Fluid expansion improve ventriculo-arterial coupling in preload patients: a prospective observational study

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Abstract

Background

Given that the ventricular and arterial systems operate simultaneously, ventricular-arterial (V-A) coupling (i.e the E_A/E_{es} ratio) determines the stroke volume and ejection pressure (i.e. arterial blood pressure).

Methods

30 patients admitted to cardio-thoracic ICU in whom the physician decided to perform FC were included. Arterial pressure, cardiac output (CO), E_A, and E_{LV}, were measured before and after FC with 500 ml of lactated Ringer's solution. Fluid responders were defined as patients with more than a 15% increase in SV after fluid challenge. V-A coupling was evaluated by the ratio E_A/E_{es}.

Results

Twenty-three (77%) of the 30 patients included in the study were fluid responders. Before FC, responders had higher mean E_A and E_A/E_{es} ratio. FC significantly increased mean arterial pressure, LVEF, SV and CO, and significantly decreased SVRi, E_A and consequently the E_A/E_{es} ratio. A pre-challenge E_A/E_{es} ratio greater than 1.4 was predictive of fluid responsiveness (area under the curve [95% confidence interval]: 0.84 [0.66–1]; $p < 0.0001$).

Conclusions

In FC responders, V-A coupling was characterized by a higher pre-challenge E_A/E_{es} ratio (due to a higher E_A). FC improve V-A coupling ratio by decreasing E_A but not E_{es}.

Background

Fluid challenge (FC) is the most commonly performed bedside haemodynamic intervention in critical care medicine. In conventional haemodynamic analysis, cardiac output (CO) is considered to be a continuous function, and the heart and vascular system are considered separately. Two different concepts have therefore been developed. In the 1950s, Guyton *et al.* considered the heart to be a pump driven by continuous flow from a purely resistive circuit - despite the pulsatile nature of this flow (mean atrial pressure – right atrial pressure = CO x systemic vascular resistance (SVR)) (1). Several authors subsequently developed a model of stroke volume (SV) based on the pressure-volume relationships of the ventricle and the vascular system (2–4). This model considers left ventricular (LV) energetics, myocardial function and ventricular performance by taking into account the interaction between the ventricle and the vascular system. Hence, LV end-systolic elastance (E_{es}) corresponds to LV contractility

and arterial elastance (E_A) corresponds to the effective elastance of the arterial system (2–4). Given that the ventricular and arterial systems operate simultaneously, ventricular-arterial (V-A) coupling (i.e the E_A/E_{es} ratio) determines the SV and ejection pressure (i.e. arterial blood pressure) (2, 4). The V-A coupling model has been used in cardiology and cardiac surgery to describe and characterize pathophysiological mechanisms and to evaluate treatment effects (5, 6). Recently, we demonstrated that V-A coupling was improved by norepinephrine infusion and that V-A coupling ratio was associated with SV increase (7).

Most of the studies on FC published in the literature have evaluated its effects according to Guyton's model (8, 9). This model has provided researchers with a comprehensive overview of the effects of FC (8, 9). However, few studies have focused on FC from the perspective of the V-A coupling model (10). Because treatment of acute circulatory failure comprises several medications (fluid infusion, inotropic or vasopressor use), it would be of interest to know the effect of each treatment on V-A coupling. The clinical relevance of this model is based on the fact that E_A/E_{es} predicts outcomes independently from other parameters in patients with cardiovascular diseases (5). A description of the cardiovascular effects of fluid expansion may improve our understanding of the pathophysiology of haemodynamic states.

The main objective of this study was therefore to evaluate the impact of FC on V-A coupling, and its determinants. The secondary objective was to determine the value of the pre-challenge E_A/E_{es} ratio as a predictor of a post-challenge increase in SV.

Methods

Ethics

The study's objectives and procedures were approved by the local independent ethics committee (Comité de Protection des Personnes Nord-Ouest II, Amiens, France; RNI2014-39) on November 26th, 2014). All patients received written information about the study and provided their verbal consent to participate. The present manuscript was drafted in compliance with the STROBE checklist for cohort studies (11).

Patients

This prospective, observational study was performed in the Amiens University Hospital cardiothoracic ICU (Amiens, France) over one year. The main inclusion criteria were as follows: age 18 or over, controlled positive ventilation, and a clinical decision to perform FC for volume expansion within the first hours of admission to ICU. Exclusion criteria were permanent arrhythmia, cardiac conduction block, pacemaker (or need for temporary pacemaker using epicardial wires), norepinephrine, epinephrine or dobutamine, poor echogenicity, aortic regurgitation, and right heart dysfunction. The indications for FC were arterial hypotension (systolic arterial pressure (SAP) less than 90 mmHg, or mean arterial pressure (MAP) less than 65 mmHg), or SV change greater than 10% during a passive leg raising manoeuvre, or clinical signs of hypoperfusion (skin mottling, and capillary refill time greater than 3 sec).

