

CLINICAL INVESTIGATIONS

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Systolic Pressure Variation as a Guide to Fluid Therapy in Patients with Sepsis-induced Hypotension

Benoît Tavernier, M.D.,* Olivier Makhotine, M.D.,† Gilles Lebuffe, M.D.,* Jacques Dupont, M.D.,* Philippe Scherpereel, M.D.‡

Background: Monitoring left ventricular preload is critical to achieve adequate fluid resuscitation in patients with hypotension and sepsis. This prospective study tested the correlation of the pulmonary artery occlusion pressure, the left ventricular end-diastolic area index measured by transesophageal echocardiography, the arterial systolic pressure variation (the difference between maximal and minimal systolic blood pressure values during one mechanical breath), and its delta down (dDown) component (= apneic - minimum systolic blood pressure) with the response of cardiac output to volume expansion during sepsis.

Methods: Preload parameters were measured at baseline and during graded volume expansion (increments of 500 ml) in 15 patients with sepsis-induced hypotension who required mechanical ventilation. Each volume-loading step (VLS) was classified as a responder (increase in stroke volume index $\geq 15\%$) or a nonresponder. Successive VLSs were performed until a nonresponder VLS was obtained.

Results: Thirty-five VLSs (21 responders) were performed. Fluid loading caused an overall significant increase in pulmonary artery occlusion pressure and end-diastolic area index, and a significant decrease in systolic pressure variation and delta down ($P < 0.01$). There was a significant difference between responder and nonresponder VLSs in end-diastolic area index, systolic pressure variation, and dDown, but not in pul-

monary artery occlusion pressure. Receiver-operator curve analysis showed that dDown was a more accurate indicator of the response of stroke volume index to volume loading than end-diastolic area index and pulmonary artery occlusion pressure. A dDown component of more than 5 mmHg indicated that the stroke volume index would increase in response to a subsequent fluid challenge (positive and negative predictive values: 95% and 93%, respectively).

Conclusion: The dDown component of the systolic pressure variation is a sensitive indicator of the response of cardiac output to volume infusion in patient with sepsis-induced hypotension who require mechanical ventilation. (Key words: Blood pressure; heart function; human; septic shock.)

SEPSIS results in a complex form of shock that often includes hypovolemia. Volume infusion is thus accepted as essential management of hypotensive patients during sepsis.¹ However, sepsis may be accompanied by cardiac dysfunction, and monitoring of left ventricular (LV) preload is critical to achieve successful fluid resuscitation in these patients. During sepsis, most patients obtain maximal LV performance with a pulmonary artery occlusion pressure (PAOP) of 12-15 mmHg,² but it is well known that data from a pulmonary catheter may be misleading. Therefore, transesophageal echocardiography has been used increasingly to monitor cardiac function and intravascular volume status in the intensive care unit. Left ventricular end-diastolic area (EDA) more accurately reflects LV preload when compared with PAOP.³ Measurements of EDA improve the ability to detect changes in LV function caused by acute blood loss⁴ and to define maximum ventricular response to intravenous fluid therapy after hemorrhage.⁵ Recent studies introduced another method to assess preload, based on the analysis of changes in the arterial pressure waveform during mechanical ventilation. The increase in intrathoracic pressure during a mechanical breath normally causes an early increase in stroke volume (and therefore in arterial pressure) because of a transient augmentation of LV end-diastolic volume, a decrease in afterload, and a diminished right ventricular volume. It is followed by a decrease in stroke volume and arterial pressure, mainly

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* Assistant Professor.

† Resident.

‡ Professor and Head, Department of Anesthesia 2.

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Address reprint requests to Dr. Tavernier: Département d'Anesthésie-Réanimation Chirurgicale 2, Hôpital Huriez, Centre Hospitalier Régional et Universitaire, 59037 Lille Cedex, France. Address electronic mail to: btavernier@chru-lille.fr

secondary to a decrease in right ventricular filling. Using the systolic arterial pressure at end-expiration as a reference point or the baseline, the increase and decrease in systolic pressure during the respiratory cycle have been defined, respectively, as delta up (dUp) and delta down (dDown).⁶ The difference between maximal and minimal systolic pressures during one mechanical breath (the sum of dUp and dDown) is called the systolic pressure variation (SPV).⁶ The SPV and dDown have been shown to be sensitive indicators of hypovolemia in animal experiments⁶⁻⁸ and, more recently, in relatively healthy humans.^{9,10} No study, however, has evaluated the usefulness of transesophageal echocardiography-derived EDA measurements and SPV analysis to guide fluid therapy during a complex hemodynamic disorder, such as septic shock.

