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Assessment of left ventricular function by pulse wave analysis in critically ill patients

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Abstract *Purpose:* Left ventricular (LV) performance is often quantified by echocardiography in critically ill patients. Pulse wave analysis (PWA) systems can also monitor cardiac function but in a continuous fashion. We compared echocardiographic and PWA-derived indices of LV function. *Methods:* We enrolled 70 critically ill patients equipped with invasive arterial pressure monitoring who required echocardiography. We simultaneously assessed LV ejection fraction (LVEF), the rate of LV pressure rise during systole (dP/dt_{MAX}) obtained with echocardiography (EC-dP/dt_{MAX}), the ratio of effective arterial elastance to LV end-systolic elastance (E_a/E_{es}) determined by echocardiography, the dP/dt_{MAX} estimated from the arterial pressure waveform (AP-dP/dt_{MAX}) and the cardiac cycle efficiency (CCE) using PWA. *Results:* Mean LVEF was 53 ± 18 % and CCE 0.16 ± 0.26. CCE was correlated linearly with LVEF ($r = 0.88$, 95 % CI 0.81 to 0.92, $P < 0.001$), and the dP/dt_{MAX} values from the two techniques were linearly correlated ($r = 0.93$, 95 % CI 0.87 to 0.96, $P < 0.001$). There was minimal bias between the techniques for measurement of dP/dt_{MAX} (23.7 mmHg/ms; 95 % CI −23.6 to 71.0). E_a/E_{es} and CCE were inversely correlated ($r = -0.81$, 95 % CI −0.88 to −0.71, $P < 0.001$). A CCE value of <0.07 predicted LVEF <40 % with a sensitivity of 0.93 and a specificity of 0.96 (AUC 0.98, 95 % CI 0.90 to 1.0, $P < 0.001$). A CCE value of >0.12 predicted LVEF ≥50 % with a sensitivity of 0.96 and a specificity of 0.82 (AUC 0.94, 95 % CI 0.87 to 1.0, $P < 0.001$). A CCE value <0.12 predicted E_a/E_{es} ≥1.3 with a sensitivity of 0.93 and a specificity of 0.89 (AUC 0.94, 95 % CI 0.83 to 1.0, $P < 0.001$). *Conclusions:* PWA-derived variables provide relevant information on cardiac contractility and performance in critically ill patients. PWA provides an easy method for online hemodynamic evaluation in critically ill patients.

Keywords Left ventricular ejection fraction · Arterial-ventricular coupling · dP/dt · Echocardiography · Pulse wave analysis

Introduction

Cardiovascular monitoring is frequently used in critically ill patients. Measurements of cardiac output and filling pressures (or volumes) provide a global evaluation of cardiovascular function, but evaluation of left ventricular (LV) contractile performance remains difficult [1]. Echocardiography has emerged as an effective diagnostic

tool in the assessment of LV function. Among the various indices that can be obtained by echocardiography, LV ejection fraction (LVEF) has become the most widely used to evaluate LV contractility [2, 3]. However, LVEF is affected by loading conditions and is an index of the interaction of the left ventricle and the arterial system. Indeed, LVEF can be derived from the relationship between effective arterial elastance (E_a), a measure of the net arterial load imposed on the left ventricle, and LV end-systolic elastance (E_{es}), a load-independent measure of intrinsic LV contractility [4]. As therapeutic interventions may have different effects on LVEF, determination of intrinsic contractility is desirable.

The relationship between E_a and E_{es} (i.e., their ratio) is termed arterial-ventricular (A–V) coupling and is a major determinant of cardiovascular performance [5]. Initial studies on E_a/E_{es} were performed in animals using high-fidelity ventricular catheters [6] and, subsequently, in humans during cardiac catheterization [7]. Recently, echocardiography has been proposed for the noninvasive measurement of E_a/E_{es} [8, 9]. However, this approach is impractical, as it requires off-line analysis and very precise synchronization of the arterial signal and echocardiography device. The rate of LV pressure rise during systole (dP/dt_{MAX}) may also provide an estimate of ventricular contractility [10] and can be measured from the mitral valve regurgitation jet using echocardiography [11].

Whatever their intrinsic capabilities, most of these methods are limited by their intermittent nature. At best, cardiac function can be estimated once and repeated after a therapeutic intervention. However, hemodynamic status can be highly variable in critically ill patients, and continuous monitoring of cardiac function may, therefore, provide important information.

