Can Changes in Arterial Pressure be Used to Detect Changes in Cardiac Output during Volume Expansion in the Perioperative Period?

Yannick Le Manach, M.D., Ph.D.,* Christoph K. Hofer, M.D., Ph.D.,†
Jean-Jacques Lehot, M.D., Ph.D.,‡ Benoît Vallet, M.D., Ph.D.,§ Jean-Pierre Goarin, M.D.,‖
Benoît Tavernier, M.D., Ph.D.,§ Maxime Cannesson, M.D., Ph.D.#

ABSTRACT

Background: Cardiac output (CO) is rarely monitored during surgery, and arterial pressure remains the only hemodynamic parameter for assessing the effects of volume expansion (VE). However, whether VE-induced changes in arterial pressure accurately reflect changes in CO has not been demonstrated. The authors studied the ability of VE-induced changes in arterial pressure and in pulse pressure variation to detect changes in CO induced by VE in the perioperative period.

* Associate Professor, ‖ Staff Anesthesiologist, Department of Anesthesiology and Critical Care Medicine, Centre Hospitalier Universitaire Pitié-Salpêtrière, Paris, France. † Associate Professor, Institute of Anesthesiology and Intensive Care Medicine, Triemli City Hospital, Zurich, Switzerland. ‡ Professor, Department of Anesthesiology and Critical Care, Hopital Louis Pradel, Lyon, France. § Professor, Department of Anesthesiology and Critical Care Medicine, Centre Hospitalier Universitaire de Lille, Lille, France. # Associate Professor, Department of Anesthesiology and Perioperative Care, School of Medicine, University of California, Irvine, California.

Address correspondence to Dr. Cannesson: Department of Anesthesiology and Perioperative Care, University of California, Irvine, 333 City Boulevard West Side, Orange, California 92868–3301. maxime_cannesson@hotmail.com.
Information on purchasing reprints may be found at www.anesthesiology.org or on the masthead page at the beginning of this issue. ANESTHESIOLOGY's articles are made freely accessible to all readers, for personal use only, 6 months from the cover date of the issue.

What We Already Know about This Topic

- Despite evidence showing that cardiac output optimization improves clinical outcome and decreases the cost of high-risk surgery, a recent survey conducted among American Society of Anesthesiolgists and European Society of Anaesthesiology members showed that only one third of anesthesiologists monitor cardiac output
- This study compared the ability of volume expansion–induced changes in arterial pressure and in pulse pressure variation to detect changes in cardiac output using a gray zone approach

What This Article Tells Us That Is New

- Only changes in pulse pressure variation accurately detect volume expansion–induced changes in cardiac output

Methods: The authors studied 402 patients in four centers. Hemodynamic variables were recorded before and after VE. Response to VE was defined as more than 15% increase in CO. The ability of VE-induced changes in arterial pressure to detect changes in CO was assessed using a gray zone approach.

Results: VE increased CO of more than 15% in 205 patients (51%). Areas under the receiver operating characteristic curves for VE-induced changes in systolic, diastolic, means, and pulse pressure ranged between 0.64 and 0.70, and sensitivity and specificity ranged between 52 and 79%. For these four arterial pressure–derived parameters, large gray zones were found, and more than 60% of the patients lay within this inconclusive zone. A VE-induced decrease in pulse pressure variation of 3% or more allowed detecting a fluid-induced increase in CO of more than 15% with a sensitivity of 90% and a specificity of 77% and a gray zone between 2.2 and 4.7% decrease in pulse pressure variation including 14% of the patients.

◆ This article is accompanied by an Editorial View. Please see: Vincent J-L, Fagnoul D: Do we need to monitor cardiac output during major surgery? ANESTHESIOLOGY 2012; 117:1151–2.

Conclusion: Only changes in pulse pressure variation accurately detect VE-induced changes in CO and have a potential clinical applicability.

INTRAOPERATIVE fluid optimization based on cardiac output (CO) maximization has the ability to improve postoperative outcome and to decrease cost of high-risk noncardiac surgery.[1–6] The studies demonstrating this improvement rely on intraoperative oxygen delivery and CO monitoring using either invasive (such as pulse contour analysis devices)[7,8] or noninvasive devices (esophageal Doppler).[1–4] However, despite evidence showing that CO optimization improves outcome and decreases the cost of high-risk surgery, a recent survey conducted among American Society of Anesthesiologists and European Society of Anaesthesiology members showed that only one third of anesthesiologists monitor CO in this setting.[9] As a matter of fact, most anesthesiologists do not monitor CO during high-risk surgery and still rely on arterial pressure monitoring alone to conduct hemodynamic optimization and make clinical decisions regarding fluid management.[9]

Interestingly, recent studies have suggested that volume expansion (VE)–induced changes in arterial pressure (especially mean arterial pressure [MAP] and pulse pressure [PP]) may reflect changes in CO in septic patients.[10,11] This hypothesis is of major importance because, if proven true, this would suggest that arterial pressure could be used to conduct CO optimization during high-risk surgery. This would be an inexpensive and universally available way to achieve the same goal. However, these monocentric studies were performed in the intensive care unit, in limited numbers of septic patients, used linear regression and receiver operating characteristic (ROC) curve analysis to assess this hypothesis,[10,11] and their results cannot be extrapolated to the perioperative setting. Moreover, some studies have suggested that VE-induced changes in pulse pressure variation (dPPV) are well related to changes in CO induced by VE. However, the ability of dPPV to detect changes in CO has never been tested, although it could be an alternative way to detect fluid responders.

By using a gray zone approach, we have recently demonstrated that PPV is the best predictor of fluid responsiveness in the perioperative setting[12] (*i.e.*, that PPV predicts the effects of VE before VE is performed). However, after VE has been administered, it is essential to validate whether CO has increased or not, even in the absence of a CO monitoring system. To date, there is no clinical study evaluating the ability of changes in arterial pressure or in PPV to reflect VE-induced changes in CO in the perioperative setting. In other words, although it has been demonstrated that PPV can be used as a screening tool (to predict fluid responsiveness), it is not clear whether dPPV can be used as a diagnostic tool (to detect fluid responsiveness after fluid administration).