Haemodynamic parameters

Transthoracic echocardiography (with the CX50 ultrasound system and an S5-1 Sector Array Transducer, Philips Medical System, Suresnes, France) was performed by a physician blinded to the study outcomes. Left ventricular ejection fraction (LVEF), end-systolic volume (ESV), and end-diastolic volume (EDV) were measured using Simpson's method on a four-chamber view. The aortic velocity-time integral (VTIAo), pre-ejection time and systolic time were measured by pulsed Doppler at the left ventricular outflow tract on a five-chamber view. Stroke volume (SV; mL) was calculated as VTIAo × SAo, and was expressed as indexed SV (SVi) = SV/body surface area ($ml.m^{-2}$). Cardiac output (CO) was calculated as SV × heart rate (HR), and was expressed as indexed CO (CI) = CO/ body surface area ($ml\ min^{-1}\ m^{-2}$). Mean echocardiographic parameters were calculated from five measurements (regardless of the respiratory cycle) and analysed retrospectively.

Left ventricular end-systolic elastance, arterial elastance, ventricular-arterial coupling

E_{es}, an index of ventricular contractility, was evaluated by using the noninvasive, single-beat method described by Chen *et al.* (12). This method is based on the assumption that time-variation of LV elastance is not influenced by loading conditions or heart rate. E_{es} was calculated by the formula: E_{es}= (Pd – ($E_{Nd(test)}$ * Pes * 0.9)) / (SV * $E_{Nd(test)}$). $E_{Nd(test)}$ was obtained from a group-averaged normalized elastance curve value at this same time td ($E_{Nd(avg)}$), baseline LVEF and the ratio of diastolic to systolic arterial pressure (Pd / Pes) (14). $E_{Nd(avg)}$ was determined by a seven-term polynomial function that includes the ratio of pre-ejection period to total systolic period (12). We calculated the coefficient of variation (CV), precision and least significant change (LSC) for E_{es} in the first ten patients. CV was 7.7% ± 0.6 and LSC was 10.9% ± 0.8.

Sunagawa *et al.* demonstrated that arterial load could be characterized in the time domain as E_A (3). Because calculation of E_A is based on several assumptions that can be influenced by perioperative clinical conditions (site of arterial pressure measurement, vasomotor tone, central to peripheral arterial decoupling, aortic stiffness), we evaluated E_A by several methods: $E_{A(ESP)}$ as ESP/ SV ($mmHg\ ml^{-1}$) where ESP is 0.9 x systolic arterial pressure (SAP) (13), $E_{A(MAP)}$ as MAP/ SV ($mmHg\ ml^{-1}$) (14), and $E_{A(R/T)}$ as total peripheral resistance / cardiac cycle ($mmHg\ ml^{-1}$) (3). Arterial pressure was measured by an invasive radial artery approach. In healthy men and women, mean E_A/E_{es}, E_A, and E_{es} values measured invasively at rest are 1.0 ± 0.36, 2.2 ± 0.8 $mmHg.ml^{-1}$, and 2.3 ± 1.0 $mmHg.ml^{-1}$, respectively (15–17). An abnormal E_A/E_{es} ratio was defined as a value greater than 1.36 (17).

The total energy generated by each cardiac contraction is called the "pressure-volume area" (PVA), corresponding to the sum of the external mechanical work exerted during systole (SW) and the potential energy (PE) stored at the end of systole: PVA = SW + PE (18). SW is calculated as ESP x SV. PE is calculated as ESP x ((ESV-V_0)/2), and assumes that V_0 is negligible compared to ESV. The SW/PVA ratio corresponds to the mechanical efficiency of converting the total mechanical energy (PVA) available to the LV SW (18).

Total SVRi ($mmHg.ml^{-1}.m^{-2}$) was calculated as MAP-CVP/CI and total arterial compliance (C_A) ($ml.mmHg^{-1}$) was calculated as SV/arterial pulse pressure (19).

Study procedures

The following clinical parameters were recorded: demographic, ventilation parameters, and primary diagnosis. After an equilibration period, capillary refill time (measured at the distal phalanx of the index finger), HR, SAP, MAP, diastolic arterial pressure (DAP), central venous pressure (CVP), SVi, CI, EDV, ESV, pre-ejection time, systolic time interval, and blood gas levels were measured at baseline. In the present study, FC always consisted of a 10-minute infusion of 500 ml of lactated Ringer's solution (20). A second set of measurements was performed immediately after FC. All patients were mechanically ventilated in volume-controlled mode with a tidal volume set at 7–9 ml kg^{-1} ideal body weight, and a positive end-expiratory pressure (PEEP) of 5–8 cmH_2O. Ventilator settings were not modified during the study period.

Statistical analysis

The sample size was calculated on the reproducibility initially measured in the study reported by Chen et al (12). With a reproducibility of 20%, we calculated that a sample of thirty patients would be sufficient to demonstrate an absolute change of more than 20% in the E_A/E_{es} ratio in response to FC. The distribution of the variables was assessed by a Shapiro-Wilk test. Data are expressed as number, proportion (in per cent), mean ± standard deviation (SD) or median [interquartile range (IQR)], as appropriate. Fluid response was defined as a greater than 15% increase in SV after FC (21). This cutoff value was considered to be clinically relevant and in accordance with measurement variability. The non-parametric Wilcoxon rank sum test, Student's paired t test, Student's t test, and the Mann-Whitney test were used to assess statistical significance, as appropriate. A receiver-operating characteristic curve was established for the ability of E_A, E_{es}, the E_A/E_{es} ratio to predict a greater than 15% increase in SV. The limit for statistical significance was $p < 0.05$. SPSS® software (version 22, IBM, New York, NY, USA) was used for all statistical analyses.

