Original Article

Dynamic Arterial Elastance for Predicting Mean Arterial Pressure Responsiveness after Fluid Challenges in Acute Respiratory Distress Syndrome Patients

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Background: Blood pressure is controlled by stroke volume and afterload. Arterial load is an effective measure of afterload because it represents all extracardiac factors that oppose left ventricular ejection. Dynamic arterial elastance (Ea_{dyn}; pulse pressure variation over stroke volume variation) is a dynamic parameter of arterial load that can be continuously monitored. Ea_{dyn} was reported to predict mean arterial pressure (MAP) responsiveness after a fluid challenge.

Objective: To assess whether Ea_{dyn} can predict MAP responsiveness in acute respiratory distress syndrome (ARDS) patients ventilated with low tidal volume.

Materials and Methods: The authors performed a prospective study of diagnostic test accuracy in adult ARDS patients with acute circulatory failure and fluid responsiveness. All patients received continuous blood pressure monitoring via an arterial line connected to a Flotrac™ transducer and Vigileo™ monitor. When the attending physicians decided to load intravenous fluid, the authors recorded the pulse pressure variation over stroke volume variation and other hemodynamic parameters before and after fluid bolus. MAP responsiveness was defined as increased MAP of 10% or more from baseline after fluid challenge.

Results: Twenty-three events were included. Nine events (39.13%) were MAP-responsive. Cardiac output, heart rate, and stroke volume were similar in both MAP-responder and MAP-non-responder groups. Baseline MAP, diastolic blood pressure, and pulse pressure were significantly different after fluid challenge in the MAP-responder group. Ea_{dyn} of the pre-infusion phase failed to predict MAP responsiveness after fluid challenge (area under the curve 0.603, 95% confidence interval 0.38 to 0.798).

Conclusion: Arterial load parameters, including Ea_{dyn}, derived from non-calibrated pulse contour analysis failed to predict MAP responsiveness in ARDS patients with low tidal volume ventilation.

Keywords: Acute respiratory distress syndrome, Dynamic arterial elastance, Mean arterial pressure, Pulse contour analysis

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Blood pressure (BP) is controlled by stroke volume (SV) and afterload. Arterial load is an effective measure of afterload because it represents all extracardiac factors that oppose left ventricular ejection. Effective arterial elastance is the ratio between pressure and volume, and represents arterial load. Theoretically, effective arterial elastance can predict whether a volume infusion will increase BP. However, effective arterial elastance is a static parameter because pulse pressure (PP) and SV are used in the calculation. By contrast, dynamic arterial elastance (Ea_{dyn}) derived from PP variation (PPV) and SV variation (SVV) reflects dynamic changes in both hemodynamic parameters, which continuously change according to a patient's intravascular volume status. Ea_{dyn} was previously reported to predict mean arterial pressure (MAP) responsiveness after fluid bolus[1,2].

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The authors were particularly interested in the use of Ea_{dyn} for predicting MAP responsiveness in acute respiratory distress syndrome (ARDS), because liberal fluid management can prolong the duration of intensive care unit (ICU) stay and mechanical ventilator days[3]. Therefore, intravenous fluid infusion in ARDS requires careful adjustment when patients need resuscitation. Furthermore, vasopressors or inotropic drugs may be added during resuscitation instead of intravenous fluid. Thus, in the present study, the authors examined the hypothesis that Ea_{dyn} derived from the pulse contour analysis technique would predict an increase in MAP after fluid bolus in ARDS patients ventilated with a low tidal volume with hypotensive stages or suspected hypoperfusion.

Materials and Methods

The present prospective study of diagnostic test accuracy was conducted at the medical ICUs in Ramathibodi Hospital between March 2017 and January 2018. The study was approved by the Ethics Committee of the Institute (no.2560/13). Informed consents were obtained from close relatives of the patients because most of the patients were under deep sedation or neuromuscular blocking agents.

