalloid in mechanically ventilated patients in the operating room.

Methods: A total of 44 mechanically ventilated patients undergoing neurosurgery were included. Volume expansion (250 ml saline 0.9%) was given to maximize cardiac output during surgery. Stroke volume index (monitored using pulse contour analysis) and pulse pressure variations were recorded before and after 50 ml infusion (given for 1 min), after another 50 ml infusion (given for 1 min), and finally after 150 ml infusion (total = 250 ml). Changes in stroke volume index induced by 50, 100, and 250 ml were recorded. Positive fluid challenges were defined as an increase in stroke volume index of 10% or more from baseline after 250 ml.

Results: A total of 88 fluid challenges were performed (32% of positive fluid challenges). Changes in stroke volume index induced by 100 ml greater than 6% (gray zone between 4 and 7%, including 19% of patients) predicted fluid responsiveness with a sensitivity of 93% (95% CI, 77 to 99%) and a specificity of 85% (95% CI, 73 to 93%). The area under the receiver operating curve of changes in stroke volume index induced by 100 ml was 0.95 (95% CI, 0.90 to 0.99) and was higher than those of changes in stroke volume index induced by 50 ml (0.83 [95% CI, 0.75 to 0.92]; $P = 0.01$) and pulse pressure variations (0.65 [95% CI, 0.53 to 0.78]; $P < 0.005$).

Conclusions: Changes in stroke volume index induced by rapid infusion of 100 ml crystalloid predicted the effects of 250 ml crystalloid in patients ventilated mechanically in the operating room. (**ANESTHESIOLOGY 2017; 127:450-6**)

RATIONAL fluid administration is the cornerstone of perioperative hemodynamic optimization.¹⁻³ Hypovolemia increases the risk of organ hypoperfusion, sepsis, and multiorgan failure, whereas a large amount of fluid may induce pulmonary and peripheral edema and increase cardiac demands.^{4,5} Broadly, there are two strategies that can be used in the operating room. The first is based on the prediction of fluid responsiveness. For more than 15 yr, dynamic variables based on heart-lung interactions have been proposed.⁶ Among these indices, respiratory variations in pulse pressure (PPV) and respiratory variations in stroke volume are the most popular. They are very effective in predicting the effects of volume expansion but under very strict conditions.⁷ The main limitation is the use of low tidal volume.⁸ It is well known nowadays that a protective ventilation strategy is associated with a decrease in postoperative pulmonary complications.^{9,10} When tidal volume is less than 7 ml/kg of ideal body weight, high PPV values remain accurate to predict fluid responsiveness, but low values are not informative.¹¹ The second strategy is based on titration and monitoring of the effects of volume

What We Already Know about This Topic

- Optimal fluid administration remains an important but elusive goal in the operating room
- Stroke volume maximization with fluid challenge is a potentially useful technique to optimize fluid management, although recommended fluid challenges may have some potential risks of fluid overload

What This Article Tells Us That Is New

- The authors provide a prospective trial demonstrating that a mini-fluid challenge of 100 ml can predict the hemodynamic effects of larger fluid boluses in neurosurgical patients
- The study has important implications to future fluid challenge algorithms and patient management to maximize hemodynamic stability and minimize the risk of fluid overload in the operating room

expansion. Several randomized control trials suggest that stroke volume maximization with fluid challenge decreases both the postoperative length of hospital stay and morbidity.^{2,3} The main algorithm used is based on the administration of 250 ml of crystalloid or colloid for more than 10 min.

This article is featured in "This Month in Anesthesiology," page 1A.

Submitted for publication August 2, 2016. Accepted for publication February 23, 2017. From the Department of Anesthesiology and Critical Care III, Bordeaux University Hospital, Bordeaux, France (M.B., H.d.C., R.L., G.B., M.G., M.S., K.N.-G.); Institut National de la Santé et de la Recherche Médicale, U1034, Biology of Cardiovascular Diseases, Pessac, France (M.B.); University of Bordeaux, Bordeaux, France (M.B., K.N.-G.); Biostatistics Unit, Délégation Recherche Clinique & Innovation, CHU de Clermont-Ferrand, Clermont-Ferrand, France (B.P.); and Institut National de la Santé et de la Recherche Médicale, U12-11, Laboratoire de Maladies Rares: Génétique et Métabolisme, Bordeaux, France (K.N.-G.).

Copyright © 2017, the American Society of Anesthesiologists, Inc. Wolters Kluwer Health, Inc. All Rights Reserved. Anesthesiology 2017; 127:450-6

Volume expansion is continued until the volume of ejection does not increase and another volume expansion is performed if the stroke volume decreases. This protocol is recommended by the National Institute for Clinical Excellence and by the French Society of Anesthesiologists.^{12,13} Although this algorithm is associated with good outcome, this method may result in repeated ineffective fluid boluses. During lengthy surgery, the repetition of ineffective fluid challenge should be avoided. Indeed, perioperative fluid overload and positive fluid balance are associated with poor outcome.^{4,5} One way to limit unnecessary fluid infusion is the mini-fluid challenge.