Results

Thirty patients were included and analysed (Fig. 1). These patients had undergone cardiovascular surgery (n = 29) or thoracic surgery (n = 1) (Table 1). The main indications for fluid expansion were arterial hypotension (n = 17), SV change greater than 10% with PLR (n = 9), skin mottling (n = 4). No significant difference in indications was observed between SV responders and SV non-responders (p = 0.336). Values for $E_{A(ESP)}$, E_{es} and E_A/E_{es} ratio were not significantly different between men and women, or according to type of surgery or medical characteristics (p value > 0.05), therefore allowing pooled analysis (Table 1). No patients developed complications (arrhythmia, hypoxaemia, left heart failure) during FC.

Table 1
Baseline characteristics of the study participants. Values are expressed as mean ± SD or number (%). CABG: coronary artery bypass graft. P value refers to comparison between ventriculo-arterial uncoupled and ventriculo-arterial coupled patients. Abnormal ventriculo-arterial coupling was defined as a E_A/E_{LV} ratio greater than 1.36

Variables	**Ventriculo-arterial coupled patients (n = 7)**	**Ventriculo-arterial uncoupled patients (n = 23)**	***P value***
Age (mean (SD), years)	66 (13)	66 (12)	0.947
Gender (F/M)	1/6	7/16	0.638
Disease, n (%)	5 (71)	14 (61)	1
Arterial hypertension	5 (71)	14 (61)	1
Aortic stenosis	3 (43)	3 (13)	0.120
Diabetes mellitus	5 (71)	11 (48)	0.399
Dyslipidaemia	4 (57)	10 (44)	0.675
Smoking			
Heart surgery, n (%)	5 (71)	12 (52)	0.589
Valve replacement	1 (14)	5 (22)	
CABG	0	4 (17)	
Mixed	1 (14)	1 (4)	
Other (atrial myxoma, ascending aorta)	0	1 (4)	
Thoracic surgery, n (%)			
Cardiopulmonary bypass time (min, mean (SD)) (n = 29)	90 (46)	99 (44)	0.617
Respiratory parameters	7.8 (0.5)	7.8 (0.7)	0.957
Tidal volume (ml kg^{-1} of predicted body weight, mean (SD),	5 (1)	5 (1)	0.443
Total PEEP (cmH_2O, mean (SD))			

Effect of FC on haemodynamic parameters in the overall study population

Prior to FC, median $E_{A(ESP)}$ was 2.3 [1.7–2.8] mmHg.ml^{-1}, median E_{es} was 1.5 [1-1.7] mmHg.ml^{-1}, and median $E_{A(ESP)}/E_{es}$ ratio was 1.8 [1.3–2.3]. Twenty-three (80%) of the 30 patients were classified as “uncoupled” (i.e. E_A/E_{es}>1.36).

After FC, median $E_{A(ESP)}$ was 2.1 [1.5-3], median $E_{A(ESP)}/E_{es}$ ratio was 1.6 [1.3–2.1], and median E_{es} was 1.4 [0-1.7]. Twenty-three (80%) of the 30 patients were classified as fluid responders. Most uncoupled patients (21 out of 23 (91%); p = 0.003) were fluid responders.

Effect of FC on haemodynamic parameters depending on SV changes.

At baseline, $E_{A(ESP)}$, $E_{A(ESP)}/E_{es}$, were higher and C_A, Ci, SVi were lower in fluid responders than in fluid non-responders (Table 2, Figs. 2). In fluid responders, FC was associated with higher values for blood pressure, SVi, CI, SW, PVA, and SW/PVA ratio, and lower values for HR, SVRi, $E_{A(ESP)}$ and $E_{A(ESP)}/E_{es}$ ratio (Table 2, Fig. 2). In fluid non-responders, FC was associated with higher values for CVP and $E_{A(ESP)}/E_{es}$ ratio and a lower SW/PVA ratio (Table 2).

Table 2

Comparison of haemodynamic parameters in fluid responders and non-responders. Values are expressed as mean (SD) or median [interquartile range]. **CI**, indexed cardiac output; **CVP**, central venous pressure; **DAP**, diastolic arterial pressure; **EDV**, end-diastolic volume; **ESV**, end-systolic volume; **FC**, fluid challenge; **HR**, heart rate; **LVEF**, left ventricular ejection fraction; **MAP**, mean arterial pressure; **PVA**, pressure volume area; **PP**, pulse pressure; **SAP**, systolic arterial pressure; **SVi**, indexed stroke volume; **SVRi**, indexed systemic vascular resistance; **SW**, stroke work; $^{\$}$: $p < 0.05$ within groups (pre-/post-FC).

Haemodynamic variables	Non-responders (n = 7)	Responders (n = 23)	*P value*
HR (bpm)	81 (23)	84 (22)	0.863
Pre-FC	79 (19)	77 (18) $^{\$}$	0.861
Post-FC			
SAP (mmHg)	100 (21)	103 (16)	0.704
Pre-FC	109 (22)	125 (22) $^{\$}$	0.085
Post-FC			
DAP (mmHg)	58 (11)	58 (11)	0.829
Pre-FC	60 (12)	66 (13) $^{\$}$	0.265
Post-FC			
MAP (mmHg)	71 (12)	73 (12)	0.746
Pre-FC	76 (12)	86 (14) $^{\$}$	0.110
Post-FC			
CVP (mmHg)	6 (3)	6 (3)	0.775
Pre-FC	8 (2) $^{\$}$	8 (3) $^{\$}$	0.981
Post-FC			
LVEF (%)	54 (11)	48 (11)	0.202
Pre-FC	51 (8)	50 (10) $^{\$}$	0.917
Post-FC			
ESV (ml)	52 (21)	58 (25)	0.566
Pre-FC	58 (23)	60 (26)	0.835
Post-FC			