Analysis of the arterial signal can provide information on cardiac performance. The PiCCO continuous cardiac output monitoring system (Pulsion Medical Systems AG, Munich, Germany) provides dP/dt online, but the cardiac function index, a surrogate of LVEF, is only obtained intermittently during recalibration [12]. The PRAM (pressure recording analytical method) Most Care system (Vygon Health, Padua, Italy), an uncalibrated pulse wave analysis system that has been validated for cardiac output measurement in various clinical conditions [13], also measures dP/dt_{MAX}, which represents the maximal value of the first derivative of the radial or femoral pulse wave [14], and cardiac cycle efficiency (CCE), an indirect index of A–V coupling, which represents the dynamic equilibrium between preload, arterial elastance and contractility [15–18]. CCE reflects the sum of the energies required to generate stroke volume (SV), which depends on the interaction between pump function and the arterial system. The factors involved in the arterial component of this process are arterial elastance and reflected waves. Reflected waves are composed of a multitude of wavelets generated by reflection of previous beats at branchpoints (backward waves) and also at the aortic valve (forward waves). The energy generated by backward waves either increases (counted as positive in CCE) or decreases (counted as negative in CCE) heart efficiency, depending on their location according to the dicrotic notch, whereas energy generated by forward wavelets is positive, facilitating ejection. CCE is the ratio of systolic energy to total energy expenditure, and can thus be positive or negative, depending on the sum of the individual energies (see the Electronic supplementary material for physiologic explanation and details of computation).

The aim of this study was to evaluate whether analysis of the arterial pressure waveform could be useful for evaluating some indices of LV function. We hypothesized that the dP/dt_{MAX} estimated from the arterial pressure waveform (AP-dP/dt_{MAX}) would reflect the dP/dt_{MAX} obtained with echocardiography (EC-dP/dt_{MAX}) and that the CCE would reflect the LVEF and E_a/E_{es} determined by echocardiography.

Materials and methods

Patients

In this prospective, observational study, patients admitted to a 35-bed university hospital medicosurgical ICU during a 6-month period who were (1) undergoing echocardiography in the setting of circulatory or respiratory failure, and (2) monitored with a standard arterial catheter line (radial or femoral artery) for invasive arterial blood pressure measurement were enrolled. Exclusion criteria were: (1) patients less than 18 years of age; (2) the presence of pathologies that could affect the quality and reliability of the arterial signal (aortic valve pathologies, ascending aorta pathologies, and cardiac arrhythmias); and (3) insufficient echogenicity preventing echocardiographic assessment. Approval from the Institutional Review Board was obtained but informed consent was waived because of the purely observational nature of the study.

Study protocol

In each patient, echocardiographic and arterial waveform measurements were simultaneously obtained during periods of hemodynamic stability, defined as no more than a 5 % variation in heart rate and mean systemic arterial pressure with respect to baseline during the time needed for echocardiography. During measurements, no changes to ventilation, sedation, vasoactive drugs or fluid infusions were made.

Echocardiography measurements

A single experienced examiner (L.B.) performed echocardiography using a 3-MHz transthoracic probe and a

dedicated unit (Xario SSA-660A; Toshiba, Japan). LV systolic and diastolic volumes and EF were estimated using the Simpson discs method. LVEF was then calculated as: $100 \times$ [(LV end-diastolic volume $-$ LV end-systolic volume)/LV end-diastolic volume] [3, 19]. EC-dP/dt_{MAX} was evaluated by estimating the mitral valve regurgitation jet, according to the method proposed by Bargiggia et al. [11]. For measurements of E_a/E_{es}, we used the simplified method proposed by Chen et al. [8]. E_a was approximated from the ratio of end-systolic pressure (ESP) to SV, where ESP was estimated as $0.9 \times$ systolic blood pressure [20] and SV was computed as the product of the velocity–time integral, obtained using pulse wave Doppler in an apical four-chamber view, and the LV outflow tract cross-sectional area, measured in the parasternal long-axis view. E_{es} was calculated as ESP/(end-systolic volume $- V_0$), in which V_0, the intersection of the end-systolic elastance line with the x axis (the "volume" axis) of a LV pressure–volume loop, can be considered negligible [21–23]. In a secondary analysis, we used the pressure wave dicrotic notch as an alternative way to estimate ESP. However, as we could not directly evaluate the aortic dicrotic notch, which best represents ESP [8], we used the dicrotic notch determined on the peripheral waves as a surrogate for the central dicrotic notch.