Muller *et al.*¹⁴ demonstrated in their intensive care unit (ICU) that the increase in stroke volume induced by rapid infusion of 100 ml colloid (mini-fluid challenge) is able to predict stroke volume increase induced by 500 ml. In other words, the plateauing of stroke volume after 100 ml might preclude the need for additional volume expansion and thus avoid administering the remaining 400 ml. More recently, Mallat *et al.*¹⁵ showed that the decrease in PPV or stroke volume variations after a mini-fluid of colloid predicted fluid responsiveness.

We hypothesized that changes in stroke volume index induced by rapid infusion of a small quantity of crystalloid could predict the effects of a larger amount of fluid in patients ventilated mechanically in the operating room. Therefore, the present study sought to evaluate the degree to which changes in stroke volume index (Δ SVI) induced by the rapid infusion of 50 and 100 ml crystalloid could predict the effects of administering 250 ml crystalloid.

Materials and Methods

Patients

This study obtained the approval of the institutional review board (Comité de Protection des Personnes Sud-Ouest et Outre Mer III, Bordeaux, France, No. DC2015/117), and oral informed consent was obtained from all of the patients (the institutional review board waived the need for written informed consent because the studied strategy did not change the current strategy of fluid administration). The inclusion of patients lasted for 1 yr, from July 2014 to July 2015. Inclusion criteria were as follows: patients older than 18 yr scheduled for neurosurgery, equipped with radial arterial catheter and cardiac output monitor, surgery in supine position, and the absence of arrhythmia. Volume expansion (250 ml saline 0.9%) was performed at the discretion of the attending physician.

Perioperative Management

Patients were monitored with noninvasive blood pressure, oxygen saturation measured by pulse oximetry, and electrocardiogram. Total IV anesthesia was used by target-controlled infusion of remifentanyl and propofol. Patients were mechanically ventilated using a volume-control mode with a tidal volume of 6 to 8 ml/kg of ideal body weight, respiratory rate was adjusted to maintain normocapnia, positive expiratory pressure was set between 3 and 6 cm H₂O, inspired oxygen

fraction was adjusted to maintain pulse oximetry above 95%, and inspiratory/expiratory ratio was 0.5.

Hemodynamic Monitoring

A radial arterial catheter was linked to a bedside monitor on one side and to a specific transducer (ProAQ[®]; Pulsion Medical System, Germany) for stroke volume index monitoring on the other side. The initial value of cardiac output was estimated with a proprietary algorithm performing an autocalibration. Cardiac output was then determined by pulse contour analysis. PPV was continuously displayed on the Pulsioflex (Pulsion Medical System, Germany) monitor.

Study Design

The design of the study is shown in figure 1. Hemodynamic measurements included heart rate; systolic, diastolic, mean, and pulse arterial pressure; stroke volume index; and PPV. Volume expansion consisted of an infusion of 250 ml saline 0.9% over 10 min. Sets of measurements were performed before volume expansion, 1 min after the infusion of 50 ml given over 1 min, 1 min after the infusion of another 50 ml (total = 100 ml) given over 1 min, and 1 min after the infusion of the remaining 150 ml (total = 250 ml) given over 5 min.

Statistical Analysis

In view of previous results (PPV area under the receiver operating characteristics curves of 0.51 in nonselected conditions),¹⁶ sample size estimation showed that at least 42 patients were necessary to highlight a difference of 0.25 between Δ SVI 100 and PPV areas under the receiver operating characteristics curves (two-tailed type I error at 5%, power equal to 80%, and ratio of sample sizes in negative/positive groups at 1/4).^{17,18} Positive fluid challenge was defined as an increase in stroke volume index of 10% or higher from baseline after an infusion of 250 ml.

Results were expressed as mean \pm SD if data were normally distributed or median (25 to 75% interquartile range) if not. Hemodynamic parameters were compared at baseline between positive and negative fluid challenges using the Mann–Whitney U test. The effects of volume expansion on hemodynamic parameters were studied using the Friedman nonparametric repeated measures comparisons, and *post hoc* analyses were performed using the Wilcoxon test with Bonferroni adjustment. To take into account the fact that several fluid challenges were performed in the same patient, random-effects models were performed to study between- and within-patient variability, as well as generalized linear mixed models (logit link function to dichotomous endpoint). The same statistical approach was used for repeated measures in the receiver operating characteristic curve and the gray zone.^{19,20} Receiver operating characteristic curves were generated for PPV, Δ SVI 50, and Δ SVI 100 by varying the discriminating threshold of each parameter, and areas under the receiver operating characteristics curves (95% CIs) were calculated and compared as proposed by DeLong *et al.*¹⁷ The