Patients

The authors included patients 18 years or older who were diagnosed as ARDS, with a partial pressure of oxygenation in the arterial blood over fraction of inspired oxygen ratio of less than 300 and a positive end expiratory pressure of 5 cmH_2O or more on a mechanical ventilator with a tidal volume of less than 8 mL/kg of predicted body weight, and who developed acute circulatory failure with one of the following criteria:

- MAP of less than 65 mmHg, or systolic BP (SBP) of less than 90 mmHg or decrease from baseline of 40 mmHg
- Urine output of less than 0.5 mL/kg/hour
- Serum arterial lactate of 4 mmol/L or more

All patients' intravascular volume status were in fluid responsiveness according to:

- Passive leg raising test: cardiac output (CO) increase of 10% or more, assessed using the Vigileo™ after leg raising under deep sedation or paralysis, or
- Mini-fluid challenge test: increase in velocity time integral by 10% or more after 100 mL crystalloid infusion over one minute.

The exclusion criteria were arrhythmias, poor left ventricular ejection fraction, on inotropic drugs, ratio of heart rate (HR) to respiratory rate of less than 3.6, and patients or their relatives' refusal. If the patients were in fluid responsiveness, 500 mL of the crystalloid such as normal saline or Acetar® was infused over 15 minutes. The hemodynamic parameters were recorded both before and after fluid bolus.

Hemodynamic measurements

CO was continuously monitored in all patients using a monitor and specific transducer (Vigileo™, Flotrac™; Edwards Lifesciences, Irvine, CA, USA) connected to an arterial line system. The Vigileo™ was also used to calculate SV and SVV every 20 seconds. PPV, SBP, diastolic BP (DBP), MAP, and HR were obtained from a vital signs monitor (Intellivue MP70; Philips, Petaluma, CA, USA). SVV and PPV were obtained as an average of three consecutive values from each monitor. Ea_{dyn} was calculated from the PPV over SVV ratio. Ventilator settings and dosage of vasopressors were unchanged during the study period.

Sample size calculation and statistical analysis

Garcia et al reported that baseline Ea_{dyn} as a measure of arterial load could predict an increase in MAP response to fluid administration with an area under the receiver operating characteristic curve (AUC) of 0.94 (95% confidence interval [CI] 0.86 to 0.98; $p<0.0001$)[2]. In that study, a pre-infusion Ea_{dyn} value of 0.73 or greater discriminated MAP responder patients with a sensitivity of 90.9% and a specificity of 91.5%, while the incidence of MAP responsiveness after fluid challenge was 41.2%. Based on these findings, the authors recruited twenty-three fluid challenge events in the present study. The Kolmogorov-Smirnov test was used to test the normality of data distribution. Normally distributed continuous data were shown as mean ± standard deviation. Non-normally distributed continuous data were shown as median (25^{th} to 75^{th} interquartile range). Categorical variables were presented as percent. Comparisons of continuous dependent variables in non-normally distributed data were performed using the Wilcoxon signed rank test. The relationship between Ea_{dyn} and MAP after fluid challenge was examined using a linear regression analysis. The AUC curve and the 95% CI were calculated and compared for sensitivity and specificity. A p-value of less than 0.05 was considered statistically significant. All statistical analyses were performed using statistical software (Stata, version 14.1; StataCorp LP, College Station, TX, USA). Graphs were created

Table 1. Patients' characteristics (n=23)

Parameters	Value Mean±SD
Age (year)	61.39±19.23
Sex (male/female)	11/12
Actual body weight (kg)	61.72±9.55
Predicted body weight (kg)	58.16±10.15
Ideal body weight (kg)	59.25±6.66
Height (cm)	163.83±9.09
BMI (kg/m^2)	22.84±4.83
APACHE II score at admission	26.43±6.50
Arterial lactate (mmol/L); median (range)	2.2 (1.5 to 4.0)
Norepinephrine; n, median (range[1])	12, 0.27 (0.23 to 0.38)
Cause of acute circulatory failure; n (%)	
Hypotension	19 (82.6)
Hyperlactatemia	4 (17.4)
Analgesic, sedative, and neuromuscular blocking agents	
Fentanyl; n, median (range[2])	19, 1.52 (0.90 to 1.89)
Propofol; n, median (range[3])	3, 0.91 (0.61 to 1.05)
Midazolam; n, median (range[3])	12, 0.05 (0.04 to 0.17)
Cisatracurium; n, median (range[3])	15, 0.09 (0 to 0.15)