Haemodynamic variables	Non-responders (n = 7)	Responders (n = 23)	*P value*
EDV (ml)	101 (22)	86 (33)	0.300
Pre-FC	95 (20)	112 (42) $	0.331
Post-FC			
SVi (ml m^{-2})	28 (8)	22 (7)	0.050
Pre-FC	25 (5)	29 (10) $	0.401
Post-FC			
CI (ml min^{-1} m^{-2})	2.3 (0.9)	1.7 (0.5)	0.045
Pre-FC	1.9 (0.8)	2.2 (0.6) $	0.487
Post-FC			
Arterial elastance ($E_{A(ESP)}$) (mmHg ml^{-1})	1.8 [1.4–2.2]	2.5 [1.8–3.1]	0.033
Pre-FC	2 [1.6–2.6]	2.2 [1.5–3.2] $	0.774
Post-FC			
Arterial elastance ($E_{A(MAP)}$) (mmHg ml^{-1})	1.3 (1.1–1.8)	1.9 (1.5–2.4)	0.037
Pre-FC	1.5 (1.3–1.8)	1.7 (1.2–2.3) $	0.811
Post-FC			
Arterial elastance ($E_{A(R/T)}$) (mmHg ml^{-1})	1.9 (1.7–2.7)	3 (2.2–3.5)	0.037
Pre-FC	2.2. (1.9–2.7)	2.6 (1.8–3.5)$	0.666
Post-FC			
Arterial compliance (ml $mmHg^{-1}$)	1.6 (0.9)	0.94 (0.32)	0.014
Pre-FC	1.1 (0.5)	0.98 (0.37)	0.455
Post-FC			
SVRi (mmHg ml^{-1} m^{-2})	34 (13)	47 (14)	0.055
Pre-FC	37 (10)	38 (11) $	0.672
Post-FC			

Haemodynamic variables	Non-responders (n = 7)	Responders (n = 23)	*P value*
Ventricular elastance (E_{es}) (mmHg ml^{-1})	1.6 (1.1-2)	1.5 (0.9–1.7)	0.564
Pre-FC	1.5 (1.1–2.4)	1.5 (0.9–1.7)	0.564
Post-FC			
$E_{A(ESP)}/E_{es}$ ratio	1.2 (0.9–1.4)	1.9 (1.7–2.2)	0.007
Pre-FC	1.4 (0.9–1.8) $	1.5 (1.3-2) $	0.144
Post-FC			
SW (joules)	4769 (1513)	3672 (1349)	0.077
Pre-FC	4691 (1690)	6032 (2040) $	0.126
Post-FC			
PVA (joules)	6919 (1705)	6111 (9132)	0.329
Pre-FC	7319 (1964)	9164 (2868) $	0.124
Post-FC			
SW/PVA ratio	0.69 (0.13)	0.60 (0.14)	0.136
Pre-FC	0.64 (0.13) $	0.66 (0.12) $	0.761
Post-FC			

Changes In Haemodynamic Parameters, E, E, And E/e Parameters

Changes in MAP (5% (-4 to 9) vs 16% (12 to 22), $p < 0.05$), SAP (6% (1 to 10) vs 18% (12 to 31%), $p < 0.005$), $E_{A(ESP)}$ (-13% (− 16% to -6) vs 0% (11 to 56), $p < 0.05$) were significantly different between SV responders and SV non-responders

Predictive value of E_A, E_{es}, E_A/E_{es} ratio and PPV.

At baseline, the E_A/E_{es} ratio had a similar predictive value regardless of the E_A formula used ($E_{A(ESP)}/E_{es}$: 0.84 [95% confidence interval (95%CI)] (0.66-1), $E_{A(MAP)}/E_{es}$: 0.83 (0.62-1), $E_{A(R/T)}/E_{es}$: 0.82 (0.62-1), $p < 0.05$). A $E_{A(ESP)}/E_{es}$ cut-off of 1.4 gave a sensitivity of 87% [66–97], a specificity of 86% [42–100], a positive likelihood ratio of 6.1, negative likelihood ratio of 0.15, a positive predictive value of 95 and a negative predictive value of 67.

With an AUC [95%CI] of 0.75 [0.58–0.94] (p = 0.001), $E_{A(ESP)}$ was fairly predictive of fluid responsiveness. With an AUC [95%CI] of 0.39 [0.13–0.66] (p = 0.541), E_{es} did not predict fluid responsiveness.

Discussion

In fluid responders, V-A coupling was characterized by a high pre-challenge E_A/E_{es} ratio (due to high E_A). FC improvement in V-A coupling was associated to SV response. This effect was associated with a decrease in E_A but no change in E_{es}. Increased V-A coupling was associated with greater myocardial work efficiency. The pre-challenge E_A/E_{es} ratio was a good predictor of fluid responsiveness.

Few studies have specifically evaluated the effect of FC on V-A coupling. One study in cardiac surgery patients found an increase in SW, PVA and afterload, as a result of increased SV (10). A subsequent study of septic shock patients assessed the impact of FC on E_A and its components, but did not measure E_{es} (19). In contrast with the results mentioned above and the report by Mangano *et al.*, we observed a decrease in arterial load after FC (10). Several explanations for our findings can be proposed.