To test the correlation between indexes of LV preload and the response of cardiac output to intravenous volume expansion during sepsis, we simultaneously measured EDA, SPV, dDown, PAOP, and cardiac output during progressive fluid volume administration in patients with sepsis-induced hypotension.

Materials and Methods

Patients

After institutional approval of the study protocol (by the Comité Consultatif de Protection des Personnes dans la Recherche Biomédicale de Lille), 16 patients admitted to our surgical intensive care unit for sepsis-induced hypotension, as defined by the American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference Committee¹¹ (systolic blood pressure < 90 mmHg or its reduction by ≥ 40 mmHg from usual values, in the absence of other causes for hypotension), were studied prospectively. Signs of sepsis included two or more of the following conditions as a result of infection: body temperature more than 38°C or less than 36°C; an increased heart rate of more than 90 beats/min; a respiratory rate of more than 20 breaths/min, or a partial pressure of carbon dioxide in arterial blood less than 32 mmHg; and an altered leukocyte count of more than 12,000 cells/mm³ or less than 4,000 cells/mm³, or the presence of 10% immature neutrophils.¹¹ No patient had a history of congestive heart failure. Patients with cardiac rhythm other than sinus rhythm were not included in the study. Before participating in the study, all patients received fluid or catecholamine therapy (or both) as part of initial treatment

(before or during admission in the intensive care unit). Microbiological documentation of infection was available for 10 patients. Mechanical ventilation was used in all patients in the controlled mode, with a tidal volume of 8–11 ml/kg and an inspiratory:expiratory ratio of 1:2. Respiratory rate was set to keep the partial pressure of carbon dioxide in arterial blood within normal values (40 ± 5 mmHg), and the end-expiratory pressure level ranged from 0–10 cm H₂O. No changes in the ventilator setting were made during the study period. Pulse oximetry was monitored in all patients during the study. Sedation was provided by intravenous administration of fentanyl (300–600 μ g/h) or sufentanil (20–60 μ g/h) with midazolam (5–15 mg/h). Whenever necessary, spontaneous breaths were eliminated by paralyzing the patient with vecuronium.

Hemodynamic Measurements

All patients were monitored using a pulmonary artery catheter (Swan-Ganz catheter, 7.5 French; Baxter Edwards Critical, Irvine, CA) and a 20-g radial artery catheter. Transducers were positioned at the mid axillary level, with atmosphere pressure used as the zero reference level. Ensuring that the cyclic changes caused by mechanical ventilation in PAOP and in pulmonary artery pressure were within the same range (ratio close to 1) confirmed that the catheter tip had an adequate zone 3 position.¹² End-diastolic PAOP was determined at end-expiration from a tracing provided by a PPG Hellige RM 300 monitor (Best, The Netherlands) and averaged from four or five successive respiratory cycles. Cardiac output was measured by the thermodilution technique, using the average of six determinations obtained by the injection of 10 ml of room-temperature dextrose manually initiated throughout the ventilatory cycle at points identified by changes in airway pressure¹³ (beginning, middle, and end of inspiration and expiration). The systemic arterial blood pressure curve, obtained from the radial artery catheter, was recorded on a calibrated chart recorder (7041 M XY recorder; Hewlett-Packard, Andover, MA). Pressure waveform analysis was performed off-line with the reviewer unaware of hemodynamic data in the following manner (fig. 1). The SPV, which is the difference between maximal systolic pressure and minimal systolic pressure during one cycle of a mechanical breath, was determined from the chart. The mean of the SPV values during three consecutive breaths was calculated. The value of the systolic blood pressure during a period of 7–12 s of end-expiratory pause (without disconnection of the endotracheal tube from the ventilator)