Pulse waveform analysis measurements

Pulse waveform analysis was performed with the Most Care device. This device analyzes the arterial signal using a sampling frequency of 1,000 Hz. The high-frequency sampling enables analysis of the shape of the pressure waveform and correct measurement of pressures (systolic, diastolic, mean, dicrotic).

After zeroing the arterial pressure-transducer system and before each measurement, the arterial waveform signal fidelity was checked visually using a fast flush test to assess the adequacy of the damping of the arterial shape [24]. If there was a resonance effect of the catheter-transducer system [24, 25], we either adapted the pulse wave analysis system setting [26] or used the resonance over-shoot eliminator (ROSE; Becton-Dickinson, Franklin Lakes, NJ) if there was excessive under-damping/ resonance [14], to maximize the signal-to-noise ratio. The decision to improve the arterial trace quality was taken prior to collecting the pulse waveform analysis data in order to avoid any potential influence of the operators (S.S. and A.D.). Pulse wave analysis measurements were performed with both the investigators blinded to the data obtained from echocardiography and to other hemodynamic measurements except arterial pressure.

As this pulse wave analysis device does not require a dedicated catheter-transducer system, it was connected via a simple cable to the main monitoring system. Because a high-quality signal "without postprocessing" is needed for accurate estimations, we used the unprocessed arterial signal directly from the analog output of the main monitor, for continuous recording of the radial or femoral arterial pressure waveform and computation of AP-dP/dt_{MAX} and CCE. dP/dt_{MAX} was estimated from the arterial pressure waveform as the maximal rate of pressure change over time measured between two consecutive points during the systolic upstroke and is expressed in millimeters Hg per millisecond [14] (Fig. 1, Electronic supplementary material). CCE is a dimensionless variable (i.e., measured in arbitrary units) that ranges from negative values (worst values) to $+1$ (best value) (see the Electronic supplementary material for details of computation) [15–18]. Briefly, CCE is determined from the morphology of the arterial waveform and computed from the ratio of systolic power (i.e., systolic energetic performance) to the power of the entire heart beat (i.e., total energetic expenditure of the heartbeat). Systolic power and the power of the entire cardiac cycle are obtained using mathematical "power functions" of arterial pressure changes over time [17].

For all pulse wave analysis variables, values (approximately 10–15) were averaged over the time needed for each echocardiography measurement.

Statistical analysis

The Kolmogorov–Smirnov test was used to assess the normality of all the variables analyzed. The relationship between EC-dP/dt_{MAX} and AP-dP/dt_{MAX} was assessed using linear correlation analysis. Agreement between EC-dP/dt_{MAX} and EC-dP/dt_{MAX} was determined by the Bland–Altman method [27]. The percentage error was also calculated [28]. The relationship between CCE and LVEF was assessed using linear correlation analysis, and for the relationships between E_a/E_{es} and CCE a nonlinear regression model was used. Receiver operating characteristic (ROC) curves were constructed to study the ability of CCE to predict low (<40 %) or normal (≥ 50 %) LVEF [29], or altered A–V coupling ($E_a/E_{es} \geq 1.3$) [30]. A $P < 0.05$ was considered statistically significant.

Results

In this convenience sample, 70 patients were enrolled. Patient characteristics are shown in Table 1 and hemodynamic and respiratory profiles in Table 2. Eleven patients (16 %) had significant under-damping/resonance of the arterial pressure signal and needed positioning of the ROSE device before measurements. No patient was excluded after performing pulse waveform analysis measurements. Transesophageal echocardiography was used, for clinical purposes, in 15 patients who had inadequate transthoracic recordings.