Consequently, the aims of the current study were (1) to investigate the relationship between VE-induced changes in arterial pressure–derived parameters (including VE-induced changes in PPV) and in CO in the perioperative setting; and (2) to investigate the ability of VE-induced changes in arterial pressure–derived parameters to reflect the effects of VE on CO using the recently described gray zone approach.[12,13]

Materials and Methods

This study is a subanalysis of a previously published study evaluating the ability of PPV to predict fluid responsiveness using a gray zone approach.[12] Institutional review board (Comité de Protection des Personnes Hospices Civils de Lyon, Lyon, France; Comité de Protection des Personnes Paris-Ile de France, France; Comité de Protection des Personnes Nord Ouest, Lille, France; and Institutional review board Triemli City Hospital, Zurich, Switzerland) approvals were obtained. Patients were included either as part of clinical trials (in this case, written and informed consent were obtained) or as part of routine clinical care (in this case, because no randomization and only routine care was performed, informed consent was waived). Data were collected prospectively (clinical trials) or retrospectively (routine clinical care).

Data Collection

Four European institutions (Hôpital Louis Pradel, Lyon, France; Hôpital La Pitié-Salpêtrière, Paris, France; Triemli City Hospital Zurich, Switzerland; and Centre Hospitalier Universitaire, Lille, France) participated in this study. We first defined preload responsiveness evaluation as an intravenous volume load of 500 ml colloid solution given over 10–20 min, immediately preceded and followed (2–5 min later) by hemodynamic measurements performed with the aim of measuring the change in CO induced by VE. Each investigator collected every sequence of hemodynamic evaluation, which was prospectively recorded and available in his/her own database, provided that (1) the patient was an adult, with no history of arrhythmia, right ventricular failure, valvular heart disease, or intracardiac shunt; (2) he/she was under general anesthesia, muscle paralysis, and mechanical ventilation in the controlled volume mode (muscle relaxant was used to avoid spontaneous breathing); (3) measurements and volume loading were performed in the operative room or in the early postoperative period, in closed-chest condition; and (4) hemodynamic and ventilatory data chosen for analysis in the current study had been obtained in predefined conditions as described in the Data acquisition and experimental protocol section. When more than one sequence of preload responsiveness evaluation was available for a given patient, only the first fluid challenge per patient was retained for analysis.

Data Acquisition and Experimental Protocol

All patients had a 3- or 5-French catheter inserted in radial or femoral artery for arterial blood pressure monitoring. Pressure transducers were leveled at the mid-axillary line and fixed to keep the transducer at the atrial level all along the study protocol. All transducers were zeroed to atmospheric

pressure. CO was measured in all patients (1) by thermo-dilution *via* a pulmonary artery catheter (pulmonary artery catheter, Swan Ganz catheter, 7.5 French; Edwards, Life-science, Irvine, CA), using the average of five successive measurements obtained by injection of 10 ml of dextrose at room temperature randomly during respiratory cycle; or (2) by the pulse contour method using a 4-French thermistor-tipped arterial catheter (Pulsiocath thermodilution catheter; Pulsion Medical System, Munchen, Germany) inserted into the left femoral artery and connected to a standalone PiC-COplus or PiCCO$_2$ monitor (Pulsion Medical Systems). In that case, continuous stroke volume measurement was initiated after initial calibration of the system by three injections of 20 ml ice-cold normal saline into the central venous catheter (transpulmonary thermodilution); or (3) *via* trans-esophageal echocardiography: All echo-Doppler data were recorded (Vivid Q; GE Healthcare®, Milwaukee, WI) by trained observers and analyzed offline by another investigator (Dr. Goarin), who was not aware of the characteristics of the patients; or (4) esophageal Doppler (Hemosonic 100; Arrow, Reading, PA) allowing measurements of aortic diameter and aortic blood flow, adjusted to obtain the best aortic blood velocity signal and not moved until the end of the fluid challenge, as previously reported.[14]

The following variables were collected in all patients before and after VE: Heart rate, systolic, diastolic, and MAP (systolic arterial pressure [SAP], diastolic arterial pressure [DAP], and MAP, respectively), (defined as SAP – DAP) (PP), and CO. PPV was also recorded before and after VE as described in the previously published study from this group of patients.[12]

All patients were studied after a 2- to 3-min period of hemodynamic stability with no changes in anesthetic protocol or ventilator settings and no VE. Baseline hemodynamic measurements were obtained and then followed by an intravenous VE consisting of 500 ml of colloid solution (hetastarch 6% or modified fluid gelatin), given over 10–20 min. Hemodynamic measurements were performed within 2–5 min after VE.

Changes in arterial pressure induced by VE were expressed as relative changes (arterial pressure after VE – arterial pressure before VE)/arterial pressure before VE. Only changes in PPV were expressed as PPV after VE – PPV before VE.

These changes were expressed for %SAP, %DAP, and %MAP and for %PP and PPV (dPPV).

Endpoint Definition

A positive fluid response was usually defined by an increase in CO of more than or equal to 15%.[15] Consequently, patients were divided into two groups according to the percent change in CO after VE: Responders were defined as patients demonstrating an increase in CO more than 15% after VE and nonresponders as patients whose CO changed

less than 15%. An increase in CO of 10% was also considered as secondary endpoint to be comparable with studies that retained it as a threshold for a positive fluid response, such as the study by Pierrakos *et al.*[11]

Statistical Analysis

All data are presented as mean ± SD. Changes in hemodynamic parameters induced by VE were assessed using paired or unpaired Student *t* test. Spearman rank method was used to test correlation. ROC curves were generated for SAP, DAP, MAP, and PP before VE and for their variations %SAP, %DAP, %MAP, %PP, and dPPV. The area under the ROC curves for each parameter was compared to null hypothesis = 0.5 using a paired nonparametric technique.[13] ROC curves were obtained by averaging 1,000 populations bootstrapped from the original study population, as previously described.[13] This method limits the impact of outliers and allows the provision of more robust presentations. CIs of the average ROC curve were depicted using box plots. Presented area under the ROC curves and best threshold were the average of the 1,000 populations, as previously reported.[12]

Threshold and Gray Zone Determination

The best threshold of an ROC curve was chosen as that which maximizes the Youden index (sensitivity + specificity – 1), as previously justified.[16] The "gray zone" determination was determined using a two-step procedure. The first step consisted of the determination of the best threshold in each of the 1,000 bootstrapped populations for each parameter. The 95% CI of the best thresholds was defined by the observed distributions of the thresholds in the 1,000 populations. This 95% CI is linked to the study population characteristics (mainly sample size and frequency of the primary endpoint). The second step was conducted to determine the value for which the variables of interest did not provide conclusive information. It corresponds to a range of values for which formal conclusions could not be obtained. We defined inconclusive responses for values presenting with either sensitivity lower than 90% or specificity lower than 90% (diagnosis tolerance of 10%). Two-curve (sensitivity, specificity) representation was provided to illustrate this second step.

