

critical care review

Predicting Fluid Responsiveness in ICU Patients*

A Critical Analysis of the Evidence

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Study objective: To identify and critically review the published peer-reviewed, English-language studies investigating predictive factors of fluid responsiveness in ICU patients.

Design: Studies were collected by doing a search in MEDLINE (from 1966) and scanning the reference lists of the articles. Studies were selected according to the following criteria: volume expansion performed in critically ill patients, patients classified in two groups (responders and nonresponders) according to the effects of volume expansion on stroke volume or on cardiac output, and comparison of responder and nonresponder patients' characteristics before volume expansion.

Results: Twelve studies were analyzed in which the parameters tested were as follows: (1) static indicators of cardiac preload (right atrial pressure [RAP], pulmonary artery occlusion pressure [PAOP], right ventricular end-diastolic volume [RVEDV], and left ventricular end-diastolic area [LVEDA]); and (2) dynamic parameters (inspiratory decrease in RAP [Δ RAP], expiratory decrease in arterial systolic pressure [Δ down], respiratory changes in pulse pressure [Δ PP], and respiratory changes in aortic blood velocity [Δ Vpeak]). Before fluid infusion, RAP, PAOP, RVEDV, and LVEDA were not significantly lower in responders than in nonresponders in three of five studies, in seven of nine studies, in four of six studies, and in one of three studies, respectively. When a significant difference was found, no threshold value could discriminate responders and nonresponders. Before fluid infusion, Δ RAP, Δ down, Δ PP, and Δ Vpeak were significantly higher in responders, and a threshold value predicted fluid responsiveness with high positive (77 to 95%) and negative (81 to 100%) predictive values.

Conclusion: Dynamic parameters should be used preferentially to static parameters to predict fluid responsiveness in ICU patients. (CHEST 2002; 121:2000–2008)

Key words: arterial pressure; cardiac output; cardiac preload; fluid responsiveness; left ventricular end-diastolic area; pulmonary artery occlusion pressure; right atrial pressure; right ventricular end-diastolic volume; stroke volume; volume expansion

Abbreviations: Δ down = expiratory decrease in arterial systolic pressure; LVEDA = left ventricular end-diastolic area; PAOP = pulmonary artery occlusion pressure; PEEP = positive end-expiratory pressure; Δ PP = respiratory changes in arterial pulse pressure; RAP = right atrial pressure; Δ RAP = inspiratory decrease in right atrial pressure; RVEDV = right ventricular end-diastolic volume; Δ Vpeak = respiratory changes in aortic peak velocity

Volume expansion is frequently used in critically ill patients to improve hemodynamics. Because of the positive relationship between ventricular end-diastolic volume and stroke volume,¹ the expected hemodynamic response to volume expansion is an

increase in right ventricular end-diastolic volume (RVEDV), left ventricular end-diastolic volume, stroke volume, and cardiac output. The increase in end-diastolic volume as a result of fluid therapy depends on the partitioning of the fluid into the different cardiovascular compliances organized in

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series. The increase in stroke volume as a result of end-diastolic volume increase depends on ventricular function since a decrease in ventricular contractility decreases the slope of the relationship between end-diastolic volume and stroke volume.¹ Therefore, only 40 to 72% of critically ill patients have been shown to respond to volume expansion by a significant increase in stroke volume or cardiac output in studies²⁻¹³ designed to examine fluid responsiveness. This finding emphasizes the need for predictive factors of fluid responsiveness in order to select patients who might benefit from volume expansion and to avoid ineffective or even deleterious volume expansion (worsening in gas exchange, hemodilution) in nonresponder patients, in whom inotropic and/or vasopressor support should preferentially be used.

Beside indicators of ventricular preload have been proposed as predictors of fluid responsiveness.^{2-4,6-9,11-13} In this regard, a postal survey in Germany showed that right atrial pressure (RAP) and pulmonary artery occlusion pressure (PAOP) are used by a majority of ICU physicians when deciding to administer fluid,¹⁴ and several recommendations support the use of cardiac filling pressures in order to guide fluid therapy in critically ill patients.^{15,16} Other bedside indicators of ventricular preload, namely RVEDV and left ventricular end-diastolic area (LVEDA), have also been tested as predictors of the hemodynamic effects of volume expansion in critically ill patients.^{2-4,6-9,11,13}

The respiratory changes in RAP, arterial pressure,

and aortic blood velocity, assumed to be dynamic indicators of the sensitivity of the heart to changes in preload induced by changes in pleural pressure, have also been proposed to predict fluid responsiveness in critically ill patients.^{5,9,10,12,13} Therefore, the aim of the present study was to analyze the clinical studies investigating predictive factors of fluid responsiveness in critically ill patients in order to assess the value of each parameter tested.