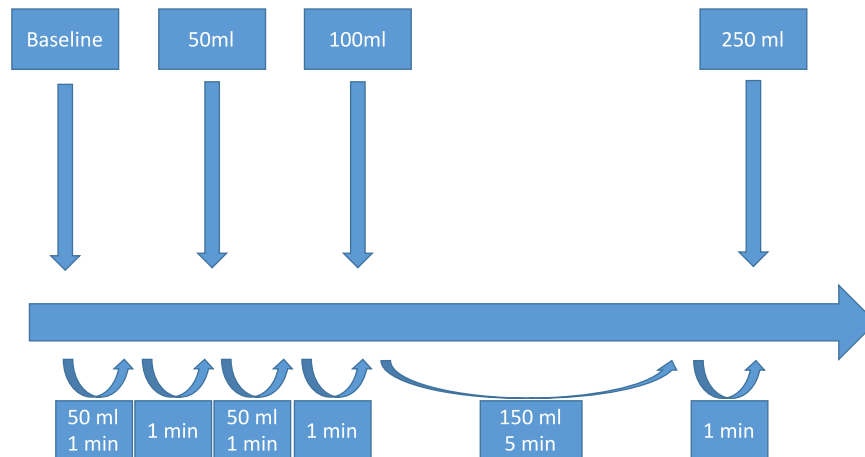


Fig. 1. Study design. Hemodynamic measurements included heart rate; systolic, diastolic, mean, and pulse arterial pressure; stroke volume index; and pulse pressure variations. Volume expansion consisted of an infusion of 250 ml saline 0.9% given over 10 min. Sets of measurements were performed before volume expansion, 1 min after the infusion of 50 ml given over 1 min, 1 min after the infusion of another 50 ml (total = 100 ml) given over 1 min, and 1 min after the infusion of the remaining 150 ml (total = 250 ml) given over 5 min.

best cutoff value was chosen so as to maximize the Youden index (sensitivity + specificity – 1). A *P* value less than 0.05 was considered to be statistically significant. Receiver operating characteristics curve methodology does not take into account the existence of an overlap between positive and negative fluid challenges. The gray zone methodology avoids the binary response proposed by the receiver operating characteristics curves and proposes a low cutoff value that excludes positive fluid challenge in 90% of patients, whereas a high cutoff value predicts positive fluid challenge in 90% of cases.^{21–23}

Estimation of the gray zone was based on two major steps. First, receiver operating characteristics curves were created by using a bootstrap methodology, which creates multiple samples (1,000) by randomly drawing instances, with replacement, from the original study population. So, this first step was useful to determine 95% CI of the best thresholds of the bootstrap population (1,000).²⁴ The second step was performed to define a threshold related to a sensitivity of 90% and another threshold related to a specificity of 90% using the 1,000 population. Finally, the larger gray zone obtained using these two steps was retained.

Statistical analysis was performed using Medcalc (software 11.6; Mariakerke, Belgium), R Development Core Team (<http://www.R-project.org>, version R 3.4.0, accessed January 2017), and NCSS 8 (NCSS, LLC, USA).

Results

Patient Characteristics

Eighty-eight volume expansions (positive fluid challenge = 28, negative fluid challenge = 60) were performed in 44 non-consecutive patients. The main characteristics of the patients are reported in table 1, and their hemodynamic variables are shown in table 2.

Hemodynamic Changes during Volume Expansion

Hemodynamic variables in positive fluid challenge and negative fluid challenge at different steps of volume expansion are shown in table 2. The evolution of stroke volume index in positive and negative fluid challenges at different steps of volume expansion are shown in figure 2.

Prediction of Positive Fluid Challenge

The intraclass correlation coefficient, estimated from random-effects generalized linear models used to predict the effect of volume expansion, was approximately 0 (intraclass correlation coefficient = 0.02), thereby describing a low patient effect and little impact on results.^{19,20,25} The ability

Table 1. Main Characteristics of Patients (n = 44)

Characteristics	
Age (yr)	57 ± 14
Sex, male/female (n)	18/26
Height (cm)	172 (160–178)
Weight (kg)	75 (64–82)
Ideal body weight (kg)	63 (52–73)
Tidal volume (ml)	422 (380–485)
Tidal volume (ml/kg of ideal body weight)	6.9 (6.5–7.2)
Respiratory rate (cycles/min)	14 (12–15)
Positive end expiratory pressure (cm H ₂ O)	5 (5–5)
F _{IO₂} (%)	50 (45–50)
Driving pressure (cm H ₂ O)	10 ± 3
Surgery (n)	
Cerebral tumor	21
Metastasis	17
Aneurysm	3
Cortectomy	3
No. volume expansions/patient	2 (1–3)
No. patients receiving 1/2/3/4 fluid challenges (n)	17/12/13/2

Values are mean ± SD, median (25th to 75th percentile), or number (n).

F_{IO₂} = inspired oxygen fraction.