The gray zone was then defined as the values of the parameters that did not allow having 10% of diagnosis tolerance. Nevertheless, if the characteristics of the study population produce a 95% CI of the best thresholds larger than the inconclusive zone, the values obtained during the first step were retained as gray zone.

This two-step procedure allows us to provide robust results not impacted by potential outliers. This approach is peculiarly interesting when small samples (or rare endpoints) are considered.

All *P* values were two-sided, and a *P* value less than 0.05 was considered significant. MedCalc 8.0.2.0 (MedCalc Software, Mariakerke, Belgium) and R 2.14** software were used for statistical analyses.

** www.cran.r-project.org. Accessed February 2, 2012.

Table 1. Demographic Data According to the Center

	Lille	Lyon	Paris	Zurich
No. patients, n	60	80	183	79
Age, yr	60 ± 13	66 ± 10	67 ± 7	66 ± 9
Height, cm	166 ± 3	170 ± 9	173 ± 8	172 ± 8
Weight, kg	70 ± 14	76 ± 15	77 ± 11	82 ± 12
Sex (F/M)	20/40	19/61	37/146	25/54
Type of surgery				
Cardiac, n	0	80	0	79
Digestive, n	49	0	0	0
Vascular, n	11	0	183	0
Cardiac output measurement				
Thermodilution, S.G.	46	80	0	0
Pulse contour, Picco	0	0	45	79
Ultrasound	14	0	138	0

Data are presented as mean ± SD.

S.G. = Swan Ganz.

Results

Demographic data are presented in the following section and reproduce the data from the original study published previously[12]:

Of the 413 patients included in the study, 11 patients (2.6%) were excluded because arterial pressure data set was not complete after VE. Consequently, we studied 402 patients (Hôpital La Pitié-Salpêtrière, Paris: 183 patients; Hôpital Louis Pradel, Lyon: 80 patients; Triemli City Hospital, Zurich, Switzerland: 79 patients; and Centre Hospitalier Universitaire de Lille, France: 60 patients) (table 1). Type of surgery was open abdominal aorta surgery in 194 (48%) patients, cardiac surgery (before chest opening) in 159 (40%) patients, and open abdominal (nonvascular) surgery in 49 (12%) patients (table 1). CO was measured using pulmonary artery catheter in 126 patients, pulse contour method in 124 patients, and aortic echo-Doppler in 152 patients (table 1). The whole group consisted of 303 (75%) men and 99 (25%) women between 31 and 90 yr (mean age, 65 ± 9 yr; mean height, 171 ± 12 cm; mean weight, 77 ± 13 kg; body surface area, 2.4 ± 0.2 m²).

Effects of VE on Hemodynamic Variables

Of the 402 patients included in the study, VE-induced a 17 ± 15% increase in CO, an 11 ± 18% increase in SAP, a 10 ± 20% increase in DAP, a 10 ± 18% increase in MAP, and a 21 ± 50% increase in PP. At the same time, VE-induced a 4.6 ± 5.6% decrease in PPV. VE increased CO of more than 15% in 205 patients (51; table 2). In these patients, VE increased CO by 30 ± 12%, SAP by 16 ± 18%, DAP by 14 ± 23%, MAP by 16 ± 17%, and PP by 30 ± 52%, whereas it decreased PPV by 8 ± 5%. VE induced less than 15% increase in CO in 200 patients (49%). In these patients, VE increased CO by 4 ± 8%, SAP by 5 ± 13%, DAP by 5 ± 17%, MAP by 6 ± 13%, and PP by 13 ± 45% (table 2), whereas it decreased PPV by 1 ± 4%.

Relationship between Changes in Arterial Pressure and Changes in Stroke Volume

Percent changes in CO (%) induced by VE were correlated with percent changes in SAP ($r = 0.38$; $P < 0.01$), DAP ($r =$

Table 2. Hemodynamic Variables before and after Volume Expansion in Responders and Nonresponders

	Before Volume Expansion	After Volume Expansion
Heart rate, beats/min		
Responders (n = 205)	70 ± 20	70 ± 19
Nonresponders (n = 197)	65 ± 15*	64 ± 15*
Systolic arterial pressure, mmHg		
Responders (n = 205)	103 ± 18	118 ± 17†
Nonresponders (n = 197)	109 ± 17*	114 ± 18*
Diastolic arterial pressure, mmHg		
Responders (n = 205)	54 ± 13	59 ± 11†
Nonresponders (n = 197)	58 ± 13	59 ± 10
Mean arterial pressure, mmHg		
Responders (n = 205)	70 ± 12	80 ± 12†
Nonresponders (n = 197)	76 ± 12*	80 ± 12†
Pulse pressure, mmHg		
Responders (n = 205)	50 ± 16	59 ± 14†
Nonresponders (n = 197)	52 ± 15	55 ± 13*
Central venous pressure, mmHg		
Responders (n = 205)	8 ± 5	10 ± 5†
Nonresponders (n = 197)	9 ± 4*	8 ± 4
Cardiac output, l/min		
Responders (n = 205)	4.7 ± 1.4	6.0 ± 1.8†
Nonresponders (n = 197)	5.2 ± 1.7*	5.4 ± 1.8*
Pulse pressure variation, %		
Responders (n = 205)	16 ± 6	8 ± 4†
Nonresponders (n = 197)	8 ± 4*	6 ± 3