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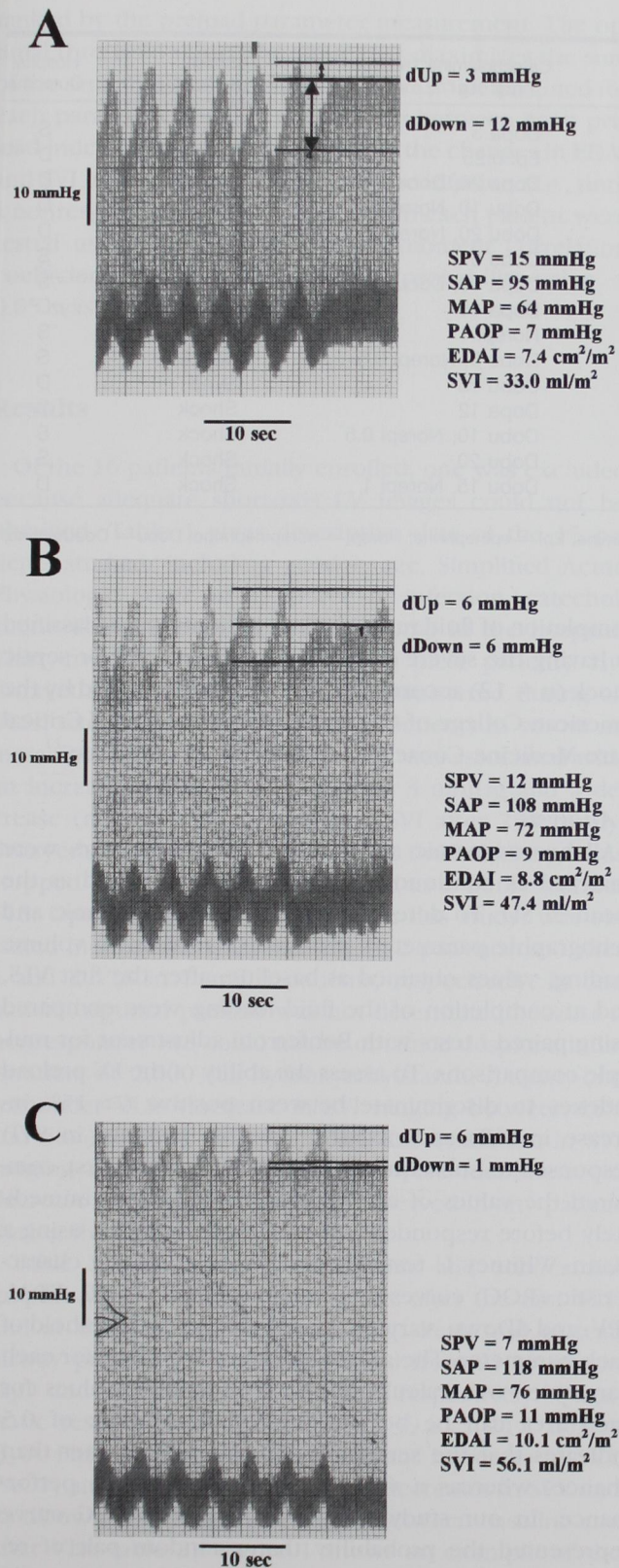


Fig. 1. Systemic arterial blood pressure curve recorded in one patient before (A) and after 500 ml (B) and 1,000 ml (C) administration of hydroxyethylstarch. The difference between the maximal systolic pressure and the minimal systolic pressure during one cycle of mechanical breath defines the systolic pressure variation (SPV). The value of the systolic arterial pressure (SAP) during a short period of end-expiratory pause is used as a reference pressure to measure the delta up (dUp) and delta down (dDown) components of the SPV. The difference between the systolic pressure during end-expiratory pause and the maximum systolic pressure defines dUp. The difference between the systolic pressure during end-expiratory pause and the minimum systolic pressure defines dDown. EDAI = left ventricular end-diastolic area index. HR = heart rate; MAP = mean arterial pressure; PAOP = pulmonary artery occlusion pressure; SVI = stroke volume index.

was used as a reference pressure to measure the dDown and the dUp. Because the arterial pressure may have an additional nonrespiratory low-frequency fluctuation (Mayer waves), the dUp and dDown were determined during the two or three respiratory cycles that immediately preceded the apnea period. The magnitude of dDown also was expressed as a percentage of the systolic arterial pressure⁶ (%dDown) at each intervention.

Echocardiographic Measurements

A Toshiba PEF-510 SB 5-MHz-phased array ultrasonic transducer (Tokyo, Japan), fitted to the end of a standard gastroscope, was inserted into the patient's esophagus. A Toshiba Sonolayer SSA-270 A ultrasonograph was used for two-dimensional echocardiographic imaging. The probe was positioned to obtain a LV short-axis image at the mid papillary muscle level and was not moved during the study. Recordings were analyzed off-line with the reviewer unaware of the hemodynamic data. Two-dimensional echo images were reviewed for single-frame, stop-motion analysis from the videotape recording. End-diastole was defined as the frame corresponding to the largest LV cross-sectional area immediately after the R-wave peak on the electrocardiogram. The LV short-axis, end-diastolic, cross-sectional area was measured by manual planimetry of the area circumscribed by the leading edge of the LV endocardial border. The anterolateral and posteromedial papillary muscles were included within the ventricular area. All echocardiographic dimensions used for analysis were the mean of measurements performed during a whole respiratory cycle (the number of consecutive cardiac cycles to be analyzed was obtained by dividing the heart rate by the respiratory rate recorded simultaneously with that of the echocardiographic