Table 1 Characteristics of the 70 patients

Characteristic	Value
Age (years), mean ± SD	58 ± 15
Men/women	45/25
SOFA score at inclusion, mean ± SD	7.3 ± 3.7
APACHE II score at inclusion, mean ± SD	24 ± 7
Medical/surgical	52/18
Reason for ICU admission, n (%)	
Septic shock	19 (27)
Heart failure	37 (53)
Respiratory failure	14 (20)
Mechanical ventilation	41 (59)
Positive end-expiratory pressure, cmH$_2$O ($n = 41$), mean ± SD	7.3 ± 2.5
Continuous renal replacement therapy/intermittent hemodialysis, n (%)	13/1 (18/1.5)
Survivors, n (%)	52 (74)
Patients receiving vasoactive drugs, n (%)	
Norepinephrine	23 (32)
Dobutamine	12 (17)
Norepinephrine and dobutamine	9 (13)
Vasoactive drug doses (µg kg^{-1} min^{-1})	
Norepinephrine	0.15 ± 0.11
Dobutamine	7 ± 5

SOFA sequential organ failure assessment, *APACHE* acute physiology and chronic health evaluation.

Table 2 Hemodynamic and respiratory profile of the patients

Variable	Mean ± SD
Heart rate (bpm)	94 ± 22
Systolic arterial pressure (mmHg)	127 ± 21
Diastolic arterial pressure (mmHg)	66 ± 14
Dicrotic arterial pressure (mmHg)	104 ± 17
Mean arterial pressure (mmHg)	87 ± 16
Pulse pressure (mmHg)	61 ± 16
Central venous pressure (mmHg)	13 ± 4
Left ventricular ejection fraction (%)	53 ± 18
Central venous oxygen saturation (%)	69 ± 13
Cardiac output (L/min)[a]	6.5 ± 2.3
Mixed venous oxygen saturation (%)[a]	67 ± 11
Systemic vascular resistance (dyn s cm^{-5})[a]	1,108 ± 398
Pulmonary artery occlusion pressure (mmHg)[a]	17 ± 5
Mean pulmonary artery pressure (mmHg)[a]	31 ± 8

[a] Data obtained in 21 patients equipped with a pulmonary artery catheter.

All patients had LVEF assessed by echocardiography. The mean LVEF was 53 ± 18 % (range 12–90 %). Mean CCE was 0.16 ± 0.26 (range −0.56 to +0.89). There was a good correlation between LVEF and CCE ($r = 0.88$, 95 % CI 0.81–0.92, $P < 0.001$; Fig. 1). Further analyses for patients with LVEF ≤40 % ($n = 16$) and >40 % ($n = 54$) showed similar correlations between LVEF and CCE ($r = 0.59$ and $r = 0.67$, respectively; Figs. 2, 3, Electronic supplementary material).

Of the 70 patients, 44 (63 %) had a detectable mitral regurgitation jet so that dP/dt_{MAX} could be estimated by echocardiography. In these patients, the mean EC-dP/
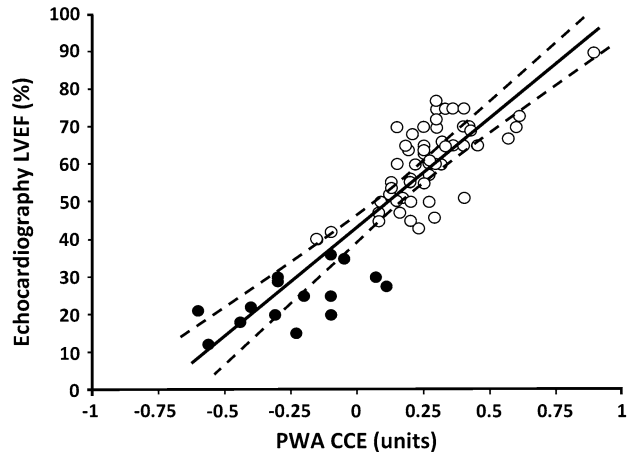

Fig. 1 Relationship between CCE and LVEF. CCE was estimated by pulse wave analysis and LVEF by echocardiography. The correlation coefficient is 0.88 (95 % CI 0.81–0.92, $P < 0.001$). *Black dots* represent LVEF <40 %, *white dots* LVEF ≥40 %. The *solid line* is the line of regression, *dashed lines* are the 95 % CI

dt_{MAX} was 1,240 ± 477 mmHg/s (range 450–2,000 mmHg/s). Mean AP-dP/dt_{MAX} was 1,216 ± 410 mmHg/s (range 400–1,900 mmHg/s). Values of dP/dt_{MAX} from the two techniques were significantly correlated ($r = 0.93$, 95 % CI 0.87–0.96, $P < 0.001$; Fig. 2a). The mean bias between EC-dP/dt_{MAX} and AP-dP/dt_{MAX} was 23.7 mmHg/s (95 % CI −23.6 to 71.0) with limits of agreement of −372 to +383 mmHg/s (lower 95 % CI −454 to −290; upper 95 % CI 338 to 502) and a relative percentage error of 28 % (Fig. 2b).