The sympathetic nervous system plays a key role (via the baroreflex) in regulating blood volume, blood flow and blood pressure (22). Accordingly, preload-dependent patients probably have higher levels of sympathetic activation than non-dependent patients, as evidenced by higher E_A, higher SVRi, and lower C_A values at a given blood pressure. This response is designed to adapt blood flow to the patient's needs, which appears to be effective, as $ScVO_2$ and arterial lactate levels were not significantly different between the two groups of patients. FC restores preload and CO, and thus meets the patient’s needs. A decrease in E_A might be caused by several interlinked mechanisms affecting the resistive component (HR and SVR) and the pulsatile component (C_A) of arterial load. The increase in blood pressure induced by an increase in CO decreases sympathetic activation, SVRi and E_A. The baroreflex has been shown to maintain adequate blood pressure by modulating E_A, E_{es} and blood volume (23). An increase in blood flow decreases vascular tone by activating the NO pathway and by initiating vascular recruitment (24). As a result of shear stress, blood flow modulates the diameter of blood vessels and can influence aortic compliance (25). Segers *et al.* used a heart-artery interaction model to show that the contribution of the resistive component to this effect is threefold higher than that of the pulsatile component (26).

Our results evidenced a slight increase in LVEF in response to FC. This result is in line with the literature data; LVEF is described as a preload-dependent and afterload-dependent variable. Nevertheless, LVEF is more sensitive to afterload at low preloads (27). As LVEF can be expressed as $E_{es}/(E_{es}+ E_A)$, it is determined by V-A coupling (27). The observed increase in LVEF is therefore induced by a decrease in ventricular load, as represented by a decrease in E_A and constant E_{es}. These findings are consistent with the results of studies of the effect of beta-blockers in patients with high blood pressure or heart failure (5).

In the present study, we demonstrated that the pre-challenge E_A/E_{es} ratio is also predictive of fluid responsiveness. These results suggest that the differences between SV responders and SV non-responders were mostly due to changes in V-A coupling. These results are not surprising and may be explained by the E_A/E_{es} ratio, which characterizes the interaction between the ventricle and the arterial vascular system. E_{es} was assessed by the noninvasive method developed by Chen *et al.*, in which measurements of pre-ejection and ejection times in patients are used to calculate E_{es} (12, 28). Studies have demonstrated that the aortic pre-ejection time can predict fluid responsiveness (29). Cheng *et al.* subsequently demonstrated that the pre-ejection time/ejection time ratio was useful to identify heart failure patients with V-A uncoupling (30). Interesting, the cut-off found in the present study is close to the upper normal value of the E_A/E_{es} ratio.

This study presents a number of limitations. We specifically included patients not treated with vasopressors and inotropes to avoid any treatment-related bias. Vasopressors are known to alter the cardiovascular response to FC (31). Hence, we can safely assume that our results were related to the sole effect of FC. The study population may have differed from septic shock patients. Most of our patients presented perioperative hypovolaemia, whereas septic patients generally have acute circulatory failure with a combination of hypovolaemia, changes in microvascular perfusion and central-to-peripheral arterial decoupling (32). The methods used to calculate E_{es} and E_A can be open to criticism because we did not use a high-fidelity ventricular pressure catheter. We measured E_{es} by a noninvasive single-beat method based on a linear end-systolic pressure-volume relationship, and a constant volume axis intercept of the end-systolic pressure volume relationship (11, 33). Calculation of E_{es} assumes that the end-systolic pressure-volume relationship is load-independent, with a linear slope, and that V_0 is not influenced by inotropes (33). We calculated ESP from a radial artery signal, which may differ from the aortic pressure signal (34). However, radial artery pressure has been reported to provide a good estimate of ESP (15, 35). We used several methods to assess E_A that all gave similar results in the overall population and in the two groups, supporting the findings of our study. Although it can be argued that estimation of ESP from the radial artery has not been fully validated, any error in this method would only affect the precision of absolute values of E_A and $E_{es,}$ but not the E_A/E_{es} ratio, as the error in end-systolic pressure would be similar. The predictive value of E_A/E_{es} for increased SV can therefore be considered to be valid. Arterial load assessment was based on a two-element Windkessel model and integrative simplification. More precise models have been developed, such as three- and four-element Windkessel models that include arterial impedance and wave reflection. However, these methods would be difficult to apply at the bedside. Despite these limitations, noninvasive evaluation of E_{es} and E_A was validated against the gold standard method, and has been used in cardiac surgery (5–7). In the present study, E_A and E_{es} must be considered to be approximations of E_A and E_{es}.

Conclusions

In fluid responders, V-A coupling was characterized by a high pre-challenge E_A/E_{es} ratio (due to high E_A). FC decreased the V-A coupling ratio. This effect was associated with a decrease in E_A but not E_{es}. Measuring V-A coupling can characterize the patient's haemodynamic status and predict the cardiovascular system's response to FC.

Abbreviations

C_A; arterial compliance, CO; cardiac output, CVP; central venous pressure, E_A; arterial elastance, E_V; ventricular elastance, FC; fluid challenge, HR; heart rate, LVEF; left ventricular ejection fraction, V-A coupling; ventriculo-arterial coupling, SVR; systemic vascular resistance, SV; stroke volume,

Declarations

Ethics Approval and Consent to Participate:

Ethical approval was granted by the *Comité de Protection des Personnes Nord-Ouest II*, Amiens, France, RNI2014-39).