Table 1. Clinical Characteristics of the Patients

Patient Number	Sex	Age (yr)	SAPS 2	Source of Infection	Catecholamine Treatment ($\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$)	Sepsis Classification	Hospital Outcome
1	M	50	53	Intestinal (infarction)	Dopa 3	Synd	S
2	M	71	69	Peritoneal	Epi 0.25	Shock	D
3	M	72	84	Peritoneal	Dopa 20, Dobu 10	Shock	D
4	F	72	62	Peritoneal	Dobu 10, Norepi 0.3	Shock	D
5	F	81	65	Biliary	Dobu 20, Norepi 1	Shock	D
6	F	61	54	Renal	Dobu 5	Synd	S
7	M	50	46	Pancreas	Dopa 10, Dobu 10	Shock	S
8	M	57	70	Biliary	Dopa 15	Shock	D
9	M	49	43	Peritoneal	Norepi 1	Shock	S
10	M	58	53	Biliary	Dobu 5, Norepi 0.5	Shock	S
11	M	76	56	Pulmonary	Dobu 15	Synd	D
12	M	61	49	Peritoneal	Dopa 12	Shock	S
13	F	73	54	Pancreas	Dobu 10, Norepi 0.5	Shock	S
14	F	64	48	Peritoneal	Dobu 20	Shock	S
15	M	67	57	Peritoneal	Dobu 15, Norepi 1	Shock	D

M = male; F = female; SAPS 2 = simplified acute physiologic score; Dopa = dopamine; Epi = epinephrine; Norepi = norepinephrine; Dobu = Dobutamine; Synd = severe sepsis syndrome; Shock = septic shock; S = survived; D = died.

graphic images). Left ventricular areas were divided by the surface body area of the patient to obtain indexed LV areas at end-diastole (EDAI).

Volume Infusion Technique and Protocol

A complete set of hemodynamic measurements and echocardiographic images was obtained first (baseline values). In addition, respiratory parameters were obtained from the ventilator monitoring panel. Quasi-static respiratory compliance was calculated according to the following equation: quasi-static compliance = tidal volume / (plateau pressure - [positive end-expiratory pressure + auto-positive end-expiratory pressure]), with auto-PEEP determined by occluding the airway at end-expiration.¹⁴ Volume loading was then performed with increments of colloid solution (6% hydroxyethylstarch) according to a fluid-challenge technique adapted from Weil and Henning.¹⁵ The goal was to infuse 500 ml over 30 min during each volume-loading step (VLS) in all patients. After each VLS, 5-10 min was allowed for equilibration, and a complete set of hemodynamic and echocardiographic measurements was repeated. Responder VLS ($\geq 15\%$ increase in stroke volume index [SVI]) and nonresponder VLS ($< 15\%$ increase in SVI) were identified. In each patient, successive VLSs were performed until a nonresponder VLS was obtained. Thus, in all patients, the fluid loading was completed by a nonresponder VLS, and the set of measurements performed immediately before this final VLS corresponded to the optimal preload. No changes in vasoactive drug therapy (table 1) were made during the study. After

completion of fluid resuscitation, patients were classified as having the severe sepsis syndrome ($n = 3$) or septic shock ($n = 12$) according to the criteria described by the American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference Committee.¹¹

Analysis

All hemodynamic and echographic parameters were analyzed as continuous variables and expressed as the mean \pm SD. To determine whether hemodynamic and echographic parameters changed in relation to volume loading, values obtained at baseline, after the first VLS, and at completion of the fluid loading were compared using paired *t* tests with Bonferroni adjustment for multiple comparisons. To assess the ability of the LV preload indexes to discriminate between positive ($\geq 15\%$ increase in SVI) and negative ($< 15\%$ increase in SVI) responses to subsequent fluid challenge, we first compared the values of each parameter measured immediately before responder and nonresponder VLSs using a Mann-Whitney U test. Then receiver operating characteristic (ROC) curves were generated for PAOP, EDAI, SPV, and dDown, varying the discriminating threshold of each parameter. The area under the ROC curve for each parameter was calculated and compared.¹⁶ Values for each area can be between 0 and 1. A value of 0.5 indicates that the screening measure is no better than chance, whereas a value of 1 implies perfect performance. In our study, the area under the ROC curve represented the probability that a random pair of responder and nonresponder VLSs would be correctly

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ranked by the preload parameter measurement. The optimal threshold value (the value that maximizes the sum of the sensitivity and specificity) was also determined for each parameter. Finally, the relation between each preload index measured at baseline and the changes in EDAI and SVI in response to overall volume infusion (*i.e.*, until a nonresponder VLS was obtained) in each patient were tested using the Pearson product moment correlation coefficient. For all comparisons, a probability value < 0.05 was considered significant.