The mean E_a/E_{es} was 0.86 ± 0.74 (range 0.07–3.90). E_a/E_{es} and CCE were inversely related ($r = -0.81$, 95 % CI −0.88 to −0.71, $P < 0.001$; Fig. 3). A similar correlation was observed between CCE and E_a/E_{es} when peripheral dicrotic pressures were used to estimate ESP (Fig. 4, Electronic supplementary material).

A CCE value <0.07 predicted LVEF <40 % with a sensitivity of 0.93 and a specificity of 0.96. The area under the ROC curve for detecting LVEF <40 % by CCE was 0.98 (95 % CI 0.90–1.0, $P < 0.001$; Fig. 4a). A CCE value of >0.12 predicted LVEF ≥50 % with a sensitivity of 0.96 and a specificity of 0.82. The area under the ROC curve to detect LVEF ≥50 % by CCE was 0.94 (95 % CI 0.87–1.0, $P < 0.001$; Fig. 4a). A CCE value <0.12 predicted E_a/E_{es} ≥1.3 with a sensitivity of 0.93 and a specificity of 0.89. The area under the ROC curve for detecting E_a/E_{es} ≥1.3 by CCE was 0.94 (95 % CI 0.83–1.0, $P < 0.001$; Fig. 4b).

We observed similar correlations and agreements between parameters derived from pulse waveform analysis and echocardiography in patients with sepsis ($n = 19$; 27 %), low systemic vascular resistance ($n = 36$; 51 %) and norepinephrine infusion ($n = 23$; 32 %) as in the other patients (Figs. 5–13, Electronic supplementary material). In
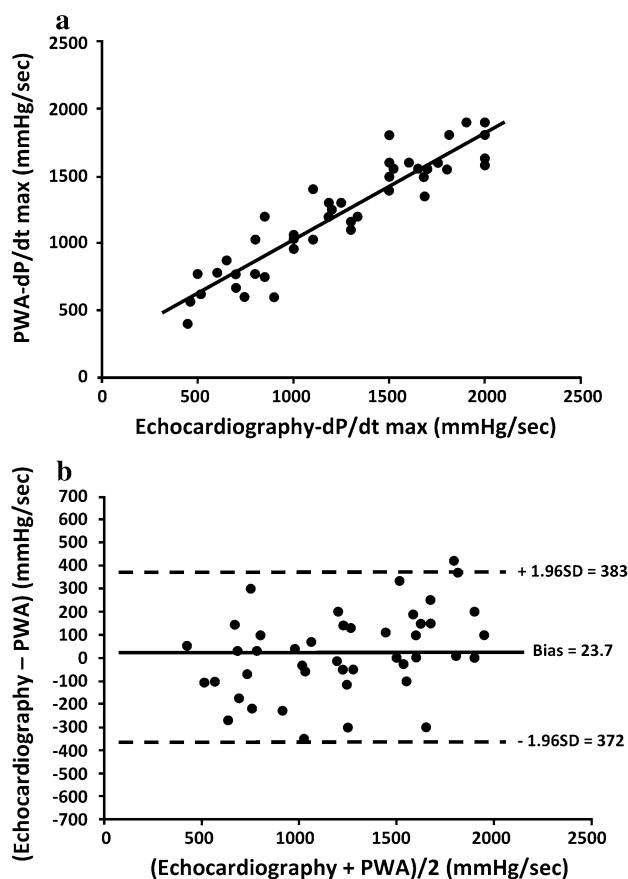
Fig. 2 Relationship between dP/dt_{MAX} estimated by echocardiography and pulse wave analysis. **a** Linear regression: correlation between dP/dt_{MAX} estimated by echocardiography and pulse wave analysis ($r = 0.93$, 95 % CI 0.87–0.96; $P < 0.001$) for 44 patients with mitral insufficiency. *Solid line* line of regression. **b** Bland–Altman analysis. *Solid line* mean difference (bias); *dashed lines* limits of agreement (LoA, bias 1.96 SD). Lower 95 % CI of LoA, −454 to −290; upper 95 % CI of LoA, 338 to 502)

addition, similar relationships were observed using radial and femoral lines (femoral dP/dt vs. echo dP/dt $r^2 = 0.80$ and radial dP/dt vs. echo dP/dt $r^2 = 0.88$).