Table 2. Hemodynamic Variables at Baseline and after 50, 100, and 250 ml Saline Infusion in Positive Fluid Challenges (n = 28) and Negative Fluid Challenges (n = 60)

	Baseline	50 ml	100 ml	250 ml	P Value
Heart rate (bpm)					
Positive fluid challenges	65 (60–70)	64 (60–68)*	64 (60–71)*	63 (59–69)*	< 0.00001
Negative fluid challenges	67 (59–76)	67 (56–75)*	66 (57–74)*	67 (56–73)*	< 0.0005
Mean arterial pressure (mmHg)					
Positive fluid challenges	69 (60–73)	68 (60–75)	69 (63–74)	71 (66–75)	< 0.05
Negative fluid challenges	65 (60–74)	67 (59–74)	67 (61–74)	67 (62–77)	> 0.05
Stroke volume index (ml/m ²)					
Positive fluid challenges	37 (29–40)	38 (32–42)*	41 (33–45)*	43 (35–47)*	< 0.00001
Negative fluid challenges	41 (35–45)	41 (36–47)*	42 (37–47)*	42 (37–47)*	< 0.00001
PPV (%)					
Positive fluid challenges	11 (8–14)	10 (8–13)*	9 (6–11)*	7 (5–9)*	< 0.00001
Negative fluid challenges	9 (7–11)†	8 (6–10)*†	8 (6–10)*	7 (6–9)*	< 0.00001

Values are median (25th to 75th percentile). Positive fluid challenges were defined as an increase in stroke volume index by 10% or higher after 250-ml intra-vascular volume expansion. Baseline was before volume expansion, 50 ml was after 50 ml saline infusion, 100 ml was after 100 ml saline infusion, and 250 ml was after 250 ml saline infusion. P value shows multiple comparisons among baseline, 50 ml, 100 ml, and 250 ml using Friedman test for repeated measures.

* $P < 0.0125$ versus T0 using Wilcoxon test with Bonferroni adjustment. † $P < 0.05$ between positive and negative fluid challenges (comparison not performed for stroke volume index).

Bpm = beats per minute; PPV = pulse pressure variation.

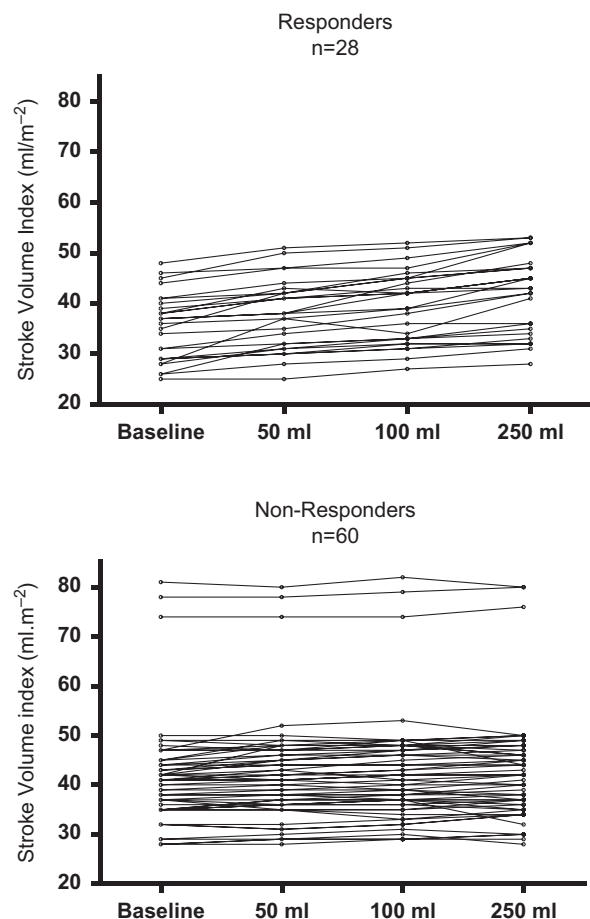


Fig. 2. Individual values of stroke volume index (in milliliters per meter squared) at baseline and after administration of 50, 100, and 250 ml saline 0.9% in positive and negative fluid challenges. Positive fluid challenge was defined as an increase in stroke volume index of 10% or greater from baseline after an infusion of 250 ml.

of Δ SVI 50, Δ SVI 100, and PPV to predict the effect of volume expansion is shown in table 3 and figure 3. Areas under the receiver operating characteristics comparison demonstrated the superiority of Δ SVI 100 over Δ SVI 50 ($P < 0.005$) and over PPV ($P < 0.0001$) and the superiority of Δ SVI 50 over PPV ($P = 0.01$).

Mini-fluid Challenge for Limiting Unnecessary Fluid Infusion: An a Posteriori Analysis

If volume expansion was stopped when Δ SVI 100 was not above 4% (low value of the gray zone), it would have avoided 150 ml inefficient fluid challenge in 44 (73%) of 60 with negative fluid challenge.

Discussion

This study demonstrates that, in neurosurgical patients ventilated with low tidal volume in the operating room, (1) the performance of Δ SVI 100 is better than that of Δ SVI 50 and PPV to predict the effect of volume expansion; (2) the probability of a positive response to volume expansion is greater than 90% when Δ SVI 100 is greater than 7%; (3) the probability of a negative response to volume expansion is greater than 90% when Δ SVI 100 is less than 4%; and (4) 19% of patients are in the gray zone (Δ SVI 100 between 4 and 7%).