* $P < 0.05$ compared with responders. † $P < 0.05$ compared with before volume expansion.
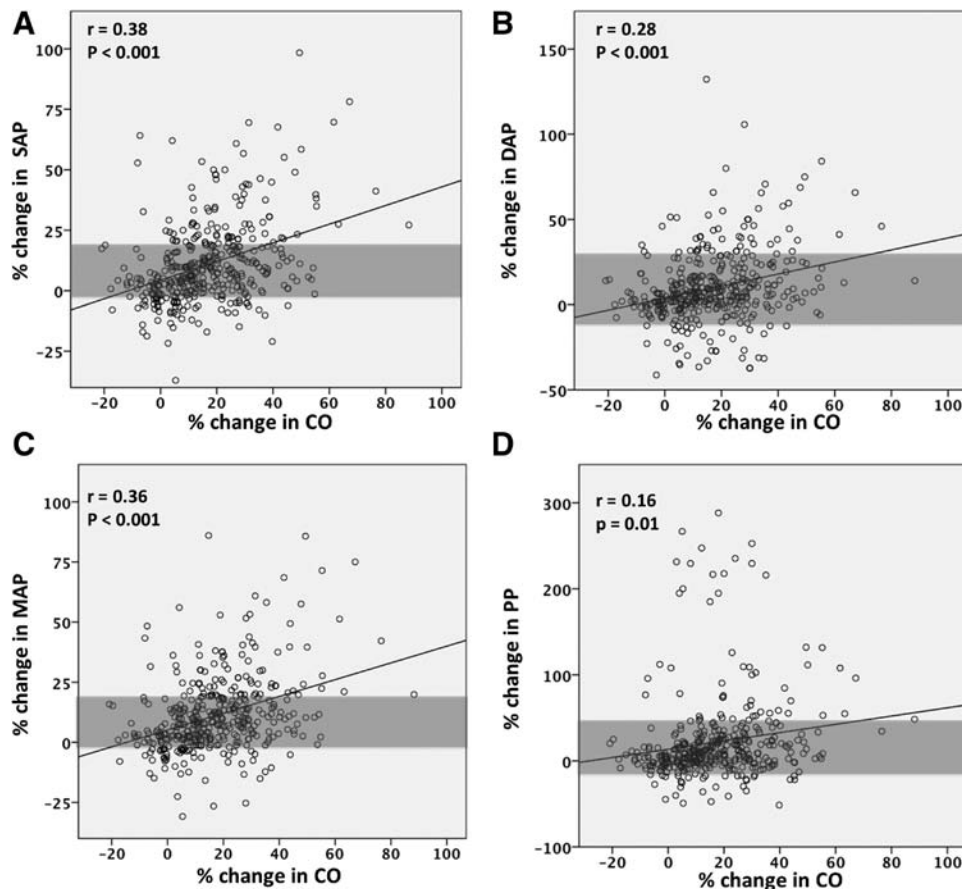
Fig. 1. Relationships between volume expansion–induced changes in arterial pressure–derived parameters and CO. Relationship between percent changes in SAP (*A*), DAP (*B*), MAP (*C*), and PP (*D*) induced by volume expansion. Percentage change in CO = percent changes in cardiac output induced by volume expansion; DAP = diastolic arterial pressure; MAP = mean arterial pressure; PP = pulse pressure; SAP = systolic arterial pressure.

0.28; $P < 0.01$), MAP ($r = 0.36$; $P < 0.01$), and PP ($r = 0.16$; $P = 0.01$) (fig. 1). We also observed a significant negative relationship between VE-induced changes in PPV and volume-induced changes in CO ($r = -0.61$; $P < 0.001$) (fig. 2).

Ability of the Changes in Arterial Pressure to Detect Fluid Responsiveness

The ability of the changes in the different values of arterial pressure to detect a fluid-induced increase in CO greater than 15% is described in table 3 and figure 3. The VE-induced changes (in %) in SAP, MAP, DAP, or PP detected a fluid-induced increase in CO greater than 15% with similar areas under the ROC curves, ranging between 0.64 and 0.70, and sensitivity and specificity ranging between 52 and 79%. For these four arterial pressure–derived parameters, large gray zones were found, and more than 60% of the patients lay within this inconclusive zone, as shown in table 3 and figure 4.

On the other hand, a VE-induced decrease in PPV (dPPV) of more than or equal to 3% allowed detecting a fluid-induced increase in CO of more than 15% with a sensitivity of 90% and a specificity of 77%, and decrease in PPV (dPPV)

between 2.2 and 4.7% defined the gray zone and included only 14% of the patients (fig. 5). When a threshold of 10% increase in CO was used to define fluid responsiveness, the predictive values of these parameters are shown in table 4.

Discussion

This study demonstrates (1) that there is a significant relationship between VE-induced changes in arterial pressure and CO; (2) that VE-induced changes in arterial pressure detect a more than 15% increase in CO with reasonable sensitivity and specificity; and (3) that this approach has limited clinical application because most VE-induced changes in arterial pressure (>60%) lay in a gray zone. Finally, only changes in PPV (dPPV) detect a more than 15% increase in CO induced by VE with 90% sensitivity and 77% specificity, and only 14% of patients lay in the gray zone for this parameter. We previously demonstrated that PPV can be used as a screening tool (to predict fluid responsiveness) before VE is performed. This study demonstrates that dPPV can be used as a diagnostic tool (to detect fluid responsiveness) after VE is performed.
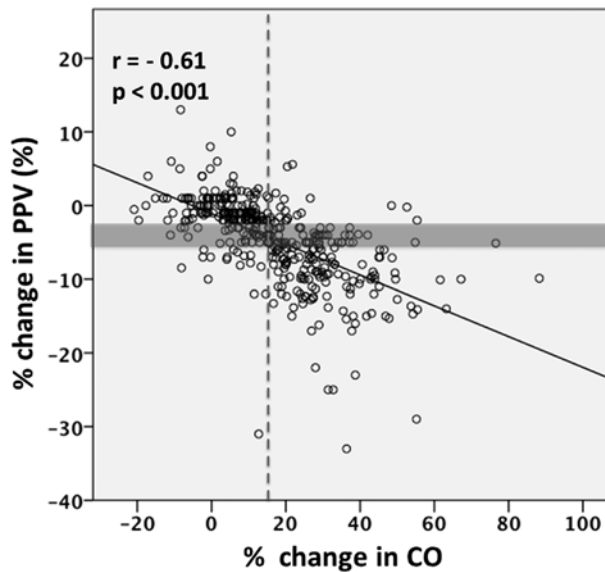
Fig. 2. Relationships between volume expansion–induced changes in PPV and CO. Percent change in PPV = percent changes in pulse pressure variation (defined as pulse pressure variation after volume expansion – pulse pressure variation before volume expansion). Percent change in CO = percent changes in cardiac output induced by volume expansion. The *dashed vertical line* shows the 15% threshold increase in CO defining fluid responsiveness.