Results

Of the 16 patients initially enrolled, one was excluded because adequate short-axis LV images could not be obtained. Table 1 gives descriptive data of the 15 patients studied, including gender, age, Simplified Acute Physiologic Score of 2, source of infection, catecholamine dosages, and the final outcome in the hospital. Thirty-five VLSs were performed in these patients. Hydroxyethylstarch (500 ml) was administered during all VLSs, except the final VLS in four patients in whom an initial PAOP of more than 12 mmHg was associated with an increase in PAOP of more than 3 mmHg and a decrease (range, -5% to -11%) in SVI after 250 ml hydroxyethylstarch. In these cases, the fluid challenge was stopped and the VLS was classified as a nonresponder VLS. Optimal preload, as defined in this study, was obtained in 14 patients: at baseline in 2 patients, and after 1 and 2 VLS in 7 and 5 patients, respectively. In one patient, optimal preload was not determined because a nonresponder VLS could not be obtained despite administration of 2,000 ml hydroxyethylstarch. Twenty-one responder VLSs (increase in SVI ranging between 18% and 58%) and 14 nonresponder VLSs (variation in SVI ranging between -11% and 5%) were identified. No decrease in pulse oximetry was observed in any patient during the study.

Table 2 summarizes hemodynamic and echocardiographic values obtained at baseline, after the first VLS, and at the end of volume loading. Peak and plateau airway pressures at baseline ranged from 21 to 45 cm H₂O and from 11 to 34 cm H₂O, respectively. Quasi-static respiratory compliance was 39.9 ± 11.1 ml/cm H₂O. Fluid loading caused significant increases in SVI, PAOP, and EDAI and concomitant decreases in SPV and its dDown component ($P < 0.01$ between baseline and after VLS; table 2). Figure 1 shows an example of the systemic arterial blood pressure curve recorded in one

Table 2. Hemodynamic and Echocardiographic Parameters Measured at Baseline, after the First Volume Loading Step (VLS 1), and at the End of Volume Loading (Final VLS) in 15 Patients

	Baseline	VLS 1	Final VLS
HR (bpm)	117 ± 19	111 ± 18*	109 ± 17*
SAP (mmHg)	102 ± 15	122 ± 19*	134 ± 26*,†
MAP (mmHg)	68 ± 9	81 ± 13*	88 ± 16*,†
CI (l · min ⁻¹ · m ⁻²)	3.7 ± 1.1	4.5 ± 1.4*	4.9 ± 1.6*
SVRI			
(dyne · s · cm ⁻⁵ · m ²)	1,523 ± 638	1,409 ± 556	1,445 ± 598
SVI (ml/m ²)	32 ± 12	41 ± 13*	45 ± 14*
PAOP (mmHg)	9 ± 4	12 ± 4*	15 ± 3*,†
EDAI (cm ² /m ²)	9.6 ± 3.6	11.5 ± 3.9*	12.8 ± 3.7*,†
SPV (mmHg)	14 ± 5	10 ± 4*	7 ± 3*,†
dDown (mmHg)	11 ± 6	6 ± 4*	2 ± 2*,†
dDown (%)	10.7 ± 5.5	4.4 ± 3.0*	1.4 ± 1.7*,†
dUp (mmHg)	3 ± 2	4 ± 2	5 ± 2*

Values are mean ± SD. For two patients, final VLS values were the same as VLS 1 values because optimal preload was obtained at baseline.

HR = heart rate; SAP = systolic arterial pressure; MAP = mean arterial pressure; CI = cardiac index; SVRI = systemic vascular resistance index; SVI = stroke volume index; PAOP = pulmonary artery occlusion pressure; EDAI = left ventricular end-diastolic area index; SPV = systolic pressure variation; dDown = delta down component of the SPV; %dDown = dDown expressed as a percentage of the SAP; dUp = delta up component of the SPV.

* Significantly different from baseline values ($P < 0.05$).