MATERIALS AND METHODS

Selection of Studies To Be Evaluated

We collected studies investigating the predictive factors of fluid responsiveness in critically ill patients by doing a search in MEDLINE (from 1966). Studies were selected according to the following criteria: volume expansion performed in critically ill patients, patients classified in two groups (responders and nonresponders) according to the effects of volume expansion on stroke volume or on cardiac output, and comparison of responder and nonresponder patients characteristics before volume expansion. The reference lists of the selected articles were scanned for additional studies. Of the 12 included studies,²⁻¹³ 11 studies were identified from the electronic database and 1 study was identified from reference tracing.⁵ The main characteristics of these studies are presented in Table 1.

Parameters Tested as Predictors of Fluid Responsiveness

Ten studies have investigated the value of ventricular preload indicators in predicting fluid responsiveness. The parameters tested were RAP in five studies,^{2-4,8,12} PAOP in nine studies,^{2-4,6-9,11,12} RVEDV in six studies,^{2-4,6-8} and

Table 1—Main Characteristics of Clinical Studies Investigating the Predictive Factors of Fluid Responsiveness in ICU Patients*

Source	Patients, No.	FC, No.	Fluid Infused	Volume Infused, mL	Speed of FC, min	Definition of Response	Rate of Response, %	Parameters Tested
Calvin et al ²	28	28	5% Alb	250	20-30	$\Delta SV > 0\%$	71	RAP, PAOP, RVEDV
Schneider et al ³	18	18	FFP	500	30	$\Delta SV > 0\%$	72	RAP, PAOP, RVEDV
Reuse et al ⁴	41	41	4.5% Alb	300	30	$\Delta CO > 0\%$	63	RAP, PAOP, RVEDV
Magder et al ⁵	33	33	9% NaCl	100-950		$\Delta CO > 250$ mL/min	52	ΔRAP
Diebel et al ⁶	15	22	R. lactate Colloids	300-500 500		$\Delta CO > 10\%$	59	PAOP, RVEDV
Diebel et al ⁷	32	65	R. lactate	300-500		$\Delta CO > 20\%$	40	PAOP, RVEDV
Wagner and Leatherman ⁸	25	36	9% NaCl 5% Alb, FFP	938 ± 480 574 ± 187	7-120	$\Delta SV > 10\%$	56	RAP, PAOP, RVEDV
Tavernier et al ⁹	15	35	HES	500	30	$\Delta SV > 15\%$	60	PAOP, LVEDA, Δ_{down}
Magder and Lagonidis ¹⁰	29	29	25% Alb 9% NaCl	100 150-400	15	$\Delta CO > 250$ mL/min	45	ΔRAP
Tousignant et al ¹¹	40	40	HES	500	15	$\Delta SV > 20\%$	40	PAOP, LVEDA
Michard et al ¹²	40	40	HES	500	30	$\Delta CO > 15\%$	40	RAP, PAOP, ΔPP
Feissel et al ¹³	19	19	HES	8 mL/kg	30	$\Delta CO > 15\%$	53	LVEDA, ΔV_{peak}
Total	334	406					52	

*FC = fluid challenge; Alb = serum albumin; FFP = fresh frozen plasma; NaCl = serum saline solution; R. lactate = Ringer's lactate; HES = hydroxyethylstarch; ΔSV = volume expansion-induced changes in stroke volume; ΔCO = volume expansion-induced changes in cardiac output.

LVEDA in three studies^{9,11,13} (Table 1). In all studies, the RAP and PAOP were measured at end-expiration without ventilator disconnection or removal of positive end-expiratory pressure (PEEP). In four studies,^{4,6–8} RVEDV was calculated from the measurement of right ventricular ejection fraction and cardiac output by using a fast-response thermistor pulmonary artery catheter as follows: RVEDV = (cardiac output/heart rate)/right ventricular ejection fraction. In two other studies,^{2,3} RVEDV was evaluated by cardiac scintigraphy. LVEDA was measured by transesophageal echocardiography using the transgastric short-axis view of the left ventricle.^{9,11,13}