Two recent studies hypothesized that changes in arterial pressure can detect changes in CO during VE.[10,11] These two studies have different conclusions. Monnet *et al.*[10] studied 228 septic patients and concluded that changes in SAP and PP can detect changes in CO induced by VE. This study demonstrated a significant relationship between arterial pressure and CO and a fair predictive value for changes in PP to detect changes in CO. However, even though ROC curve analysis provides with information regarding the predictive value of a diagnostic test, it is a weak tool to reflect the clinical reality.[12,13] In clinical practice, most hemodynamic variables cannot discriminate between subjects with and without a given status with a perfect accuracy. The so-called gray zone approach has been proposed to avoid the binary approach of a "black or white" decision that does not reflect the clinical

reality.[12,13] In our study, this approach emphasizes the inability of VE-induced changes in arterial pressure parameters to detect the effects of VE on CO because more than 60% of the patients are inside this gray zone. More recently, Pierrakos *et al.*[11] studied the same hypothesis in 51 septic patients, and they concluded that changes in arterial pressure do not reflect changes in CO induced by VE. Our study, which included a larger number of patients in a standardized setting, found more mitigated results. Despite the significant relationship and the fair predictive value, more than 60% of VE-induced changes in arterial pressure lay within the gray zone. Consequently, interpreting changes in arterial pressure to infer changes in CO induced by VE can be misleading. Finally, the studies by Monnet *et al.*[10] and Pierrakos *et al.*[11] were conducted in septic patients, whereas our study focuses on surgical patients. Septic patients present with a different cardiovascular physiology compared with perioperative patients. Their cardiac function is often impaired and some recent studies suggest that their vascular function may present some abnormalities such as a peripheral vascular decoupling.[17,18] Because our study specifically focuses on perioperative patients, our results cannot be extrapolated to the intensive care setting. However, because we included a wide range of pathologies and patients, we believe that these results have a broad potential clinical application in the perioperative setting.

Despite evidence showing that CO monitoring and optimization leads to a decrease in postoperative morbidity, mortality, and cost of high-risk surgery,[5,6] arterial pressure and ventricular filling pressure are frequently monitored for the intraoperative hemodynamic management of most high-risk surgery patients, whereas CO is rarely monitored.[9] This may be induced by the belief that CO and arterial pressure are closely related. Classical parameters such as SAP, DAP, and MAP are daily used in the operating rooms and recorded in the patients' medical records. These values are used to assess cardiovascular status because they are easy to measure in clinical practice[19] and may be related to postoperative outcome.[20] However, these values depend on many parameters. As discussed by others,[18,21,22] a fluid-induced increase in stroke volume may result in arterial pressure increases of various amplitude according to patient's vasomotor tone, and

Table 3. Predictive Values of Volume Expansion–Induced Changes in Arterial Pressure–Derived Parameters to Detect a More than 15% Increase in Cardiac Output

	AUC	95% CI	P vs. 0.05	Cutoff (%)	Sensitivity (%)	Specificity (%)	Gray Zone	Patients in the Gray Zone (%)
Percent changes in SAP	0.70	(0.65–0.75)	<0.001	6.4	56	77	(−1.9 to 21.1)	252 (63%)
Percent changes in DAP	0.64	(0.59–0.69)	<0.001	8.8	52	72	(−6.9 to 23.9)	276 (69%)
Percent changes in MAP	0.69	(0.64–0.74)	<0.001	8.3	74	56	(−1.0 to 20.9)	260 (65%)
Percent changes in PP	0.66	(0.60–0.70)	<0.001	18.3	53	79	(−9.7 to 35.6)	281 (70%)
Changes in PPV	0.89	(0.85–0.91)	<0.001	3	90	77	(−4.7 to −2.2)	56 (14 %)

AUC = area under the curve; DAP = diastolic arterial pressure; MAP = mean arterial pressure; PP = pulse pressure; PPV = pulse pressure variation; SAP = systolic arterial pressure.
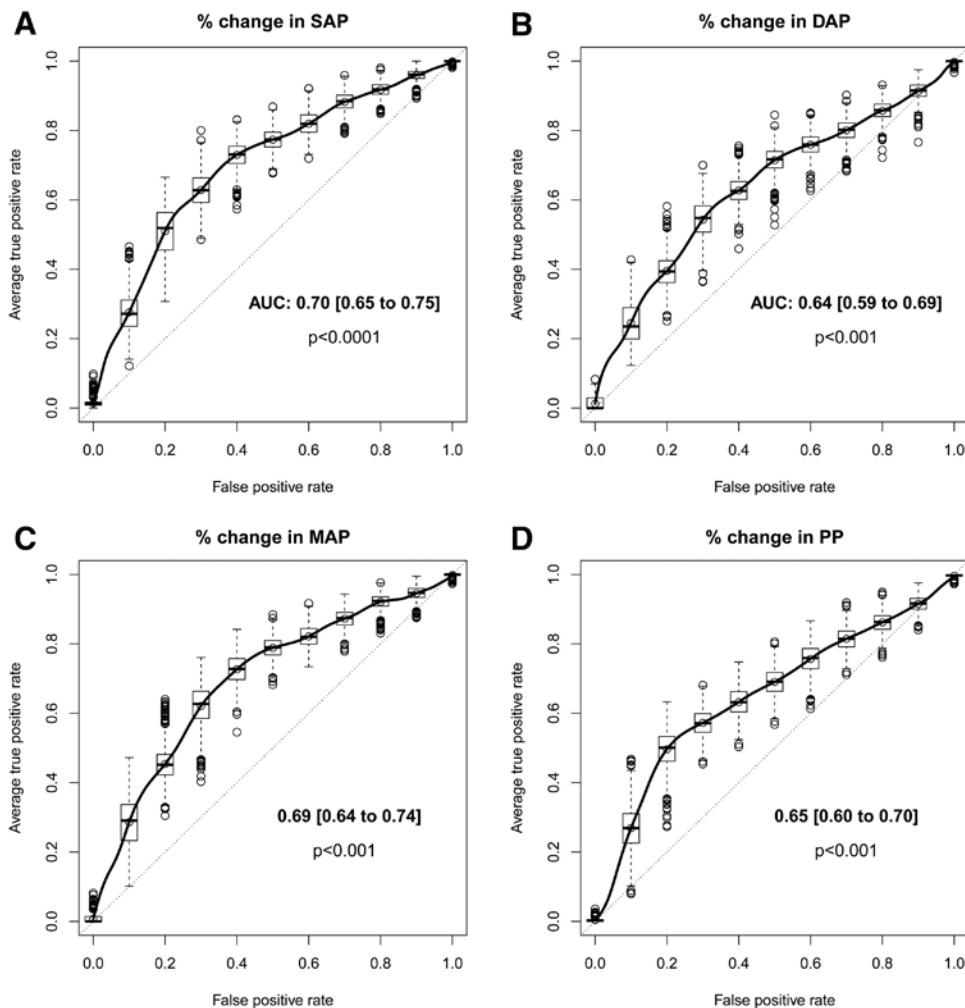
Fig. 3. Receiver operating characteristics curves representing the discriminative power of volume expansion–induced changes in arterial pressure to detect an increase of more than 15% of cardiac output after volume expansion. Receiver operating characteristics curves representing the discriminative power of volume expansion–induced percent changes in SAP (*A*), DAP (*B*), MAP (*C*), and PP (*D*) to detect an increase of more than 15% of cardiac output after volume expansion. AUC = area under the curve; DAP = diastolic arterial pressure; MAP = mean arterial pressure; PP = pulse pressure; SAP = systolic arterial pressure.