Finally, data regarding SV values obtained by echocardiography and pulse wave analysis, and from a pulmonary artery catheter, are provided in the Electronic supplementary material Tables 1 and 2.

Discussion

This study showed that arterial pressure waveform analysis can provide useful information on cardiac function in critically ill patients, with reliable estimation of LV contractility and performance. Arterial pressure waveform-derived dP/dt_{MAX} reliably estimated EC-dP/dt_{MAX}, an index of LV contractility, and CCE was a reliable indicator of cardiac function and A–V coupling.
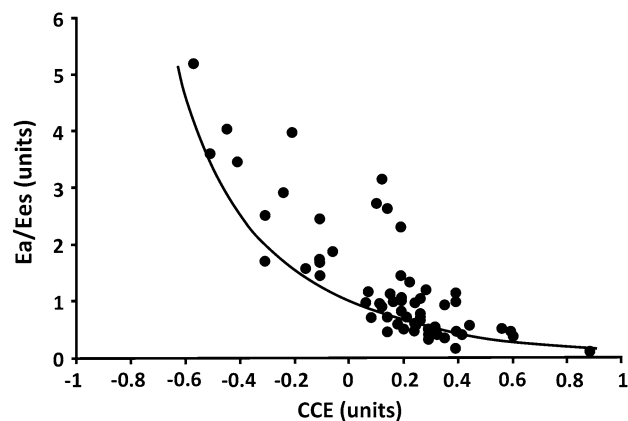

Fig. 3 Relationship between CCE and A–V coupling. CCE was calculated with pulse wave analysis and A–V coupling (E_a/E_{es}) estimated by echocardiography. For E_{es} evaluation, ESP was determined as $0.9 \times$ systolic arterial pressure. E_a/E_{es} and CCE were inversely related ($r = -0.81$, 95 % CI -0.88 to -0.71, $P < 0.001$)

LV dP/dt_{MAX} is an index of LV function, and especially contractility, representing the rate of pressure rise during the isovolumetric contraction period [31]. LV dP/dt_{MAX} occurs before opening of the aortic valve, which limits the influence of afterload [32]. LV dP/dt_{MAX} may thus reflect LV function better than LVEF [1], even though it remains a preload-dependent variable. The estimation of LV dP/dt_{MAX} requires LV catheterization with a high-fidelity pressure catheter, but it can also be estimated from the mitral regurgitant jet [3, 11]. Admittedly, LV dP/dt_{MAX} and peripheral artery-derived dP/dt_{MAX} represent different phases in the cardiac cycle: LV dP/dt_{MAX} is a measure of isovolemic contraction (pre-ejection phase variable), whereas peripheral artery-derived dP/dt_{MAX} is actually measured after aortic valve opening as it occurs during the LV ejection phase (ejection phase variable). Factors affecting vascular tone (elastance, compliance and stiffness) may lead to over- or underestimation of the true LV dP/dt_{MAX}. In addition, the arterial pulse is amplified during travel in the arterial tree [33], which may affect the reliability of peripheral artery-derived dP/dt_{MAX}. However, the relative contributions of left ventricular and arterial factors in peripheral artery-derived dP/dt_{MAX} are not well defined.