The main interest of mini-fluid is to limit unnecessary fluid infusion. Interestingly, our study suggested that volume expansion would be stopped after 100 ml in 73% of negative fluid challenges. Results of Δ SVI 50 are disappointing because best threshold value (2%) and lower value of the gray zone (0%) are very small and thus not clinically relevant. Furthermore, almost half of the patients (47%) are in the gray zone.

Recently, MacDonald *et al.*²⁶ published a substudy of the OPTIMISE Trial. This article reported 556 fluid challenges

Table 3. Ability to Predict Increase in Stroke Volume of 10% or Greater after Infusion of 250 ml Saline over 10 min

Index	Best Threshold, %	Gray Zone, range, %	Patients Whose Measurements Were in the Gray Zone, %	AUROC (95% CI)	Sensitivity (95% CI), %	Specificity (95% CI), %	Youden Index J
Δ SVI 50	> 2	0–7	47	0.83 (0.75–0.92)	89 (72–98)	67 (53–78)	0.56
Δ SVI 100	> 6	4–7	19	0.95 (0.90–0.99)	93 (77–99)	85 (73–93)	0.78
PPV	> 10	6–14	75	0.65 (0.53–0.78)	54 (34–73)	68 (55–80)	0.22

Best threshold value was determined using the Youden index. Data show the specificity (95% CI).

AUROC = area under receiver operating characteristics curves; Δ SVI 50 = changes in stroke volume index induced by rapid 50-ml volume expansion; Δ SVI 100 = changes in stroke volume index induced by rapid 100-ml volume expansion; PPV = pulse pressure variation; Youden index J = sensitivity + specificity – 1.

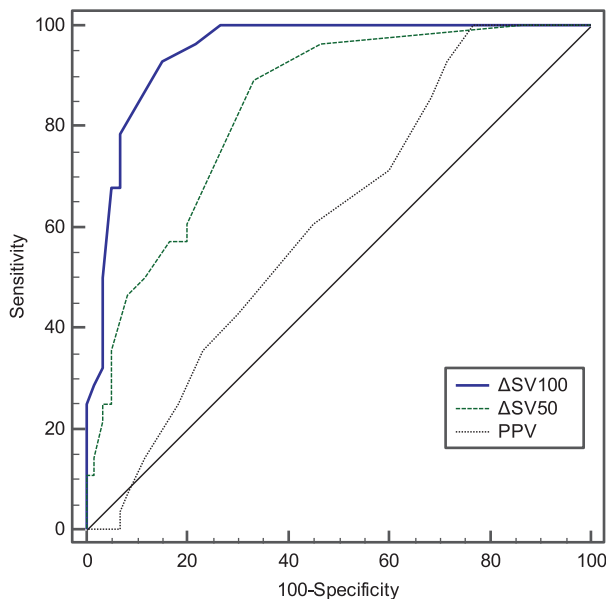


Fig. 3. Receiver operating characteristics curves generated for Δ SVI 50 (changes in stroke volume index [SVI] induced by a rapid 50 ml volume expansion), Δ SVI 100 (changes in stroke volume index induced by a rapid 100 ml volume expansion), and pulse pressure variations (PPV) showing the ability to predict the effect of a 250 ml volume expansion given over 10 min. Positive fluid challenge was defined as an increase in stroke volume index of 10% or greater from baseline after an infusion of 250 ml.

in 100 patients. Only 159 fluid challenges (28.6%) were associated with increased stroke volume. Our results are close to theirs (32% of positive fluid challenges). The mini-fluid approach in the operating room makes sense because several fluid challenges are performed per patient. Avoiding 150 ml per patient has little impact on fluid balance, but, as demonstrated by this recent study,²⁶ several fluid challenges are performed per patient during surgery. In this way, the mini-fluid approach may impact fluid balance and significantly avoid unnecessary fluid administration.

Three studies evaluated the performance of mini-fluid challenge in critically ill patients. Muller *et al.*¹⁴ investigated 39 critically ill ventilated patients with acute circulatory failure. They showed that an increase of 10% or higher in aortic blood flow (measured using echocardiography) after rapid infusion (1 min) of a mini-fluid challenge (100 ml

hydroxyethyl starch) could predict the effects of a 500-ml infusion. Wu *et al.*²⁷ demonstrated in 55 critically ill patients that the increase in aortic blood flow (measured using echocardiography) after an ultra-rapid (10-s) micro-fluid challenge (50 ml crystalloid) was able to predict the effects of 500 ml. More recently, Mallat *et al.*¹⁵ studied 49 critically ill patients and showed that the increase in stroke volume (measured using pulse contour) after a rapid infusion of 100 ml colloid accurately predicted fluid responsiveness but with a large gray zone.

Our study differs on many points with the abovementioned studies. First, it was performed in the operating room and not in an ICU, so the goals, therapeutics, and monitoring were different. Second, fluid challenge was not performed in acute circulatory failure patients but was given to maximize cardiac output and to bring the patient's heart to the beginning of the flat portion of the Frank–Starling curve. Third, volume expansions were performed with a smaller quantity of fluid (250 ml) than in ICU studies (recommendations are different between ICU and operating room),^{13,28} and only crystalloids were used. Finally, the response to fluid challenge was defined as an increase in stroke volume greater than 10% from baseline.