especially to arterial elastance (which defines the relationship between the stroke volume and the PP into the central arterial compartment), and to the pulse wave amplification phenomenon (because arterial pressure is monitored at the peripheral arterial level). The present results suggest that our patients represented a relatively wide range of arterial vasomotor tone. Accordingly, arterial elastance varies with age, sex, mean blood pressure, body mass index, and expression of atherosclerosis.[18,22] Although derived from arterial pressure measurements, changes in PPV were correlated with changes in CO more closely than other arterial pressure parameters. This may likely be explained by the close relationship that exists between initial PPV and the changes in CO induced by VE, as repeatedly demonstrated in previous studies, whereas arterial pressure, including PP, depends on many other determinants.

The current study demonstrates that changes in standard arterial pressure parameters cannot be used for conducting

CO optimization in the perioperative period. However, dPPV is accurate to detect a more than 15% increase in CO induced by VE (of note, we expressed VE-induced changes in PPV as the difference between PPV after VE and PPV before VE). This is a significant addition to what we previously showed: That PPV before VE is a strong predictor of fluid responsiveness that it lays in the gray zone (between 9 and 13%) in about 25% of the cases.[12] Based on these two studies, PPV can be used as a screening tool (to predict fluid responsiveness), whereas dPPV can be used as a diagnostic tool (to detect fluid responsiveness after fluid has been given). Interestingly, dPPV presented with a narrow gray zone, and only 14% of the patients were in this gray zone, which suggests that this index presents with a significant clinical applicability. Combining PPV and dPPV may be of value for conducting CO optimization when no CO monitor is available. Considering the strong predictive value of PPV and dPPV, combining these indices could be a way
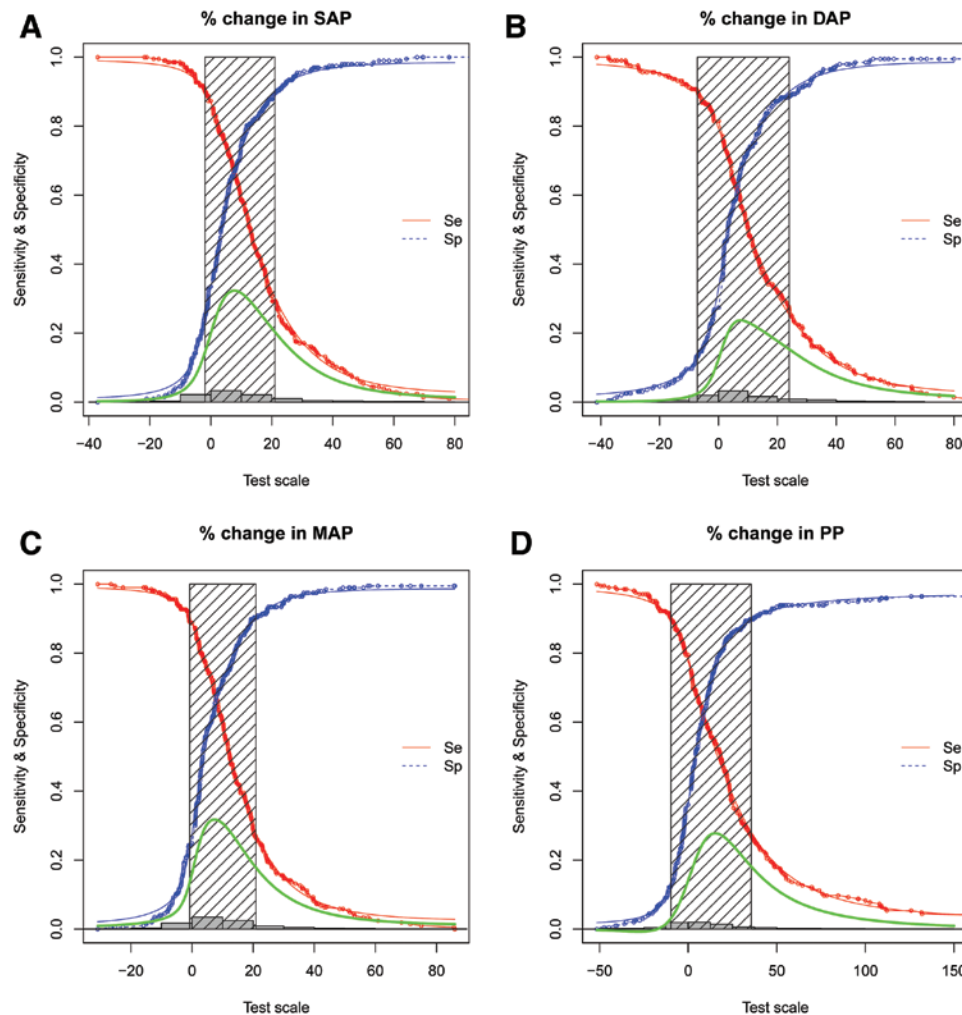
Fig. 4. Two-graph receiver operating characteristic curves: sensitivity and specificity of volume expansion–induced changes in arterial pressure according to the value of the cutoff for the detection of more than 15% increase in cardiac output after volume expansion. The inconclusive zone, which is more than 10% of diagnosis tolerance, is represented as a *hatch rectangle*. Volume expansion–induced percent changes in SAP (*A*), DAP (*B*), MAP (*C*), and PP (*D*). DAP = diastolic arterial pressure; MAP = mean arterial pressure; PP = pulse pressure; SAP = systolic arterial pressure.