† Significantly different from VLS1 values ($P < 0.05$).

patient before (fig. 1A) and after administration of 500 ml (fig. 1B) and 1,000 ml (fig. 1C) hydroxyethylstarch. The comparison of LV preload indexes measured immediately before responder and nonresponder VLSs showed that the EDAI was significantly lower and the SPV and dDown were significantly greater in the responder VLS group than in the nonresponder VLS group (table 3). There was no significant difference in PAOP between the groups (table 3). The overall performance of preload parameters was evaluated by constructing ROC curves. The area under the ROC curves were 0.67 (95% confidence interval [CI]: 0.46 to 0.83), 0.77 (95% CI: 0.59 to 0.92), 0.91 (95% CI: 0.76 to 0.98), 0.94 (95% CI: 0.81 to 0.99), and 0.97 (95% CI: 0.90 to 1.00) for PAOP, EDAI, SPV, %dDown, and dDown, respectively. The area for dDown (fig. 2) was statistically greater than those for EDAI ($P = 0.01$) and PAOP ($P = 0.001$). The optimal threshold values given by ROC analysis were 11 mmHg, 9 cm/m², 10 mmHg, 5 mmHg, and 4.5% for PAOP, EDAI, SPV, dDown, and %dDown, respectively. Thus, if a patient had a dDown value of more than 5 mmHg, he was very likely to respond to a subsequent volume load by increasing his SVI by $\geq 15\%$ (positive predictive value of 95%; 95% CI: 76-100%). In contrast,

Table 3. Left Ventricular Preload Indexes Measured before Responder ($n = 21$) and Nonresponder ($n = 14$) Volume Loading Steps in 15 Patients

	Responder	Nonresponder	<i>P</i>
PAOP (mmHg)	10 ± 4	12 ± 3	0.10
EDAI (cm^2/m^2)	9.1 ± 2.9	12.3 ± 3.5	0.005
SPV (mmHg)	15 ± 4	8 ± 3	0.0001
dDown (mmHg)	11 ± 4	4 ± 2	0.0001
%dDown (%)	10.5 ± 4.4	2.9 ± 1.8	0.0001

Values are mean \pm SD.

PAOP = pulmonary artery occlusion pressure; EDAI = left ventricular end-diastolic area index; SPV = systolic pressure variation; dDown = delta down component of the SPV; %dDown = dDown expressed as a percentage of the systolic arterial pressure.

if dDown was ≤ 5 mmHg, the patient was unlikely to respond to a fluid challenge (negative predictive value of 93%; 95% CI: 66–100%).

Finally, the baseline dDown values obtained in each patient showed a significant correlation to the increase (expressed as a percentage of the initial value) in EDAI ($r = 0.72$; $P = 0.003$) and SVI ($r = 0.76$; $P = 0.001$) in

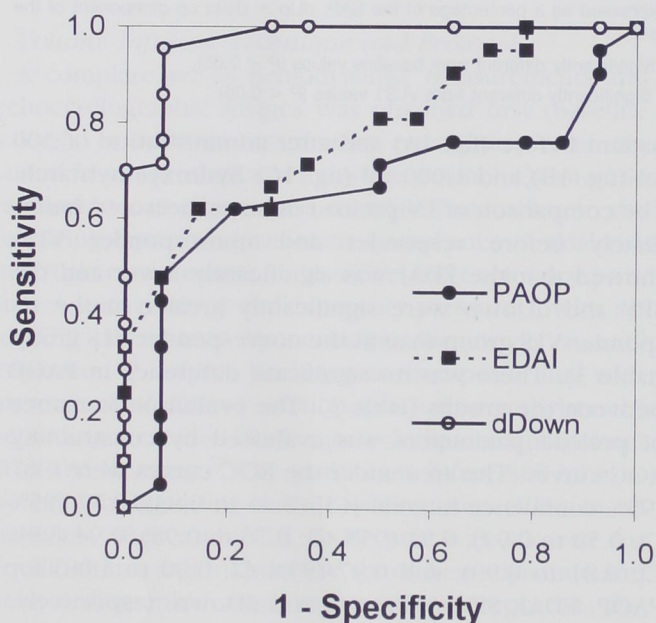


Fig. 2. Receiver operating characteristic (ROC) curves comparing the ability of the pulmonary artery occlusion pressure (PAOP), the left ventricular end-diastolic area index (EDAI), and the delta down component (dDown) of the positive pressure ventilation-induced arterial systolic pressure variation to discriminate between positive ($\geq 15\%$ increase in stroke volume index [SVI]; $n = 21$) and negative ($< 15\%$ increase in SVI; $n = 14$) responses to a subsequent volume-loading step in 15 patients. The area under the ROC curve for dDown is greater than those for EDAI ($P = 0.01$) and PAOP ($P = 0.001$). There is no significant difference between EDAI and PAOP ($P = 0.39$).