Five studies have investigated the value of dynamic parameters in predicting fluid responsiveness. These parameters were the inspiratory decrease in RAP (Δ RAP) in two studies,^{5,10} the expiratory decrease in arterial systolic pressure (Δ down) in one study,⁹ the respiratory changes in arterial pulse pressure (Δ PP) in one study,¹² and the respiratory changes in aortic blood velocity (Δ Vpeak) in one study¹³ (Table 1). The Δ RAP was calculated as the difference between the expiratory and the inspiratory RAP.^{5,10} The Δ down was calculated as the difference between the value of the systolic pressure during an end-expiratory pause and the minimal value of systolic pressure over a single respiratory cycle.⁹ The Δ PP was calculated as the difference between the maximal and the minimal value of pulse pressure over a single respiratory cycle, divided by the mean of the two values, and expressed as a percentage.¹² The Δ Vpeak was calculated as the difference between the maximal and minimal peak velocity of aortic blood flow over a single respiratory cycle, divided by the mean of the two values, and expressed as a percentage.¹³ Aortic blood flow was measured by a pulsed-wave Doppler echocardiographic beam at the level of the aortic valve.¹³

RESULTS

There were 406 fluid challenges in 334 patients (Table 1). Most of the patients were septic (55%) and receiving mechanical ventilation (84%). The decision

of volume expansion was based on criteria listed in Table 2. Fluid administration was performed using colloid solutions (albumin, fresh frozen plasma, or hydroxyethylstarch) in 253 instances, and crystalloid solutions (serum saline solution or Ringer's lactate) in 153 instances (Table 1). In nine studies, the volume infused was predetermined and ranged from 250 to 500 mL for colloids and from 300 to 500 mL for crystalloids (Table 1). In two studies,^{5,10} volume infusion was performed until a rise in RAP \geq 2 mm Hg was obtained; hence, the volume of serum saline solution infused varied from 100 to 950 mL. In another study,⁸ fluid was administered until a rise in PAOP \geq 3 mm Hg was obtained. In this case, the volume infused was 938 ± 480 mL for serum saline solution and 574 ± 187 mL for 5% albumin or fresh frozen plasma. The speeds of fluid infusion are reported in Table 1. In all studies but one,⁹ hemodynamic measurements were performed just before and immediately at the end of fluid infusion.

The hemodynamic response to volume expansion was defined by an increase in stroke volume in five studies and in cardiac output in seven studies (Table 1). The values of stroke volume or cardiac output increase used to define responder and nonresponder patients are presented in Table 1.

RAP

Before volume expansion, RAP was not significantly lower in responders than in nonresponders in three of five studies^{2,4,12} (Fig 1). The two remaining studies^{3,8} reported a lower value of baseline RAP in

Table 2—Criteria Used to Decide Volume Expansion*

Source	Criteria
Calvin et al ²	Cardiac index $<$ 3.5 L/min/m ² and PAOP $<$ 12 mm Hg in septic and trauma patients
Schneider et al ³	Cardiac index $<$ 2.5 L/min/m ² and PAOP $<$ 20 mm Hg in acutely ill patients with a defined cardiac cause
Reuse et al ⁴	Systematic infusion in patients with septic shock
Magder et al ⁵	Systolic BP $<$ 90 mm Hg or cardiac index $<$ 2.5 L/min/m ² or heart rate $>$ 120/min or decreased urine output ($<$ 25 mL/h)
Diebel et al ⁶	Clinical impression that the cardiac output was inadequate for tissue needs and would respond to volume loading
Diebel et al ⁷	Oliguria (urine output $<$ 30 mL/h) or hypotension or in an attempt to optimize oxygen delivery
Wagner and Leatherman ⁸	In an attempt to increase oxygen delivery to $>$ 600 mL/min/m ² or to reach a plateau in the oxygen consumption-delivery relationship
Tavernier et al ⁹	One or more clinical conditions that suggested the possibility of inadequate preload: hypotension ($<$ 100 mm Hg), oliguria ($<$ 30 mL/h), tachycardia ($>$ 100/min), lactic acidosis, cool extremities, vasopressor wean, azotemia
Magder and Lagonidis ¹⁰	Sepsis-induced hypotension (systolic BP $<$ 90 mm Hg or its reduction by \geq 40 mm Hg from usual values)
Toussignant et al ¹¹	As part of routine testing to assess cardiac filling status if PAOP \leq 18 mm Hg
Michard et al ¹²	PAOP $<$ 20 mm Hg or inotropic support or low urine output and adequate gas exchange
Feissel et al ¹³	Systolic BP $<$ 90 mm Hg or the need of vasoactive drugs (dopamine $>$ 5 μ g/kg/min or norepinephrine) and PAOP $<$ 18 mm Hg and PaO ₂ /FIO ₂ $>$ 100 mm Hg
	Systematic infusion in septic shock patients with preserved left ventricular systolic function and PaO ₂ /FIO ₂ $>$ 100 mm Hg

*FIO₂ = fraction of inspired oxygen.