to overcome the lack of accuracy of mini invasive CO monitors[23] and could be used for goal-directed therapy during surgery. When PPV is in the gray zone (between 9 and 13%), a fluid bolus could be used to assess the changes in dPPV and then make a decision on whether or not CO increased. For this purpose, a mini fluid challenge (100 ml)[24] could be used. This approach may be of major clinical relevance in situations (institutions or countries) where CO monitoring is not available. However, this hypothesis would require a larger sample size to be tested.

Study Limitation

Our study presents some limitations. First, we classified responder and nonresponder patients using various methods of CO measurement.[23] However, all the techniques used to measure CO in this article have demonstrated high validity for measuring changes in stroke volume.[25,26] All of these

devices have already been used for defining fluid responsiveness in previous studies.[14,27,28] Second, VE was not adjusted to patients' weight. We did so to be in line with previously published articles (using a fixed 500 ml bolus). We found approximately 50% of responders to VE, which is consistent with previously published studies on the topic. In addition, we found no relationship between patients' weight and VE-induced change in CO ($r^2 = 0.001$; $P = 0.056$). Third, even if dPPV is the best variable to detect changes in CO, this index can only be used when the conditions of application of PPV are met (general anesthesia, mechanical ventilation, no arrhythmia, and tidal volume greater than 6 ml/kg). This represents the majority of patients with an arterial line in the operating room, especially considering that the limitation related to arrhythmia can be overcome[29] and considering that the tidal volume is a controlled variable that can be modified.[30] Finally, our study included more men (75%)
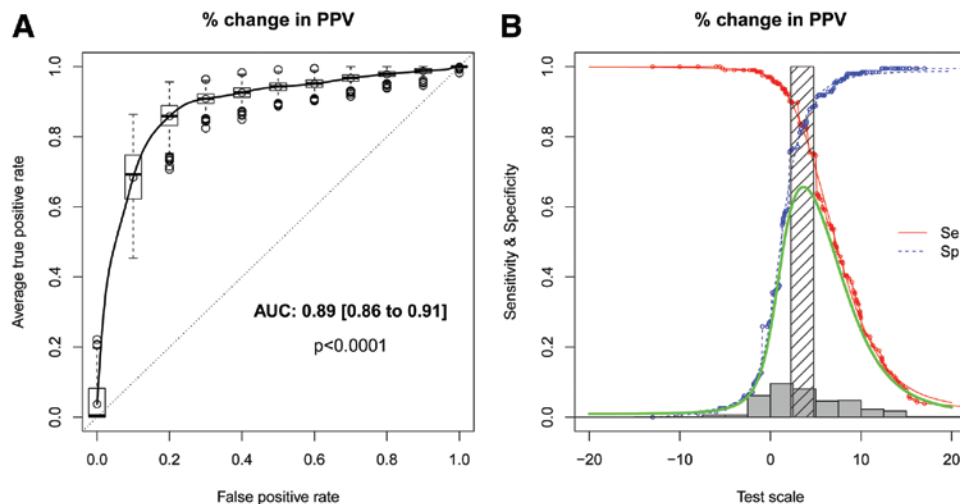
Fig. 5. Receiver operating characteristics (ROC) curves representing the discriminative power of volume expansion–induced changes in PPV to detect an increase of more than 15% of cardiac output after volume expansion (*A*) and two-graph ROC curves: sensitivity and specificity of volume expansion–induced changes in PPV according to the value of the cutoff for the detection of more than 15% increase in cardiac output after volume expansion. The inconclusive zone, which is more than 10% of diagnosis tolerance, is represented as a *hatch rectangle* (*B*). AUC = area under the curve; PPV = pulse pressure variation.

Table 4. Predictive Values of Volume Expansion–Induced Changes in Arterial Pressure–Derived Parameters to Detect a More than 10% Increase in Cardiac Output

	AUC	95% CI	*P vs.* 0.05	Cutoff (%)	Gray Zone	Patients in the Gray Zone (%)
Percent changes in SAP	0.72	(0.67–0.77)	<0.001	5.7	(2.1–17.33)	227 (56%)
Percent changes in DAP	0.67	(0.62–0.72)	<0.001	6.8	(−6.4 to 19.1)	257 (64%)
Percent changes in MAP	0.72	(0.67–0.77)	<0.001	5.1	(−0.8 to 17.6)	228 (57%)
Percent changes in PP	0.66	(0.61–0.71)	<0.001	7.1	(−10.2 to 31.6)	273 (68%)
Changes in PPV	0.86	(0.83–0.89)	<0.001	2.4	(−4.0 to −1.0)	82 (20%)

AUC = area under the curve; DAP = diastolic arterial pressure; MAP = mean arterial pressure; PP = pulse pressure; PPV = pulse pressure variation; SAP = systolic arterial pressure.

than women and more vascular and cardiac surgeries (88%) than general surgeries. However, it is likely that sex does not influence these results. Finally, the heterogeneity of the surgeries included in our study might have underestimated the specificity of the test compared with a homogeneous group of surgeries. On the other hand, including several surgeries in several centers probably provides a better estimation of the value of the test and thus better reflects clinical reality.