Another key point is that the dP/dt_{MAX} is usually estimated with pulse wave analysis over the first 20 ms of the pressure upstroke. However, the dP/dt_{MAX} can occur earlier (e.g., in LV hypertrophy) or later (e.g., in cardiac failure). We used a pulse wave analysis device that is able to measure the highest dP/dt of the pressure upstroke, even when it does not fall during the first 20 ms of the upstroke. Others have used arterial pulse derived dP/dt. Tartiere et al. [34] used applanation tonometry to noninvasively calculate the radial dP/dt_{MAX} and to compare it to LV dP/dt_{MAX} estimated by echocardiography.
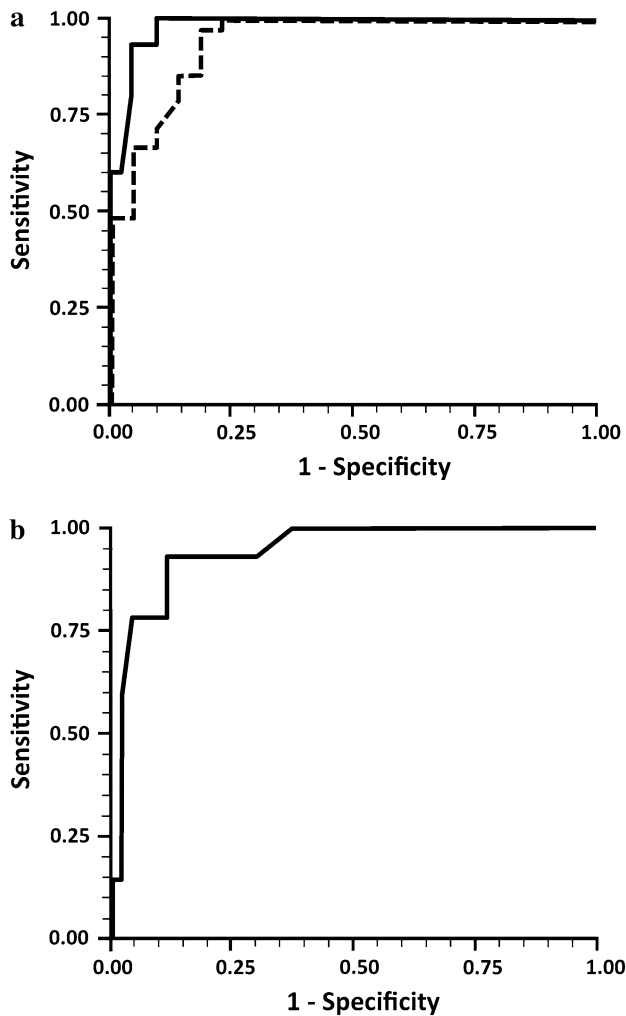
Fig. 4 Prediction of LVEF and A–V coupling by CCE. **a** ROC curves constructed to study the ability of CCE to predict a LVEF <40 % (*solid line*) and ≥50 % (*dashed line*). The area under the ROC curve is 0.98 (95 % CI 0.90–1.0, $P < 0.001$) for LVEF <40 % and 0.94 (95 % CI 0.87–1.0, $P < 0.001$) for LVEF ≥50 %. The best cut-off values were a CCE value <0.07 for predicting LVEF <40 % (sensitivity 0.93, specificity 0.96), and a CCE value >0.12 for predicting LVEF ≥50 % (sensitivity 0.98, specificity 0.82). **b** ROC curve constructed to study the ability of CCE to predict E_a/E_{es} ≥1.3. The area under the ROC curve is 0.94 (95 % CI 0.83–1.0, $P < 0.001$). A CCE value <0.12 predicted E_a/E_{es} ≥1.3 with a sensitivity of 0.93 and a specificity of 0.89

Good correlation and agreement were found between the two techniques. Using a femoral arterial line in cardiac surgery patients, De Hert et al. [35] reported that changes in femoral dP/dt_{MAX}, estimated by the transpulmonary thermodilution system, accurately reflect changes in LV dP/dt_{MAX} measured by a high-fidelity LV catheter. These data, combined with our results, suggest that peripheral artery dP/dt_{MAX} may be considered a suitable surrogate for LV dP/dt_{MAX}.

The usefulness of dP/dt_{MAX} in critically ill patients has not been established. Nevertheless, in patients with cardiac failure, alterations in dP/dt are associated with mortality however the dP/dt is measured, with a micromanometer tipped catheter [36], with echo-Doppler [37] or noninvasively from the radial pulse wave [38]. However, some major advantages of peripheral artery-derived dP/dt_{MAX} have to be mentioned. First, compared to invasive LV dP/dt_{MAX} and echocardiographic techniques, it can be obtained in most critically ill patients as they will already have had an arterial catheter inserted. Second, it is feasible even in the absence of mitral valve regurgitation. Finally, it can be used to detect abrupt changes in LV function [39].