Dynamic indices are known to predict fluid responsiveness accurately in precise conditions.²⁹ The main limitation in the operating room is the use of low tidal volume.⁸ On one hand, several studies demonstrated that, when compared with a standard strategy (using tidal volume of 10 to 12 ml/kg of ideal body weight), a protective ventilation strategy (using tidal volume of 6 to 8 ml/kg of ideal body weight) is associated with a decrease in pulmonary postoperative complications, so the interest of these indices is limited.^{9,10} Our study confirms the low ability of PPV in these conditions and the large gray zone.^{21,30} On the other hand, no published study demonstrated the superiority of tidal volume of 6 to 8 ml/kg of ideal body weight compared with 8 to 10 ml/kg. Thus, the use of dynamic parameters (which are easier to use and less expensive than cardiac output monitoring) may still be interesting in the future.

Colloids, and particularly hydroxyethyl starch solutions, are extensively used during goal-directed fluid optimization strategies in surgical patients.^{2,3} However, several randomized control trials undertaken in ICUs suggest that hydroxyethyl starch may compromise renal function and outcome.^{31,32}

On the other hand, the administration of a large quantity of saline 0.9% may induce hyperchloremic metabolic acidosis and acute kidney injury.^{33,34} Several studies suggest that colloid and crystalloid are not interchangeable in terms of volume expansion and that greater fluid volumes are necessary with crystalloids than with colloids.^{35–37} We exclusively used crystalloid in the present study and found that the increase in SVI after a bolus of 50 ml saline seemed able to predict positive fluid challenge but that the cutoff (2%) did not seem clinically relevant. We therefore hypothesize that the increase in SVI induced by a bolus of 50 ml colloid would be greater and clinically relevant so other studies investigating this issue are needed.

This study has some limitations. First, cardiac output was monitored by using pulse contour analysis without external calibration. This technology may be wanting in the event of vasoplegia and/or large changes in systemic vascular resistance, but it accurately estimates changes in cardiac output induced by volume expansion.^{38–40} We did not calculate the reproducibility and the least-significant change of the SVI measurement determined by Pulsioflex monitor. However, using the same pulse pressure analysis algorithm, Monnet *et al.*⁴¹ demonstrated that a 5% cardiac index increase during an occlusion test predicted fluid responsiveness. This result suggests that this algorithm is able to detect 5% changes in cardiac index and thus in stroke volume. Second, patients with cardiac dysfunction and/or arrhythmia were not included, so the findings cannot be extrapolated. Finally, the patients were in the supine position and were scheduled for neurosurgery, so extrapolation to patients positioned otherwise and in other types of surgery is not possible.

Conclusions

The rapid administration of 100 ml crystalloid can predict the effects of administering 250 ml crystalloid in mechanically ventilated patients undergoing neurosurgery. This strategy would permit a limitation of fluid administration during three quarters of negative fluid challenges.

Research Support

Support was provided solely from institutional and/or departmental sources.

Competing Interests

Dr. Biais received honoraria from Edwards Lifesciences, Irvine, California, and Pulsion Medical System, Munich, Germany, for lectures. The other authors declare no competing interests.

Correspondence

Address correspondence to Dr. Biais: Department of Anesthesiology and Critical Care III, Hôpital Pellegrin, CHU de Bordeaux, F-33076 Bordeaux Cedex, France. matthieu.biais@chu-bordeaux.fr. This article may be accessed for personal use at no charge through the Journal Web site, www.anesthesiology.org.