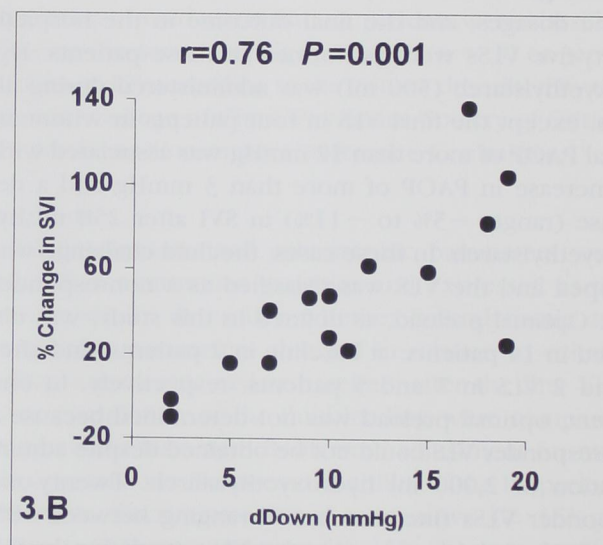
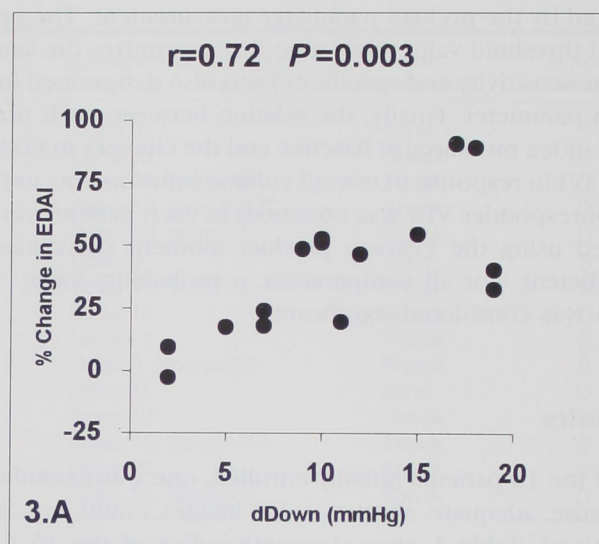


Fig. 3. The relation between delta down (dDown, the difference between the systolic arterial pressure during end-expiratory pause and the minimum systolic pressure during one cycle of a mechanical breath) measured at baseline and the increase in indexed left ventricular end-diastolic area (EDAI; A) and in stroke volume index (SVI; B) in response to volume infusion in 15 patients. The increases in EDAI and SVI are expressed as percentages of the initial (preinfusion) value. r = Pearson correlation coefficient.

response to overall volume infusion (fig. 3). Thus, the higher the initial dDown, the greater the change in EDAI and SVI after completion of volume infusion. A significant correlation also was found between baseline EDAI and the increase in EDAI ($r = -0.63$; $P = 0.01$) and SVI

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($r = -0.52$; $P = 0.046$), but not for PAOP ($r = 0.10$; $P = 0.73$, and $r = -0.08$; $P = 0.77$, with the increase in EDAI, and SVI, respectively).

Discussion

This study was designed to assess the ability of SPV analysis and transesophageal echocardiography-derived LV measurements to predict the response of cardiac output to volume infusion in patients with sepsis-induced hypotension. The results show that dDown is a sensitive indicator of the response to volume loading in patients with sepsis who are sedated and whose lungs are being ventilated. In addition, our study suggests that EDAI estimated by transesophageal echocardiography is not clearly superior to PAOP to guide fluid therapy in these patients.

The assessment of any hemodynamic parameter necessitates its correlation to an existing parameter that serves as a "gold standard." We evaluated the ability of PAOP, LVEDA, SPV, and dDown to estimate the response of thermodilution cardiac output to intravascular volume expansion because, according to the Frank-Starling relation, LV preload is an important determinant of cardiac output. The goal of fluid loading in hypotensive patients with sepsis is usually to increase cardiac output, and thermodilution cardiac output has been validated extensively in the clinical determination of cardiac output. However, because dDown also depends on arterial elastance, it does not assess absolute preload. In addition, whether cardiac output should be increased to maximal values in patients with sepsis is controversial. Limiting the increase in PAOP to minimize the development of pulmonary edema may also be important. The main value of the dDown is that it is a reflection of the response of the LV output to fluid loading. Therefore, it may offer information on a ventricular function curve, as attested by the significant correlation of the initial dDown with the increase in EDAI and SVI in response to volume infusion (fig. 3). Of note, the increasing variance as dDown increases (the data are funnel shaped) in figure 3 suggests that the highest values of dDown may not accurately correlate with the increase in SVI or EDAI in response to fluid loading.