LVEF is easily obtained by echocardiography [40] and is often used to assess the contractile performance of the left ventricle [41]. An LVEF less than 40 %, which indicates severely depressed LV systolic function [29], is associated with a markedly increased risk of death [42–44]. Our data show that CCE could serve as an easy bedside tool to detect alterations in LVEF and alert the physician to the need to perform echocardiography. CCE showed a good correlation with LVEF and was also able to discriminate normal, moderately altered and markedly altered LVEF, as CCE values <0.07 and >0.12 diagnosed LVEF <40 and ≥50 %, respectively, with good sensitivity and specificity.

E_a and E_{es} are relatively independent of loading conditions, making their relationship a more accurate index of LV function [45]. E_a is a measure of the net arterial load that is imposed on the left ventricle. E_{es} indicates how much the LV end-systolic volume will increase in response to an elevation in ESP [46]. E_a and E_{es} share common units (i.e., mmHg/ml), and their ratio, E_a/E_{es}, known as A–V coupling, represents a direct measure of the interaction between the left ventricle and the arterial system [47]. E_a and E_{es} are optimally coupled, for an optimal mechanical efficiency (best possible stroke work for the cardiovascular system), when A–V coupling is approximately 1 [48]. Physiologically, we usually operate with $E_a = 0.5 E_{es}$, a situation that corresponds to the best energetic efficiency (best ratio between stroke work and energy needed for cardiac contraction) [4, 49]. In contrast, in patients with congestive heart failure, E_a/E_{es} typically increases to as high as 4.0 [49]. We demonstrated an inverse relationship between CCE and E_a/E_{es}. Moreover, a CCE value <0.12 could predict E_a/E_{es} ≥1.3 with good sensitivity and specificity. Importantly, E_a/E_{es} is an early sign of myocardial impairment in critically ill patients, as the alteration in E_a/E_{es} occurs prior to significant LV dysfunction [50]. CCE may thus be proposed as a simple surrogate marker of E_a/E_{es} and could serve as a "wake-up call" for an echocardiographic evaluation to assess the actual cardiovascular status.

A number of limitations have to be considered when using the PRAM Most Care system. Under-damped

arterial pressure waveforms may affect both the amplitude and morphology of the pressure wave, thus affecting the precision of the tool under study [26, 51–53]. This pulse wave analysis system is highly sensitive to artifacts because its algorithm is exclusively based on the analysis of the pressure wave morphology [13]. Moreover, it is dependent on the operator, who sometimes needs to maximize the quality of the arterial signal [26]. The need for skill and the operator dependency may limit the application of pulse wave analysis in daily clinical practice.

In the present study, we corrected the resonance of the catheter-transducer system by maximizing the signal-to-noise ratio (i.e., we adapted the setting of the pulse wave analysis system) or by using the resonance over-shoot eliminator, ROSE, in patients with an under-damped pressure waveform, using morphologic criteria (i.e., the presence of a double systolic peak or dicrotic notch, and oscillations in the systolic decline and diastolic run-off of the pressure wave) and, after the fast-flush test, revealed an overshoot in the waveform [24, 25] (examples provided in the Electronic supplementary material, Figs. 14–16). Of note, no patient had to be excluded because of an inability to enhance the quality of the pressure wave signal. Aorta and aortic valve pathologies could influence the analysis of the arterial waveform [53]. Cardiac dysrhythmias can also affect the reliability of pulse wave analysis [54]. These conditions were considered as exclusion criteria in the present study. Finally, in hyperdynamic sepsis, where systemic vascular resistance is low, transmission of reflected waves can alter the morphology of the arterial signal [55]. In our trial, results were not affected by the sepsis state, low systemic vascular resistance, or norepinephrine administration.

A main limitation of this study is that we did not evaluate the respective alterations in these variables during hemodynamic changes related to different therapies or to spontaneous variations in the clinical state. Moreover, to estimate E_a/E_{es} we used a simplified method [8] and did not use a high-fidelity ventricular pressure catheter [5–7, 45]. The use of echocardiography may be suboptimal as a "gold standard", but it was the best available comparator, as left heart catheterization would have been too invasive. Finally, these results need to be confirmed in an independent cohort.

Conclusions

We demonstrated that arterial pressure-derived variables provide information on cardiac performance in critically ill patients. Pulse wave analysis cannot replace the information provided by echocardiography, but could provide online hemodynamic evaluation in ICU patients. Low CCE and AP-dP/dt_{MAX} indicate poor cardiac function and if present may be considered an indication for echocardiography.

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