APACHE II=Acute Physiology and Chronic Health Evaluation II; BMI= body mass index; SD=standard deviation

[1] Dose range in mcg/kg/minute, [2] Dose range in mcg/kg/hour, [3] Dose range in mg/kg/hour

Table 2. Ventilator settings (n=23)

Parameter	Value Mean±SD
Tidal volume (ml/kg predicted body weight)	7.17±0.79
Driving pressure (cmH_2O)	17.91±5.05
Respiratory rate (breaths/minute)	23.78±4.37
PEEP (cmH_2O)	11.52±3.45
FiO_2	0.65±0.22

cmH_2O=centimeter of water; FiO_2=fraction of inspired oxygen; PEEP=positive end expiratory pressure; SD=standard deviation

using graphing software (MedCalc for Windows v10.2.0.0; MedCalc Software bvba, Mariakerke, Belgium).

Results

Twenty-three fluid challenge events obtained from twelve patients were included in the present study. Patients' characteristics and mechanical ventilator settings are shown in Table 1 and 2, respectively.

Table 3. Effects of fluid challenge on hemodynamic parameters in responder (increase in MAP ≥10% after fluid challenge) and non-responder patients (n=23)

Parameter	Before fluid challenge Mean±SD	After fluid challenge Mean±SD	p-value
CO (L/minute)			
Responders	4.46±1.31	4.59±1.50	0.575
Non-responders	4.62±1.36	4.90±1.61	
HR (beats/minute)			
Responders	111.78±16.81	112.0±11.63	0.834
Non-responders	112.07±19.37	111.43±17.65	
SV (ml)			
Responders	40.33±11.07	41.33±13.83	0.589
Non-responders	42.43±13.07	44.79±14.60	
MAP (mmHg)			
Responders	58.78±5.91	73.11±7.08	<0.001
Non-responders	62.93±10.95	63.07±12.59	
SBP (mmHg)			
Responders	83.33±9.63	105.78±11.64	<0.001
Non-responders	85.71±16.57	87.64±20.13	
DBP (mmHg)			
Responders	46.44±6.17	56.22±5.36	0.022
Non-responders	50.93±7.88	52.21±12.42	
PP (mmHg)			
Responders	36.89±10.33	48.67±13.07	0.004
Non-responders	34.86±10.98	37.93±13.58	
PPV (%)			
Responders	15.67±6.21	10.56±4.28	0.279
Non-responders	16.14±8.86	14.14±7.34	
SVV (%)			
Responders	15.89±6.77	10.67±6.0	0.058
Non-responders	14.21±6.35	13.29±9.72	

CO=cardiac output; HR=heart rate; SV=stroke volume; MAP=mean arterial pressure; SBP=systolic blood pressure; DBP=diastolic blood pressure; PP=pulse pressure; PPV=pulse pressure variation; SVV= stroke volume variation; SD=standard deviation

p-values refer to group (responder vs. non-responder) and time (pre-infusion vs. post-infusion) interaction using a repeated measures analysis of variance

Responses of hemodynamic parameters to fluid challenge

The effects of fluid challenge on hemodynamic parameters in MAP responders and non-responders are shown in Table 3. MAP responders were defined as an increase in MAP by 10% or more after fluid challenge with crystalloid infusion (500 mL over 15 minutes). There were nine events (39%) of an increase