References

1. Michard F, Biais M: Rational fluid management: Dissecting facts from fiction. *Br J Anaesth* 2012; 108:369–71
2. Hamilton MA, Cecconi M, Rhodes A: A systematic review and meta-analysis on the use of preemptive hemodynamic intervention to improve postoperative outcomes in moderate and high-risk surgical patients. *Anesth Analg* 2011; 112:1392–402
3. Pearse RM, Harrison DA, MacDonald N, Gillies MA, Blunt M, Ackland G, Grocott MP, Ahern A, Griggs K, Scott R, Hinds C, Rowan K; OPTIMISE Study Group: Effect of a perioperative, cardiac output-guided hemodynamic therapy algorithm on outcomes following major gastrointestinal surgery: A randomized clinical trial and systematic review. *JAMA* 2014; 311:2181–90
4. Thacker JK, Mountford WK, Ernst FR, Krukas MR, Mythen MM: Perioperative fluid utilization variability and association with outcomes: Considerations for enhanced recovery efforts in sample US surgical populations. *Ann Surg* 2016; 263:502–10
5. Bellamy MC: Wet, dry or something else? *Br J Anaesth* 2006; 97:755–7
6. Biais M, Ouattara A, Janvier G, Sztark F: Case scenario: Respiratory variations in arterial pressure for guiding fluid management in mechanically ventilated patients. *ANESTHESIOLOGY* 2012; 116:1354–61
7. Benes J, Giglio M, Brienza N, Michard F: The effects of goal-directed fluid therapy based on dynamic parameters on post-surgical outcome: A meta-analysis of randomized controlled trials. *Crit Care* 2014; 18:584
8. Cannesson M, Pestel G, Ricks C, Hoeft A, Perel A: Hemodynamic monitoring and management in patients undergoing high risk surgery: A survey among North American and European anesthesiologists. *Crit Care* 2011; 15:R197
9. Futier E, Constantin JM, Paugam-Burtz C, Pascal J, Eurin M, Neuschwander A, Marret E, Beaussier M, Gutton C, Lefrant JY, Allaouchiche B, Verzilli D, Leone M, De Jong A, Bazin JE, Pereira B, Jaber S; IMPROVE Study Group: A trial of intraoperative low-tidal-volume ventilation in abdominal surgery. *N Engl J Med* 2013; 369:428–37
10. Prove Network Investigators for the Clinical Trial Network of the European Society of Anaesthesiology, Hemmes SN, Gama de Abreu M, Pelosi P, Schultz MJ: High versus low positive end-expiratory pressure during general anaesthesia for open abdominal surgery (PROVHILO trial): A multicentre randomised controlled trial. *Lancet* 2014; 384: 495–503
11. 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; 31:517–23
12. Vallet B, Blanloeil Y, Cholley B, Orliaguet G, Pierre S, Tavernier B; Société Française d'Anesthésie et de Réanimation: Guidelines for perioperative haemodynamic optimization. *Ann Fr Anesth Reanim* 2013; 32:e151–8
13. National Institute for Health and Clinical Excellence. CardioQ-ODM oesophageal doppler monitor. Available at: <http://www.nice.org.uk/nicemedia/live/13312/52624.pdf>. Accessed May 5, 2014
14. Muller L, Toumi M, Bousquet PJ, Riu-Poulenc B, Louart G, Candela D, Zoric L, Suehs C, de La Coussaye JE, Molinari N, Lefrant JY; AzuRéa Group: An increase in aortic blood flow after an infusion of 100 ml colloid over 1 minute can predict fluid responsiveness: The mini-fluid challenge study. *ANESTHESIOLOGY* 2011; 115:541–7
15. Mallat J, Meddour M, Durville E, Lemyze M, Pepy F, Temime J, Vangrunderbeeck N, Tronchon L, Thevenin D, Tavernier B: Decrease in pulse pressure and stroke volume variations after mini-fluid challenge accurately predicts fluid responsiveness. *Br J Anaesth* 2015; 115:449–56