Consent for publication:

According to French law, all patients had written information and gave verbal consent to participate.

Competing interests:

Guinot Pierre-Grégoire and Abou-Arab Osama are members of the editorial board of the BMC Anesthesiology journal (associate Editor).

Availability of data and materials:

Unfortunately, we do not have permissions to share these data. However, we would be happy to collaborate with requests from individual research groups would like to access our raw data. Please contact the corresponding author for further information.

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Authors' contributions:

Data acquisition: PGG, PH, OAA; Analysis and interpretation: PGG, PH, OAA, DL; Drafting of the manuscript for important intellectual content: PGG, DL. All authors read and approved the manuscript.

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References

1. Guyton AC. Textbook of Medical Physiology. 5th ed. Philadelphia: W.B. Saunders; 1976.
2. Sagawa K, Suga H, Shoukas AA, et al. End-systolic pressure/volume ratio: a new index of ventricular contractility. Am J Cardiol. 1977;40:748–53.
3. Sunagawa K, Maughan WL, Burkhoff D, Sagawa K. Left ventricular interaction with arterial load studied in isolated canine ventricle. Am J Physiol. 1983;245:773–80.
4. Sunagawa K, Sagawa K, Maughan WL. Ventricular interaction with the loading system. Ann Biomed Eng. 1984;12:163–89.
5. Maurer MS, Sackner-Bernstein JD, El-Khoury Rumbarger L, Yushak M, King DL, Burkhoff D. Mechanisms Underlying Improvements in Ejection Fraction With Carvedilol in Heart Failure. Circ Heart Fail. 2009;2:189–96.
6. Shabanian R, Shahbaznejad L, Razaghian A, Kiani A, Rahimzadeh M, Seifirad S, Kocharian A, Gilani JS, Navabi MA. Sildenafil and ventriculo-arterial coupling in Fontan-palliated patients: a noninvasive echocardiographic assessment. Pediatr Cardiol. 2013;34:129–34.
7. Guinot PG, Longrois D, Kamel S, Lorne E, Dupont H. Ventriculo-Arterial Coupling Analysis Predicts the Hemodynamic Response to Norepinephrine in Hypotensive Postoperative Patients: A Prospective Observational Study. Crit Care Med. 2018;46:e17–25.
8. Cecconi M, Aya HD, Geisen M, Ebm C, Fletcher N, Grounds RM, Rhodes A. Changes in the mean systemic filling pressure during a fluid challenge in postsurgical intensive care patients. Intensive Care Med. 2013;39:1299–305.
9. Monnet X, Teboul JL. Volume responsiveness. Curr Opin Crit Care. 2007;13:549–53.
10. Mangano DT, Van Dyke DC, Ellis RJ. The effect of increasing preload on ventricular output and ejection in man. Limitations of the Frank-Starling Mechanism. Circulation.1980;62:535 – 41.
11. Von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP. STROBE Initiative. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. Ann Intern Med. 2007;147:573–7.
12. Chen CH, Fetics B, Nevo E, Rochitte CE, Chiou KR, Ding PA, Kawaguchi M, Kass DA. Noninvasive single-beat determination of left ventricular end-systolic elastance in humans. J Am Coll Cardiol.

2001;38:2028–34.
13. Kelly RP, Ting CT, Yang TM, Liu CP, Maughan WL, Chang MS, Kass DA. Effective arterial elastance as index of arterial vascular load in humans. Circulation. 1992;865:513–21.
14. Asanoi H, Sasayama S, Kameyama T. Ventriculo arterial coupling in normal and failing heart in humans. Circ Res. 1989;65:483–93.
15. Kass DA. Ventricular arterial stiffening: integrating the pathophysiology. Hypertension. 2005;46:185–93.
16. Starling MR. Left ventricular-arterial coupling relations in the normal human heart. Am Heart J. 1993;125:1659–66.
17. Chen CH, Nakayama M, Nevo E, Fetics BJ, Maughan WL, Kass DA. Coupled systolic-ventricular and vascular stiffening with age: implications for pressure regulation and cardiac reserve in elderly. J Am Coll Cardiol. 1998;32:1221–7.
18. Takaoka H, Takeuchi M, Odake M, Yokoyama M. Assessment of myocardial oxygen consumption (VO2) and systolic pressure volume area (PVA) in human hearts. Eur Heart J. 1992;13:85–90.
19. Monge García MI, Guijo González P, Gracia Romero M, Gil Cano A, Oscier C, Rhodes A, Grounds RM, Cecconi M. Effects of fluid administration on arterial load in septic shock patients. Intensive Care Med. 2015;41:1247–55.
20. Guinot PG, Marc J, de Broca B, Archange T, Bar S, Abou-Arab O, Dupont H, Fischer MO, Lorne E. The predictability of dynamic preload indices depends on the volume of fluid challenge: A prospective observational study in the operating theater. Medicine. 2018;97(42):e12848.
21. Guinot PG, Urbina B, Broca B, Bernard E, Dupont H, Lorne E. Predictability of the respiratory variation of stroke volume varies according to the definition of fluid responsiveness. Br J Anaesth. 2014;112:580–1.
22. Wehrwein EA, Joyner MJ. Regulation of blood pressure by the arterial baroreflex and autonomic nervous system. Handb Clin Neurol. 2013;117:89–102.
23. Sakamoto T, Kakino T, Sakamoto K, Tobushi T, Tanaka A, Saku K, Hosokawa K, Onitsuka K, Murayama Y, Tsutsumi T, Ide T, Sunagawa K. Changes in vascular properties, not ventricular properties, predominantly contribute to baroreflex regulation of arterial pressure. Am J Physiol Heart Circ Physiol. 2015;308:H49–58.
24. Calver A, Collier J, Green D, Vallance P. Effect of acute plasma volume expansion on peripheral arteriolar tone in healthy subjects. Clin Sci (Lond). 1992;83:541–7.
25. Snow HM, McAuliffe SG, Moors JA, Brownlie R. The relationship between blood flow and diameter in the iliac artery of the anaesthetized dog: the role of endothelium-derived relaxing factor and shear stress. Exp Physiol. 1994;79:635–45.
26. Segers P, Stergiopulos N, Westerhof N. Relation of effective arterial elastance to arterial system properties. Am J Physiol Heart Circ Physiol. 2002;282:H1041-6.