Table 4. Effects of fluid challenge on arterial load parameters in responder and non-responder patients (n=23)

Parameter	Before fluid challenge Mean±SD	After fluid challenge Mean±SD	p-value
Ea_{dyn} (PPV/SVV)			
Responders	1.01±0.31	1.04±0.26	0.676
Non-responders	1.13±0.31	1.24±0.51	
Ea_{eff} (PP/SV)			
Responders	1.00±0.50	1.37±0.78	0.023
Non-responders	0.95±0.56	0.98±0.62	

Ea_{dyn}=dynamic arterial elastance; Ea_{eff}=effective arterial elastance; PP=pulse pressure; PPV=pulse pressure variation; SV=stroke volume; SVV=stroke volume variation; SD=standard deviation

in MAP by 10% or more after fluid challenge, seven (30%) of which were fluid responsive. There were no differences in hemodynamic parameters, including CO, HR, and SV before fluid challenge between MAP responders and MAP non-responders.

Effect of fluid challenge on arterial load parameters for determining MAP responders and non-responders

The effects of fluid challenge on arterial load parameters in MAP responder and non-responder patients are shown in Table 4. The distributions of individual arterial load parameters at baseline before fluid challenge in both the MAP responder and non-responder groups are shown in Figure 1. Linear regression analysis showed a poor relationship between Ea_{dyn} before fluid challenge and changes in MAP after fluid challenge (R^2=0.0579) (Figure 2). Ea_{dyn} obtained from the pulse contour analysis technique before fluid challenge failed to predict an increase in MAP after fluid administration (AUC 0.67, 95% CI 0.47 to 0.88) (Figure 3). Effective arterial elastance before fluid challenge was also unable to predict an increase in MAP after fluid challenge (AUC 0.68, 95% CI 0.55 to 0.81) (Figure 3). Furthermore, both DBP and PP were poor predictors of MAP responsiveness (DBP: AUC 0.75, 95% CI 0.61 to 0.89; PP: AUC 0.60, 95% CI 0.41 to 0.80) (Figure 3).

Discussion

The main finding of the present study was that Ea_{dyn} measurement (obtained using the pulse contour analysis technique) before fluid administration was unable to predict an increase in MAP after fluid challenge with crystalloid (500 mL over 15 minutes) in ARDS patients with poor tissue perfusion, but still in a fluid responsive stage. These findings contrast previous studies showing that Ea_{dyn} can predict an increase in MAP after fluid challenge. For example, Garcia et al demonstrated that Ea_{dyn} (SVV was derived from pulse contour analysis) could predict MAP responsiveness after fluid administration, with a cut-off point of baseline Ea_{dyn} greater than 0.89 showing a sensitivity of 93.75% (95% CI 69.8 to 99.8) and a specificity of 100% (95% CI 66.4 to 100) in predicting MAP responsiveness after fluid bolus (AUC 0.986, 95% CI 0.84 to 1.00)[1]. A limitation of that study was that PPV and SVV were also derived from arterial waveform-derived pulse contour analysis. However, in a later study using SVV derived from flow-derived parameters (i.e., esophageal Doppler imaging), Garcia et al reported that an Ea_{dyn} of 0.73 or more (AUC 0.94; 95% CI 0.86 to 0.98) could predict an increase in MAP after fluid administration with a sensitivity of 90.9%