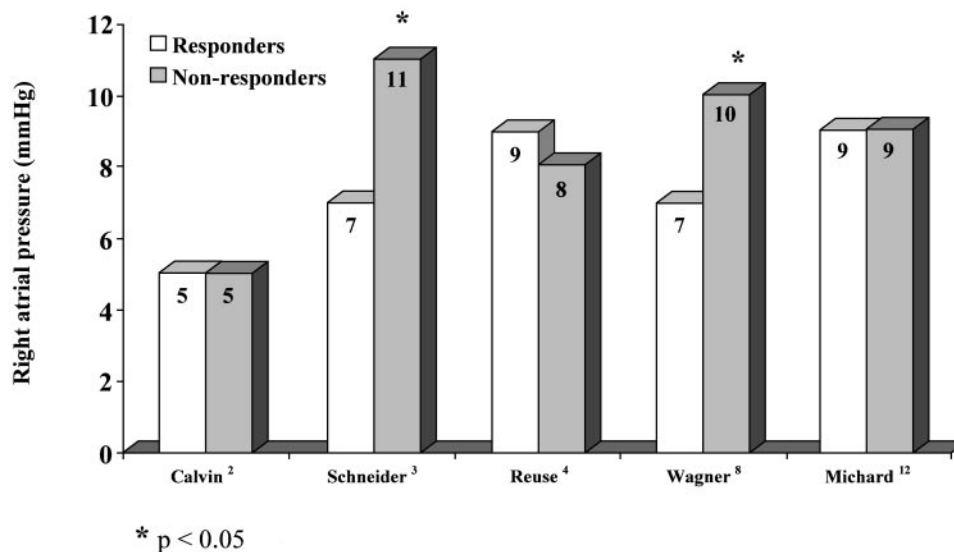


FIGURE 1. Mean RAP before volume expansion in responders and nonresponders.

responders than in nonresponders (Fig 1), and a significant relationship between the baseline RAP ($r^2 = 0.20$), and the increase in stroke volume in response to volume expansion was reported by Wagner and Leatherman.⁸ However, the marked overlap of individual RAP values did not allow the identification of a RAP threshold value discriminating responders and nonresponders before fluid was administered.

PAOP

Before volume expansion, PAOP was not significantly lower in responders than in nonresponders in seven of nine studies^{2-4,6,7,9,12} (Table 3). Three studies^{6,8,11} reported a significant difference between the baseline value of PAOP in responders and nonre-

sponders (Table 3). In the first study,⁶ the mean value of PAOP was significantly higher in responder patients (14 ± 7 mm Hg vs 7 ± 2 mm Hg, $p < 0.01$). In contrast, the two other studies^{8,11} reported a significantly lower value of PAOP at baseline in responders than in nonresponders (Table 3), and a significant relationship between the baseline PAOP ($r^2 = 0.33$) and the increase in stroke volume in response to volume expansion was reported by Wagner and Leatherman.⁸ However, in none of these studies, a PAOP cutoff value was proposed to predict the hemodynamic response to volume expansion before fluid was administered.

RVEDV

Before volume expansion, RVEDV index was not significantly lower in responders than in nonresponders in four of six studies^{2-4,8} (Fig 2). In the two remaining studies of Diebel et al,^{6,7} RVEDV index was significantly lower at baseline in responders than in nonresponders (Fig 2), RVEDV index < 90 mL/m² was associated with a high rate of response (100% and 64%, respectively), and RVEDV index > 138 mL/m² was associated with the lack of response to volume expansion. However, when the RVEDV index ranged from 90 to 138 mL/m², no threshold value was proposed to discriminate responder and nonresponder patients before volume expansion. Moreover, another study⁸ reported a positive response to volume expansion in four of nine patients with a RVEDV index > 138 mL/m², a lack of response in three of nine patients despite a RVEDV < 90 mL/m², and a significant but weak relationship between the baseline RVEDV index

Table 3—PAOP Before Volume Expansion in Responders and Nonresponders*

Source	PAOP, mm Hg	
	Responders	Nonresponders
Calvin et al ²	8 ± 1	7 ± 2
Schneider et al ³	10 ± 1	10 ± 1
Reuse et al ⁴	10 ± 4	10 ± 3
Diebel et al ⁶	14 ± 7	7 ± 2 †
Diebel et al ⁷	16 ± 6	15 ± 5
Wagner and Leatherman ⁸	10 ± 3	14 ± 4 †
Tavernier et al ⁹	10 ± 4	12 ± 3
Tousignant et al ¹¹	12 ± 3	16 ± 3 †
Michard et al ¹²	10 ± 3	11 ± 2

*Values are expressed as mean \pm SD, except for the study of Schneider et al³ (mean \pm SEM).