In conclusion, VE-induced changes in arterial pressure have limited clinical applications for the detection of VE-induced changes in CO in patients undergoing surgery. Despite a relatively fair predictive value, changes in arterial pressure induced by VE are inconclusive for the detection of a more than 15% change in CO in more than 60% of the cases and thus should not be used as a surrogate for fluid responsiveness evaluation in routine clinical care of patients undergoing high-risk surgery. However, dPPV is able to detect fluid responders with excellent sensitivity and specificity and its gray zone only includes 14% of the patients.

References

1. Gan TJ, Soppitt A, Maroof M, el-Moalem H, Robertson KM, Moretti E, Dwane P, Glass PS: Goal-directed intraoperative fluid administration reduces length of hospital stay after major surgery. ANESTHESIOLOGY 2002; 97:820–6
2. Sinclair S, James S, Singer M: Intraoperative intravascular volume optimisation and length of hospital stay after repair of proximal femoral fracture: Randomised controlled trial. BMJ 1997; 315:909–12
3. Wakeling HG, McFall MR, Jenkins CS, Woods WG, Miles WF, Barclay GR, Fleming SC: Intraoperative oesophageal Doppler guided fluid management shortens postoperative hospital stay after major bowel surgery. Br J Anaesth 2005; 95:634–42
4. Venn R, Steele A, Richardson P, Poloniecki J, Grounds M, Newman P: Randomized controlled trial to investigate influence of the fluid challenge on duration of hospital stay and perioperative morbidity in patients with hip fractures. Br J Anaesth 2002; 88:65–71
5. 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
6. Rhodes A, Cecconi M, Hamilton M, Poloniecki J, Woods J, Boyd O, Bennett D, Grounds RM: Goal-directed therapy

in high-risk surgical patients: A 15-year follow-up study. Intensive Care Med 2010; 36:1327–32

7. Cecconi M, Fasano N, Langiano N, Divella M, Costa MG, Rhodes A, Della Rocca G: Goal-directed haemodynamic therapy during elective total hip arthroplasty under regional anaesthesia. Crit Care 2011; 15:R132

8. Benes J, Chytra I, Altmann P, Hluchy M, Kasal E, Svitak R, Pradl R, Stepan M: Intraoperative fluid optimization using stroke volume variation in high risk surgical patients: Results of prospective randomized study. Crit Care 2010; 14:R118

9. 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

10. Monnet X, Letierce A, Hamzaoui O, Chemla D, Anguel N, Osman D, Richard C, Teboul JL: Arterial pressure allows monitoring the changes in cardiac output induced by volume expansion but not by norepinephrine. Crit Care Med 2011; 39:1394–9

11. Pierrakos C, Velissaris D, Scolletta S, Heenen S, De Backer D, Vincent JL: Can changes in arterial pressure be used to detect changes in cardiac index during fluid challenge in patients with septic shock? Intensive Care Med 2012; 38:422–8

12. 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

13. Ray P, Le Manach Y, Riou B, Houle TT: Statistical evaluation of a biomarker. ANESTHESIOLOGY 2010; 112:1023–40

14. Derichard A, Robin E, Tavernier B, Costecalde M, Fleyfel M, Onimus J, Lebuffe G, Chambon JP, Vallet B: Automated pulse pressure and stroke volume variations from radial artery: Evaluation during major abdominal surgery. Br J Anaesth 2009; 103:678–84

15. Michard F, Boussat S, Chemla D, Anguel N, Mercat A, Lecarpentier Y, Richard C, Pinsky MR, Teboul JL: 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; 162:134–8

16. Cannesson M, Le Manach Y, Vallet B, Tavernier B: The "gray zone" approach": Assessing the accuracy of pulse pressure variation without considering the prevalence: In Reply. ANESTHESIOLOGY 2012; 116: 741–3

17. Hatib F, Jansen JR, Pinsky MR: Peripheral vascular decoupling in porcine endotoxic shock. J Appl Physiol 2011; 111:853–60

18. Pinsky MR: Defining the boundaries of bedside pulse contour analysis: Dynamic arterial elastance. Crit Care 2011; 15:120

19. Lamia B, Chemla D, Richard C, Teboul JL: Clinical review: Interpretation of arterial pressure wave in shock states. Crit Care 2005; 9:601–6

20. Bijker JB, Persoon S, Peelen LM, Moons KG, Kalkman CJ, Kappelle LJ, van Klei WA: Intraoperative hypotension and perioperative ischemic stroke after general surgery: A nested case-control study. ANESTHESIOLOGY 2012; 116:658–64

21. Monge García MI, Gil Cano A, Gracia Romero M: Dynamic arterial elastance to predict arterial pressure response to volume loading in preload-dependent patients. Crit Care 2011; 15:R15

22. Saba PS, Roman MJ, Ganau A, Pini R, Jones EC, Pickering TG, Devereux RB: Relationship of effective arterial elastance to demographic and arterial characteristics in normotensive and hypertensive adults. J Hypertens 1995; 13:971–7

23. Peyton PJ, Chong SW: Minimally invasive measurement of cardiac output during surgery and critical care: A meta-analysis of accuracy and precision. ANESTHESIOLOGY 2010; 113:1220–35

24. 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

25. Critchley LA, Lee A, Ho AM: A critical review of the ability of continuous cardiac output monitors to measure trends in cardiac output. Anesth Analg 2010; 111:1180–92

26. 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

27. Hofer CK, Müller SM, Furrer L, Klaghofer R, Genoni M, Zollinger A: Stroke volume and pulse pressure variation for prediction of fluid responsiveness in patients undergoing off-pump coronary artery bypass grafting. Chest 2005; 128:848–54

28. Feissel M, Michard F, Mangin I, Ruyer O, Faller JP, Teboul JL: Respiratory changes in aortic blood velocity as an indicator of fluid responsiveness in ventilated patients with septic shock. Chest 2001; 119:867–73

29. Cannesson M, Tran NP, Cho M, Hatib F, Michard F: Predicting fluid responsiveness with stroke volume variation despite multiple extrasystoles. Crit Care Med 2012; 40:193–8

30. Maguire S, Rinehart J, Vakharia S, Cannesson M: Technical communication: Respiratory variation in pulse pressure and plethysmographic waveforms: Intraoperative applicability in a North American academic center. Anesth Analg 2011; 112:94–6