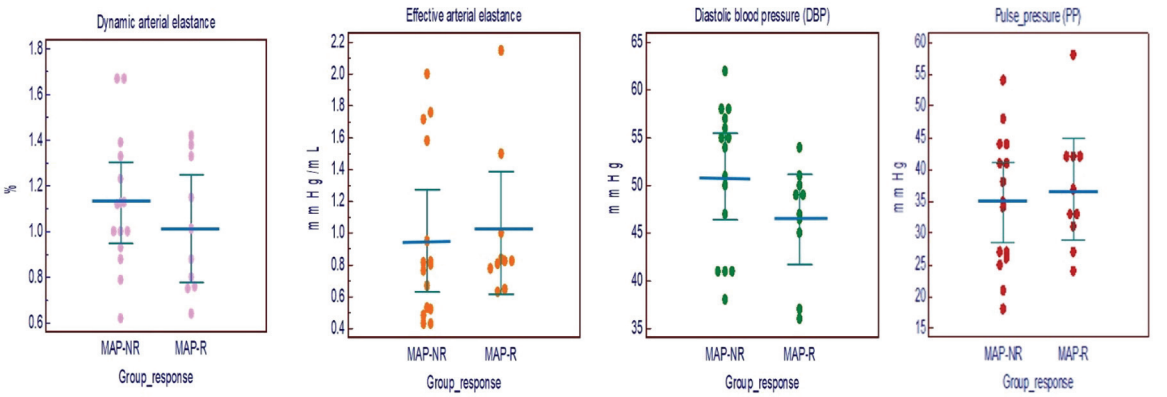

Figure 1. Distribution of arterial load parameters at baseline before fluid challenge.

MAP-NR=mean arterial pressure in non-responder patients, MAP-R=mean arterial pressure in responder patients

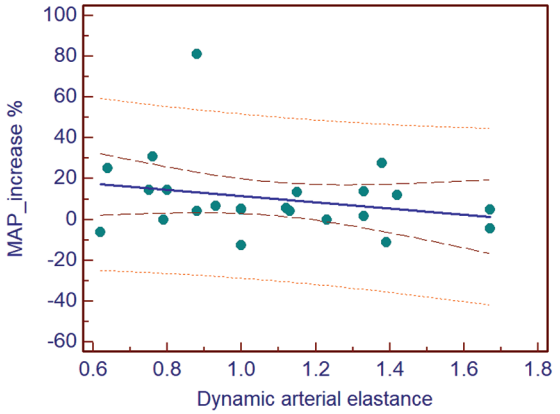

Figure 2. Linear regression analysis of the relationship between pre-infusion dynamic arterial elastance and changes in MAP after fluid challenge.

MAP=mean arterial pressure

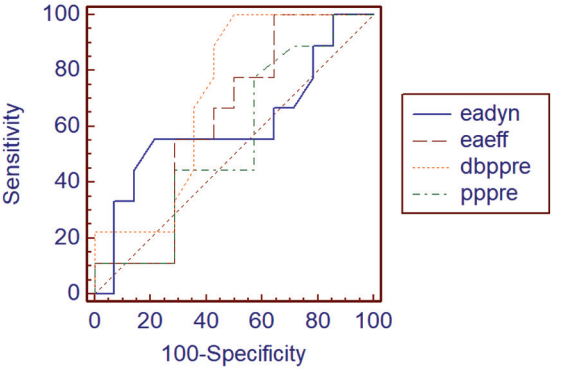

Figure 3. Receiver operating characteristics curves generated for Ea_{dyn}, Ea_{eff}, dbppre, pppre showing the ability to predict an increase in MAP after fluid challenge. MAP responsiveness defined as an increase in MAP by 10% or more after crystalloid bolus 500 ml over 15 minutes.

Ea_{dyn}=dynamic arterial elastance; Ea_{eff}=effective arterial elastance; dbppre=preinfusion diastolic blood pressure; pppre=preinfusion pulse pressure; MAP=mean arterial pressure.