†p < 0.05 responders vs nonresponders.

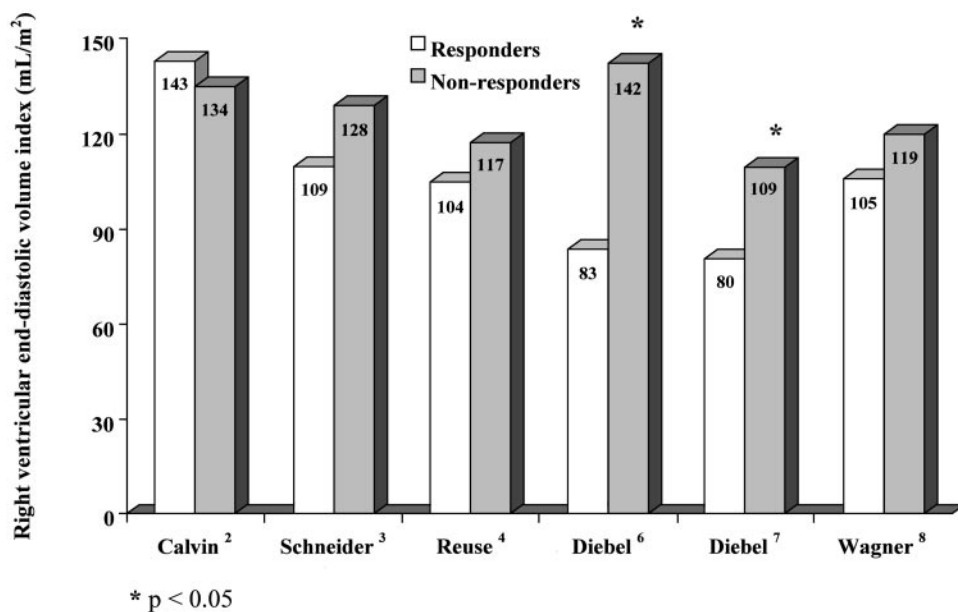


FIGURE 2. Mean RVEDV index before volume expansion in responders and nonresponders.

($r^2 = 0.19$) and the increase in stroke volume in response to volume expansion.

LVEDA

In two studies,^{9,11} the LVEDA before volume expansion was significantly lower in responders than in nonresponders (Table 4). In the study of Tavernier et al,⁹ a significant and negative relationship ($r^2 = 0.4$, $p = 0.01$) was also reported between the baseline value of LVEDA index and the percentage of increase in stroke volume in response to volume expansion. However, using receiver operating characteristic curve analysis, Tavernier et al⁹ demonstrated minimal value of LVEDA index to discriminate responder and nonresponder patients. In the study of Tousignant et al,¹¹ a marked overlap of baseline individual LVEDA values was observed so that a given value of LVEDA could not be used to predict the hemodynamic response to fluid infusion.

Table 4—LVEDA Before Volume Expansion in Responders and Nonresponders*

Source	LVEDA, cm^2/m^2	
	Responders	Nonresponders
Tavernier et al ⁹	9 ± 3	12 ± 4 †
Tousignant et al ¹¹	15 ± 5 ‡	20 ± 5 ‡
Feissel et al ¹³	10 ± 4	10 ± 2

*Data are presented as mean \pm SD.

† $p < 0.05$ responders vs nonresponders.

‡Area expressed in centimeters squared.

Moreover, in another study,¹³ responder and nonresponder patients were not different with regard to the baseline value of LVEDA index ($10 \pm 4 \text{ cm}^2/\text{m}^2$ vs $10 \pm 2 \text{ cm}^2/\text{m}^2$), and no significant relationship ($r^2 = 0.11$, $p = 0.17$) was observed between the baseline value of LVEDA index and the percentage of increase in cardiac index in response to volume expansion.

Δ RAP

In patients with spontaneous breathing activity, two studies from Magder et al^{5,10} demonstrated that an inspiratory decrease in RAP ≥ 1 mm Hg predicted a positive response to volume expansion, with positive predictive values of 77% and 84% and negative predictive values of 81% and 93% (Table 5).