16. Lansdorp B, Lemson J, van Putten MJ, de Keijzer A, van der Hoeven JG, Pickkers P: Dynamic indices do not predict volume responsiveness in routine clinical practice. *Br J Anaesth* 2012; 108:395–401
17. DeLong ER, DeLong DM, Clarke-Pearson DL: Comparing the areas under two or more correlated receiver operating characteristic curves: A nonparametric approach. *Biometrics* 1988; 44:837–45
18. Hanley JA, McNeil BJ: The meaning and use of the area under a receiver operating characteristic (ROC) curve. *Radiology* 1982; 143:29–36
19. Liu H, Li G, Cumberland W, Wu T: Testing statistical significance of the area under a receiving operating characteristics curve for repeated measures design with bootstrapping. *J Data Sci* 2005; 3: 257–78
20. Liu H, Wu T: Estimating the area under a receiver operating characteristic (ROC) curve for repeated measures design. *J Stat Softw* 2003; 12: 1–18
21. Cannesson M, Le Manach Y, Hofer CK, Goarin JP, Lehot JJ, Vallet B, Tavernier B: Assessing the diagnostic accuracy of pulse pressure variations for the prediction of fluid responsiveness: A “gray zone” approach. *ANESTHESIOLOGY* 2011; 115:231–41
22. Coste J, Jourdain P, Pouchot J: A gray zone assigned to inconclusive results of quantitative diagnostic tests: Application to the use of brain natriuretic peptide for diagnosis of heart failure in acute dyspneic patients. *Clin Chem* 2006; 52:2229–35
23. Ray P, Le Manach Y, Riou B, Houle TT: Statistical evaluation of a biomarker. *ANESTHESIOLOGY* 2010; 112:1023–40
24. Carpenter J, Bithell J: Bootstrap confidence intervals: When, which, what? A practical guide for medical statisticians. *Stat Med* 2000; 19:1141–64
25. Bataille B, Rao G, Cocquet P, Mora M, Masson B, Ginot J, Silva S, Moussot PE: Accuracy of ultrasound B-lines score and E/Ea ratio to estimate extravascular lung water and its variations in patients with acute respiratory distress syndrome. *J Clin Monit Comput* 2015; 29:169–76
26. MacDonald N, Ahmad T, Mohr O, Kirk-Bayley J, Moppett I, Hinds CJ, Pearse RM: Dynamic preload markers to predict fluid responsiveness during and after major gastrointestinal surgery: An observational substudy of the OPTIMISE trial. *Br J Anaesth* 2015; 114:598–604
27. Wu Y, Zhou S, Zhou Z, Liu B: A 10-second fluid challenge guided by transthoracic echocardiography can predict fluid responsiveness. *Crit Care* 2014; 18:R108
28. Dellinger RP, Levy MM, Rhodes A, Annane D, Gerlach H, Opal SM, Sevransky JE, Sprung CL, Douglas IS, Jaeschke R, Osborn TM, Nunnally ME, Townsend SR, Reinhart K, Kleinpell RM, Angus DC, Deutschman CS, Machado FR, Rubenfeld GD, Webb SA, Beale RJ, Vincent JL, Moreno R: Surviving Sepsis Campaign Guidelines Committee including the Pediatric Subgroup: Surviving sepsis campaign: International guidelines for management of severe sepsis and septic shock: 2012. *Crit Care Med* 2013; 41:580–637
29. 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; 37:2642–7
30. Biais M, Ehrmann S, Mari A, Conte B, Mahjoub Y, Desebbe O, Pottecher J, Lakhal K, Benzekri-Lefevre D, Molinari N, Boulain T, Lefrant JY, Muller L; AzuRea Group: Clinical relevance of pulse pressure variations for predicting fluid responsiveness in mechanically ventilated intensive care unit patients: The grey zone approach. *Crit Care* 2014; 18:587
31. Perner A, Haase N, Guttormsen AB, Tenhunen J, Klemenzson G, Åneman A, Madsen KR, Møller MH, Elkjær JM, Poulsen LM, Bendtsen A, Winding R, Steensen M, Berezowicz P, Søe-Jensen P, Bestle M, Strand K, Wiis J, White JO, Thornberg KJ, Quist L, Nielsen J, Andersen LH, Holst LB, Thormar K, Kjældgaard AL, Fabritius ML, Mondrup F, Pott FC, Møller TP, Winkel P, Wetterslev J; 6S Trial Group; Scandinavian Critical Care Trials Group: Hydroxyethyl starch 130/0.42 *versus* Ringer's acetate in severe sepsis. *N Engl J Med* 2012; 367:124–34
32. Myburgh JA, Finfer S, Bellomo R, Billot L, Cass A, Gattas D, Glass P, Lipman J, Liu B, McArthur C, McGuinness S, Rajbhandari D, Taylor CB, Webb SA; CHEST Investigators; Australian and New Zealand Intensive Care Society Clinical Trials Group: Hydroxyethyl starch or saline for fluid resuscitation in intensive care. *N Engl J Med* 2012; 367:1901–11
33. Reid F, Lobo DN, Williams RN, Rowlands BJ, Allison SP: (Ab) normal saline and physiological Hartmann's solution: A randomized double-blind crossover study. *Clin Sci (Lond)* 2003; 104:17–24
34. Yunus NM, Bellomo R, Hegarty C, Story D, Ho L, Bailey M: Association between a chloride-liberal vs chloride-restrictive intravenous fluid administration strategy and kidney injury in critically ill adults. *JAMA* 2012; 308:1566–72
35. Orbegozo Cortés D, Gamarano Barros T, Njimi H, Vincent JL: Crystalloids *versus* colloids: Exploring differences in fluid requirements by systematic review and meta-regression. *Anesth Analg* 2015; 120:389–402
36. Trof RJ, Sukul SP, Twisk JW, Girbes AR, Groeneveld AB: Greater cardiac response of colloid than saline fluid loading in septic and non-septic critically ill patients with clinical hypovolaemia. *Intensive Care Med* 2010; 36:697–701
37. Verheij J, van Lingen A, Beishuizen A, Christiaans HM, de Jong JR, Girbes AR, Wisselink W, Rauwerda JA, Huybregts MA, Groeneveld AB: Cardiac response is greater for colloid than saline fluid loading after cardiac or vascular surgery. *Intensive Care Med* 2006; 32:1030–8
38. Monnet X, Vaquer S, Anguel N, Jozwiak M, Cipriani F, Richard C, Teboul JL: Comparison of pulse contour analysis by Pulsioflex and Vigileo to measure and track changes of cardiac output in critically ill patients. *Br J Anaesth* 2015; 114:235–43
39. Monnet X, Anguel N, Naudin B, Jabot J, Richard C, Teboul JL: Arterial pressure-based cardiac output in septic patients: Different accuracy of pulse contour and uncalibrated pressure waveform devices. *Crit Care* 2010; 14:R109
40. Reubrecht V, Dingemans G, Gache A, Langeron O, Faillie JL, Gardès G, Bengler C, Lefrant JY, Muller L: Reliability of the pulse contour analysis for cardiac output measurement for assessing the fluid responsiveness [in French]. *Ann Fr Anesth Reanim* 2011; 30:877–82
41. Monnet X, Osman D, Ridet C, Lamia B, Richard C, Teboul JL: Predicting volume responsiveness by using the end-expiratory occlusion in mechanically ventilated intensive care unit patients. *Crit Care Med* 2009; 37:951–6