(95% CI 75.6 to 98.1) and a specificity of 91.5% (95% CI 79.6 to 97.6)[2]. Cecconi et al also demonstrated that an Ea_{dyn} derived from the Nexfin® monitoring system (cut-off point ≥1.06) could predict MAP responsiveness in spontaneous breathing patients who were not in heart-lung interaction (AUC 0.92, 95% CI 0.78 to 0.99)[4]. In that study, the authors suggested that the effect of non-uniform ventilation during spontaneous breathing should be comparable in both PPV and SVV, and as such, would have no effect on Ea_{dyn} because PPV is divided by SVV. Although patients in the present study were not in heart-lung interaction, the authors found no such predictive value of Ea_{dyn}. The authors used SVV derived from the Vigileo™ system, which is a pressure-derived parameter as for PPV. Nevertheless, it is possible that this system may not accurately show differences between PPV and SVV, leading to an unreliable estimate of Ea_{dyn}. However, Vigileo™ and Flotrac™ are minimally invasive CO monitoring systems that are widely used in the authors' institute. The Flotrac™ transducer calculates SV from the formula SV = Khi × AP, where AP is the standard deviation of the arterial pressure curve over 20 seconds, and Khi is a constant quantifying arterial elastance and vascular resistance. The present version of the Flotrac™ transducer has an adjusted mathematical equation, as SVV calculated from Flotrac™ is not influenced by Khi[5].

In the present study, the authors hypothesized that different arterial elastances should be reflected as different Ea_{dyn} values. Thus, the authors decided to examine Ea_{dyn} derived from the Vigileo™ and Flotrac™ system. SVV and PPV were still measured from a non-independent signal. If SVV was measured from a flow-derived signal that was independent of PPV, such as esophageal Doppler, then Ea_{dyn} may become more precise. Furthermore, all patients in the present study were predicted to be in fluid responsiveness status by a positive result in the passive leg raising test or mini-fluid challenge test. Each test has its own sensitivity and specificity, and they do not guarantee that a patient with a positive test result is actually in fluid responsive status. Recently, Lanchon et al conducted a study using Ea_{dyn} in hypotensive patients in the operating room, and found that Ea_{dyn} derived from pulse contour analysis (Vigileo™ and Flotrac™) failed to predict an increase in arterial pressure after volume expansion with colloids (500 mL given over 10 minutes; AUC 0.53, 95% CI 0.36 to 0.70)[6]. Wu et al also demonstrated that Ea_{dyn} was not different between MAP responders and MAP non-responders after fluid challenge with crystalloid (10 mL/kg over 15 minutes)[7].

The present study had several limitations. First, there were only a small number of MAP responders after fluid challenge, which may be of insufficient power to differentiate MAP responders from MAP non-responders. Second, even though the authors included patients received vasopressors, which may cause various degrees of arterial tone, the doses of the vasopressors were unchanged during the study period. Third, eight of twenty-three events (35%) in the present study occurred during the patients' effort on positive pressure ventilation because they did not

receive neuromuscular blocking agents, although they were not in forced respiration. This may cause a variable tidal volume, and thus reduce the reliability of PPV. Fourth, a decrease lung compliance can also affect the heart-lung interaction. Although, there was no record of lung compliance, the authors used driving pressure to represent the respiratory system compliance. Finally, the majority of ARDS patients in the medical ICUs exhibited varied degrees of vasoplegia, which may affect vascular tone and accuracy of SVV from the Flotrac™ transducer.

Conclusion

The arterial load parameter Ea_{dyn} derived from the non-calibrated pulse contour analysis method was unable to predict MAP responsiveness in ARDS patients with low tidal volume ventilation. Future studies examining the accuracy of Ea_{dyn} should consider the use of independent signals for measurement of PPV and SVV. The heart-lung interaction can also affect the accuracy of PPV, SVV, and Ea_{dyn}.

What is already known on this topic?

Ea_{dyn} derived from PPV and SVV continuously changes according to a patient's arterial load. Ea_{dyn} was previously reported to predict MAP responsiveness after fluid bolus even in spontaneously breathing patients who are not in heart-lung interaction.

What this study adds?

Ea_{dyn}, which both PPV and SVV derived from non-calibrated pulse contour analysis method, failed to predict MAP responsiveness after fluid bolus in ARDS patients with low tidal volume ventilation. Using PPV and SVV from independent signal may generate more precise Ea_{dyn}.

Conflicts of interest

The authors declare no conflict of interest.

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