Δ down

In sedated patients receiving mechanical ventilation with sepsis-induced hypotension, one study⁹ demonstrated that the Δ down was significantly greater (11 ± 4 mm Hg vs 4 ± 2 mm Hg, $p = 0.0001$) in responders than in nonresponders, and that the Δ down threshold value of 5 mm Hg was able to discriminate responders and nonresponders with a positive predictive value of 95% and a negative predictive value of 93% (Table 5). Moreover, this study⁹ reported a positive and good relationship ($r^2 = 0.58$, $p = 0.001$) between the baseline value of Δ down and the percentage of increase in stroke volume in response to volume expansion.

Table 5—Positive and Negative Predictive Values of Dynamic Parameters

Source	Patients, No.	Parameters Tested	Best Threshold Value	Positive Predictive Value, %	Negative Predictive Value, %
Magder et al ⁵	33	Δ RAP	1 mm Hg	84	93
Tavernier et al ⁹	35	Δ down	5 mm Hg	95	93
Magder and Lagonidis ¹⁰	29	Δ RAP	1 mm Hg	77	81
Michard et al ¹²	40	Δ PP	13%	94	96
Feissel et al ¹³	19	Δ Vpeak	12%	91	100

Δ PP

In sedated patients receiving mechanical ventilation with acute circulatory failure related to sepsis, one study¹² demonstrated that Δ PP was significantly greater ($24 \pm 9\%$ vs $7 \pm 3\%$, $p < 0.001$) in responders than in nonresponders, and that a Δ PP threshold value of 13% allowed discrimination between responder and nonresponder patients with a positive predictive value of 94% and a negative predictive value of 96% (Table 5). Moreover, in this study,¹² the value of Δ PP before fluid administration was significantly and closely correlated ($r^2 = 0.85$, $p < 0.001$) with the volume expansion-induced changes in cardiac output, such that the higher Δ PP at baseline, the greater was the increase in cardiac output in response to fluid infusion.

Δ Vpeak

In sedated patients receiving mechanical ventilation with septic shock, one study¹³ demonstrated that Δ Vpeak was significantly greater ($20 \pm 6\%$ vs $10 \pm 3\%$, $p < 0.01$) in responder patients than in nonresponder patients, and that a Δ Vpeak threshold value of 12% allowed discrimination between responder and nonresponder patients with a positive predictive value of 91% and a negative predictive value of 100% (Table 5). Moreover, a positive and tight linear correlation ($r^2 = 0.83$, $p < 0.001$) was found between the Δ Vpeak before volume expansion and the volume expansion-induced changes in cardiac output.

DISCUSSION

The present analysis emphasizes the minimal clinical value of ventricular preload indicators and the higher value of dynamic parameters (testing the cardiovascular response to respiratory changes in pleural pressure) in predicting fluid responsiveness in critically ill patients. It has been suggested that a beneficial hemodynamic effect of volume expansion cannot be expected in critically ill patients with a

RAP > 12 mm Hg¹⁷ and/or a PAOP > 12 mm Hg or > 15 mm Hg.^{15,18} In this regard, RAP and PAOP have been reported to be lower in responders than in nonresponder patients in two studies (Fig 1, Table 3). Moreover, a significant relationship between the increase in stroke volume in response to volume expansion and the baseline RAP ($r^2 = 0.20$) or the baseline PAOP ($r^2 = 0.33$) was reported by Wagner and Leatherman,⁸ suggesting that the lower RAP or PAOP before volume expansion, the greater the increase in stroke volume in response to fluid infusion. However, although statistically significant, these relationships were weak because a given value of RAP or of PAOP could not be used to discriminate responders and nonresponders before fluid was administered. Moreover, in all other clinical studies (Fig 1, Table 3), no difference between responder and nonresponder patients was observed with regard to the baseline value of RAP and of PAOP, and no relationship was reported between cardiac filling pressures before volume expansion and the hemodynamic response to volume expansion. Finally, it must be noted that fluid infusion has been shown to significantly increase cardiac output in some critically ill patients with central venous pressures > 15 mm Hg.¹⁹

Two studies of Diebel et al^{6,7} reported a lower value of RVEDV index in responder than in nonresponder patients, and suggested that a beneficial hemodynamic effect of volume expansion was likely (rate of response 100% and 64%) when the RVEDV index was below 90 mL/m² and very unlikely (rate of response of 0%) when the RVEDV index was > 138 mL/m². However, when the RVEDV index ranged from 90 to 138 mL/m², no cutoff value could be proposed to discriminate responder and nonresponder patients. Moreover, Wagner and Leatherman⁸ reported positive responses to volume expansion in patients with a RVEDV index > 138 mL/m², and the lack of response in patients with a RVEDV index < 90 mL/m². Finally, in four of six studies investigating whether RVEDV could predict fluid responsiveness, no significant difference was observed between re-

sponders and nonresponders with regard to the baseline value of RVEDV index (Fig 2).