27. Robotham JL, Takata M, Berman M, Harasawa Y. Ejection fraction revisited. Anesthesiology. 1991;74:172–83.
28. Senzaki H, Chen CH, Kass DA. Single-beat estimation of end-systolic pressure-volume relation in humans. A new method with the potential for noninvasive application. Circulation. 1996;94:2497–506.
29. Giraud R, Siegenthaler N, Morel DR, Bendjelid K. Pre-ejection period to estimate cardiac preload dependency in mechanically ventilated pigs submitted to severe hemorrhagic shock. J Trauma. 2011;71:702–7.
30. Cheng HM, Yu WC, Sung SH, Wang KL, Wang KL, Chuang SY, Chen CH. Usefulness of systolic time intervals in the identification of abnormal ventriculo-arterial coupling in stable heart failure patients. Eur J Heart Fail. 2008;10:1192–200.
31. Vane LA, Prough DS, Kinsky MA, Williams CA, Grady JJ, Kramer GC. Effects of different catecholamines on the dynamics of volume expansion of crystalloid infusion. Anesthesiology. 2004;101:1136–44.
32. Hatib F, Jansen JR, Pinsky MR. Peripheral vascular decoupling in porcine endotoxic shock. J Appl Physiol. 2011;111:853–60.
33. Nguyen M, Berhoud V, Bartamian L, Martin A, Ellouze O, Bouhemad B, Guinot PG. Agreement between different non-invasive methods of ventricular elastance assessment for the monitoring of ventricular-arterial coupling in intensive care. J Clin Monit Comput. 2019 Oct 10. doi:10.1007/s10877-019-00397-7.
34. Pauca AL, Wallenhaupt SL, Kon ND, Tucker WY. Does radial artery pressure accurately reflect aortic pressure? Chest. 1992;102:1193–8.
35. Haedersdal C, Madsen JK, Saunamäki K. The left ventricular end-systolic pressure and pressure-volume index. Comparison between invasive and auscultatory arm pressure measurements. Angiology. 1993;44:959–64.