The reduction in dDown with fluid loading observed in the current study is consistent with the significant correlation of SPV and dDown to the amount of bleeding and retransfusion found by Perel *et al.*⁶ in ventilated dogs subjected to graded hemorrhage. Recently their

results were confirmed in relatively healthy, humans who required mechanical ventilation during isoflurane anesthesia.¹⁰ It has also been shown that, in patients requiring mechanical ventilation after vascular surgery, volume loading caused a significant decrease in the SPV and its dDown component.⁹ In our study, the decrease in dDown during volume loading was more important than the decrease in SPV. This was related to an increase in the relative part of dUp (table 2) after completion of volume loading. The prominence of dUp and the absence of dDown characterize experimental hypervolemia and congestive heart failure.⁸ Thus, it is likely that, in our study, the rapid volume expansion and the myocardial dysfunction that can be encountered in patients with sepsis led to this relative increase in dUp. This underscores the importance of measuring dDown and dUp in addition to the SPV. Interpreting a high SPV, which is composed of a dominant dUp as a sign of hypovolemia, may lead to unjustified fluid administration.

Left ventricular end-diastolic dimensions did not predict the response to volume loading as accurately as dDown did. This was unexpected, because EDAI is thought to be the best means to determine LV preload in clinical practice. At least two possible factors may explain these results. First, EDAI in patients without hypovolemia is characterized by wide interindividual variability. In a recent study performed in anesthetized patients, the (mean \pm SD) EDA in baseline conditions was 18 ± 4 cm² in 17 patients with normal LV function, and 23 ± 5 cm² in 13 patients with LV wall motion abnormalities.⁴ Although EDAI values that are much less than the normal range (usually < 5 cm²/m²) strongly suggest hypovolemia, no definitive conclusion can be drawn from higher values, especially in cases of LV dysfunction. The second possible explanation is that a ventricular dilation with normal filling pressures may occur in response to fluid loading in septic patients.^{1,17} In that case, a fluid challenge may increase the SVI, regardless of the initial value of EDAI, which explains the modest predictive value of EDAI concerning the response to fluid loading.

When considering the use of SPV as a clinical monitoring tool, some factors may interfere with the consequence of the provoking maneuver (the mechanical breath) on the outcome variable (the degree of SPV or dDown). The magnitude of breath size (tidal volume) and lung compliance may influence SPV.¹⁸ More important than tidal volume itself could be the variations in intrathoracic pressure, resulting from variations in airway pressure and lung compliance. In the current study,

the plateau airway pressure, which reflects the mean alveolar pressure, ranged from 11 to 34 cm H₂O. This relatively narrow range may have contributed to the results obtained with SPV analysis.

The dDown value of 5 mmHg was the best value to separate responder and nonresponder VLs. In the study of Coriat *et al.*,⁹ a 250-ml colloid infusion significantly increased the cardiac index in patients whose mean dDown value was 4 mmHg. For Rooke *et al.*,¹⁰ a dDown of 2 mmHg or less appeared to indicate minimal intravascular volume depletion. However, both studies were performed in anesthetized patients with normal lung compliance. In the study of Coriat *et al.*,⁹ peak airway pressure ranged from 10 to 15 cm H₂O, with some values dramatically lower than the values recorded in our patients (between 21 and 45 cm H₂O). Recently, analysis of the slope of the line of best fit between the minimal systolic values obtained with four successive pressure-controlled breaths of increasing magnitude was shown to reflect the fluid responsiveness of the LV.[§] Whether this test may be more accurate than dDown measurement in patients with a wide range of lung compliance or airway pressure remains to be seen.

Expressing the SPV as a percentage of the systolic arterial pressure has been postulated to be a better measure of the effects of ventilation on systolic pressure.⁷ In the current study, although systolic arterial pressure increased during volume loading (table 2), %dDown was not a more useful variable than absolute dDown (expressed in mmHg) to assess LV response to volume infusion during septic shock.

Whether changes in systemic vascular resistance (SVR) may alter SPV remains controversial.^{9,10} Systolic pressure variation analysis may be a poor indicator of preload in patients with a low SVR, because a low SVR will influence the magnitude of SPV for a particular decrease in SVI because of mechanical ventilation. In the current study, measurements were made in patients with a relatively wide range of SVR and in the presence of vasopressors in various dosages, suggesting that the SPV analysis may be useful in states of an altered SVR. However, no conclusion can be made from these data as to whether SPV analysis is informative in patients with sepsis who have a very low SVR, especially during initial management before use of vasopressors.

In conclusion, the dDown component of the SPV was a sensitive indicator of the response of the left ventricle to volume infusion in our group of patients. Pressure waveform analysis therefore may be a useful hemodynamic variable in patients with sepsis-induced hypotension who require mechanical ventilation. Insofar as therapeutic intervention in sepsis-induced hypotension revolves around fluids and vasopressors, pressure waveform analysis may be a valuable tool for hemodynamic assessment in patients requiring mechanical ventilation.

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