The echocardiographic measurement of LVEDA has been shown to reflect more accurately the left ventricular preload when compared with PAOP,²⁰ and to improve the ability to detect changes in left ventricular function caused by acute blood loss.²¹ In nine anesthetized mongrel dogs, Swenson et al²² reported a significant relationship between baseline LVEDA and changes in cardiac output induced by IV fluid therapy, suggesting that LVEDA could be an indicator of fluid responsiveness. In this regard, LVEDA was found to be significantly lower in responders than in nonresponders in two clinical studies,^{9,11} and a significant relationship between the baseline LVEDA index and the changes in stroke volume induced by volume expansion has also been reported.⁹ However, using receiver operating characteristic curve analysis, Tavernier et al⁹ demonstrated in patients with sepsis-induced hypotension the minimal value of a given LVEDA index value to discriminate responders and nonresponders before fluid was administered. Moreover, in the study of Tousignant et al,¹¹ including medical-surgical ICU patients, considerable overlap of baseline individual values of LVEDA was observed between responders and nonresponders, supporting the interpretation that a specific LVEDA value cannot reliably predict fluid responsiveness in an individual patient. Recently, in patients with septic shock, Feissel et al¹³ did not observe any difference between the mean baseline value of LVEDA index in responders and nonresponders, neither any relationship between the baseline value of LVEDA index and the percentage of change in cardiac index in response to volume expansion.

Therefore, all clinical studies have emphasized the lack of value of ventricular preload indicators as predictors of fluid responsiveness in critically ill patients. Methodologic and physiologic reasons could be advanced to explain these findings. First, RAP, PAOP, RVEDV, and LVEDA are not always accurate indicators of ventricular preload. Indeed, RAP and PAOP have been shown to overestimate transmural pressures in patients with external²³ or intrinsic²⁴ PEEP. The PAOP is highly dependent on left ventricular compliance,²⁵ which is frequently decreased in ICU patients (sepsis, ischemic, or hypertrophic cardiopathy). Because it is the transmural pressures and not intracavitary pressures such as RAP and PAOP that are related to end-diastolic volumes via the chamber compliance, it is not surprising that those surrogates bear little relationship to fluid responsiveness. The evaluation of RVEDV by thermodilution has been shown influenced by tricuspid regurgitation,²⁶ which is frequently en-

countered in patients with pulmonary hypertension (ARDS, mechanical ventilation with PEEP). The estimation of the LVEDA by echocardiography does not always accurately reflect left ventricular end-diastolic volume²⁷ and hence LV preload. Second, in case of right ventricular dysfunction, a beneficial hemodynamic effect of volume expansion cannot be expected, even in the case of low left ventricular preload.²⁸ Third, knowing the preinfusion end-diastolic volume tells little about the diastolic chamber compliance. In this regard, hypovolemia can be associated with a normal or high LVEDA value in patients with dilated cardiopathy. Finally, two matters must be stressed: (1) the increase in end-diastolic volume as a result of fluid therapy depends on the partitioning of the fluid into the different cardiovascular compliances organized in series, and (2) the rise in stroke volume as a result of end-diastolic volume increase depends on ventricular function since a decrease in ventricular contractility decreases the slope of the relationship between end-diastolic volume and stroke volume.¹ Therefore, a patient can be nonresponder to a fluid challenge because of high venous compliance, low ventricular compliance and/or ventricular dysfunction. In this regard, it is not so surprising that bedside indicators of cardiac chambers dimensions are not accurate predictors of fluid responsiveness in ICU patients in whom venous capacitance, ventricular compliance, and contractility are frequently altered.