Figures

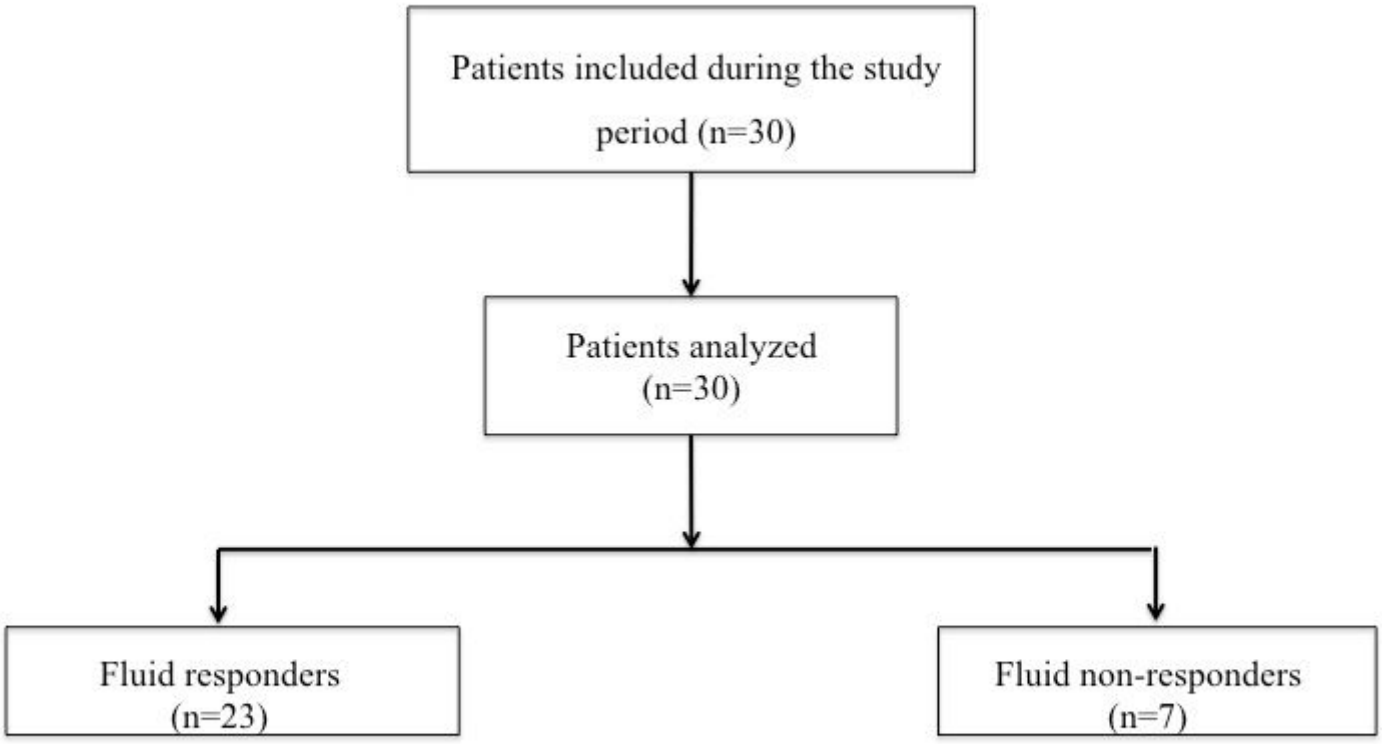

Figure 1

Study flow chart

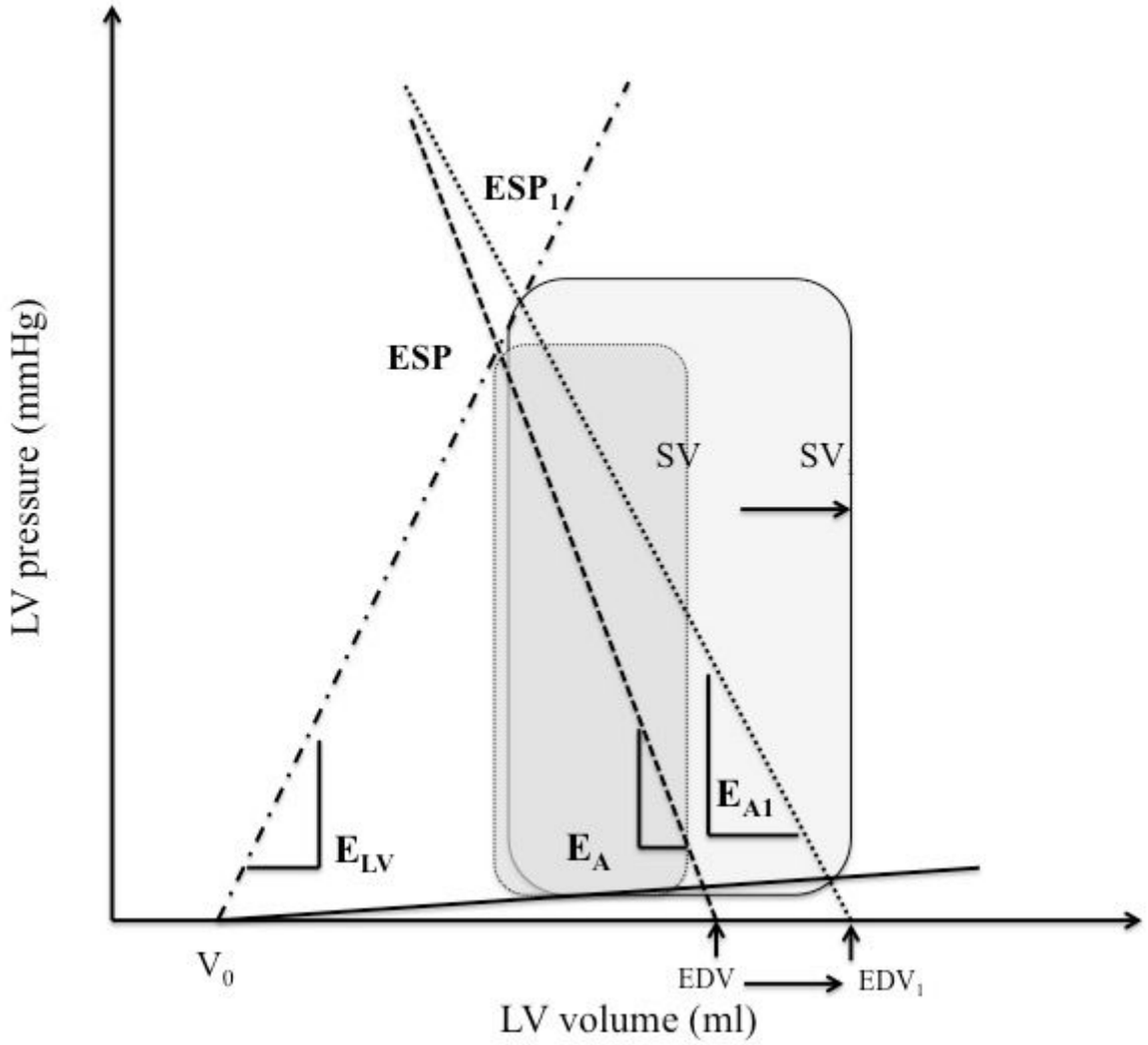

Figure 2

Changes in ventricular pressure-volume relationships in fluid responders with fluid challenge. Stroke volume increased (SV□SV1), and end-diastolic volume (EDV□EDV1) increased more than end-systolic pressure (ESP□ESP1), resulting in decreased arterial elastance (EA□EA1). Ventricular elastance (Ees) remained unchanged, resulting in a decreased EA/Ees ratio