Assuming that respiratory changes in pleural pressure induce greater changes in RAP when the right ventricle is highly compliant than when it is poorly compliant, Magder et al investigated whether the inspiratory decrease in RAP could be used to predict fluid responsiveness.^{5,10} Two studies^{5,10} demonstrated that a positive response to volume expansion was very likely in patients with an inspiratory decrease in RAP ≥ 1 mm Hg, while it was unlikely if the inspiratory decrease in RAP was < 1 mm Hg. Unfortunately, most of ICU patients with acute circulatory failure are sedated and receiving mechanical ventilation, thus are unable to produce an inspiratory decrease in pleural pressure sufficient to decrease the RAP.¹⁰ In this condition, analysis of the respiratory changes in left ventricular stroke volume has been proposed to predict fluid responsiveness. Indeed, by decreasing the venous return pressure gradient, mechanical insufflation may decrease the right ventricular filling,²⁹ and consequently the right ventricular output if the right ventricle is sensitive to changes in preload. In this condition, the following decrease in left ventricular filling may also induce a significant decrease in left ventricular output if the left ventricle is sensitive to changes in preload. Therefore, the magnitude of the respiratory changes

in left ventricular stroke volume, which reflects the sensitivity of the heart to changes in preload induced by mechanical insufflation, has been proposed as a predictor of fluid responsiveness. Because the arterial pulse pressure (systolic minus diastolic pressure) is directly proportional to left ventricular stroke volume,³⁰ the respiratory changes in left ventricular stroke volume have been shown reflected by changes in pulse pressure.³¹ Accordingly, the respiratory changes in pulse pressure have been shown to accurately predict fluid responsiveness in patients receiving mechanical ventilation with acute circulatory failure related to sepsis.¹² The analysis of the respiratory changes in systolic pressure has also been proposed to assess fluid responsiveness. However, the systolic pressure variation induced by mechanical ventilation results not only from changes in aortic transmural pressure (mainly related to changes in left ventricular stroke volume), but also from changes in extramural pressure (*ie*, from changes in pleural pressure).^{32,33} Therefore, the systolic pressure variation is a less specific indicator of changes in left ventricular stroke volume and hence a less accurate predictor of fluid responsiveness than the pulse pressure variation.¹² In this regard, it has been proposed to discriminate the inspiratory increase in systolic pressure (not necessarily due to a change in left ventricular stroke volume) from the Δ_{down} , which in contrast necessarily reflects a change in left ventricular stroke volume.³⁴ Experimental and clinical studies^{34,35} have emphasized the influence of volume status on Δ_{down} (hemorrhage increases Δ_{down} , while volume expansion decreases Δ_{down}), and Tavernier et al⁹ demonstrated that Δ_{down} is an accurate predictor of fluid responsiveness in septic patients with hypotension.

The analysis of the arterial pressure waveform is not possible in patients with cardiac arrhythmias.³⁶ Indeed, in this condition, the changes in arterial pressure do not reflect the effects of mechanical insufflation on left ventricular stroke volume. It must be emphasized that the evaluation of Δ_{down} and of Δ_{PP} requires invasive arterial pressure catheterization. However, in shock states, estimation of BP using a cuff is commonly inaccurate, and use of an arterial cannula provides a more appropriate and reproducible measurement of arterial pressure.¹⁵ Interestingly, Feissel et al¹³ have recently demonstrated that Doppler echocardiographic imaging of aortic blood velocity could be used to assess noninvasively the respiratory changes in aortic blood velocity and to predict fluid responsiveness in patients with septic shock. It must be noted that Δ_{down} , Δ_{PP} , and ΔV_{peak} have been shown to be accurate predictors of fluid responsiveness in sedated patients receiving mechanical ventilation with sepsis.

Whether they also predict fluid responsiveness in nonsedated, spontaneously breathing patients without sepsis remains to be determined.

It must be emphasized that various types and volumes of fluid, speeds of fluid infusion, and definitions of responders to volume expansion have been used in the studies analyzed (Table 1). This may have a significant influence on the results and conclusions of the studies. Indeed, the hemodynamic effects of an hypertonic colloid infusion are expected to be more dramatic than those of an equal volume of isotonic crystalloid infusion. Because of intravascular-extravascular equilibration, the speed of volume infusion should also greatly influence the hemodynamic response, particularly in septic patients with systemic capillary leakiness. Moreover, because of different definitions of responders from one study to another, some patients considered as responders in some studies, would have been considered as nonresponders in other studies. Unfortunately, because individual data were not available in all but one study, a comparison of the predictive value of each parameter using the same definition of responders was not possible. Finally, the predictive value of dynamic parameters has been tested by only few studies. Therefore, further studies are required to confirm the high value of dynamic parameters in discriminating responder and nonresponder patients before fluid infusion. However, our analysis emphasizes the minimal value of static ventricular preload parameters as predictors of fluid responsiveness and strongly supports the use of the dynamic parameters in the decision-making process concerning volume expansion in critically ill patients.

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