Ventriculo-Arterial Coupling Is Associated With Oxygen Consumption and Tissue Perfusion in Acute Circulatory Failure

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Introduction: The determination of ventriculo-arterial coupling is gaining an increasing role in cardiovascular and sport medicine. However, its relevance in critically ill patients is still under investigation. In this study we measured the association between ventriculo-arterial coupling and oxygen consumption (VO2) response after hemodynamic interventions in cardiac surgery patients with acute circulatory instability.

Material and Methods: Sixty-one cardio-thoracic ICU patients (67 ± 12 years, 80% men) who received hemodynamic therapeutic interventions (fluid challenge or norepinephrine infusion) were included. Arterial pressure, cardiac output, heart rate, arterial (EA), and ventricular elastances (EV), total indexed peripheral resistances were assessed before and after hemodynamic interventions. VO2 responsiveness was defined as VO2 increase >15% following the hemodynamic intervention. Ventriculo-arterial coupling was assessed measuring the EA/EV ratio by echocardiography. The left ventricle stroke work to pressure volume area ratio (SW/PVA) was also calculated.

Results: In the overall cohort, 24 patients (39%) were VO2 responders, and 48 patients had high ventriculo-arterial (EA/EV) coupling ratio with a median value of 1.9 (1.6–2.4). Most of those patients were classified as VO2 responders (28 of 31 patients, p = 0.031). Changes in VO2 were correlated with those of indexed total peripheral resistances, EA, EA/EV and cardiac output. EA/EV ratio predicted VO2 increase with an AUC of 0.76 [95% CI: 0.62–0.87]; p = 0.001. In principal component analyses, EA/EV and SW/PVA ratios were independently associated (p < 0.05) with VO2 response following interventions.

Conclusions: VO2 responders were characterized by baseline high ventriculo-arterial coupling ratio due to high EA and low EV. Baseline EA/EV and SW/PVA ratios were associated with VO2 changes independently of the hemodynamic intervention used. These results underline the pathophysiological significance of measuring ventriculo-arterial coupling in patients with hemodynamic instability, as a potential therapeutic target.

Keywords: ventricular-arterial coupling, oxygen delivery, oxygen consumption, fluid therapy, norepinephrine, acute circulatory failure
INTRODUCTION

Acute circulatory failure following cardiac surgery is characterized by an imbalance between oxygen delivery (DO₂) and oxygen consumption (VO₂) which results in tissue hypoxia and organ dysfunction (1). The challenge in clinical practice is the identification of parameters that are clinically relevant to become endpoints for titration of interventions. Increasing DO₂ is an accepted goal for optimization following cardiac surgery, especially if it is decreased (2, 3). However, this increase might not be beneficial in all patients. Thus, a concomitant increase in VO₂ and DO₂ could identify those patients for whom DO₂ increase through therapeutic interventions is most beneficial and cost-efficient.

Complementary to the classical heart-centered pressure-flow model, the ventriculo-arterial coupling (V-A coupling) concept describes the interactions between the ventricles and the large arteries from an integrated pressure-volume relationship (4–6). The left ventricle (LV) and the arterial system are described by their elastances [i.e. ventricular elastance (Eᵥ), arterial elastance (Eₐ)], and V-A coupling is defined by the ratio of Eₐ/Eᵥ (4). The efficacy and efficiency of the cardiovascular system are the result of regulated interactions between the heart and the vascular system. The optimal hemodynamic intervention in patients with acute circulatory failure would improve efficacy with the lowest energetic cost (high efficiency) for the cardiovascular system (7).

Cardiology studies have demonstrated that V-A coupling may represent a parameter that describes the energetic cost in particular when LV function is altered (8, 9). There is clear evidence that V-A coupling is a hemodynamic parameter associated with patient outcomes (8, 10–13). The relevance of V-A coupling as a parameter of hemodynamic optimization in patients with acute circulatory failure could be related to the fact that this represents a parameter of cardiovascular efficiency whereas the classical hemodynamic parameters are exclusively parameters of cardiovascular efficacy (2, 3). Guidelines regarding the implementation of V-A coupling in clinical use are available for cardiologists, particularly in the context of heart failure (14). However, studies evaluating V-A coupling-based hemodynamic algorithms in the setting of ICU acute circulatory failure are lacking.

The present study was designed to investigate the clinical relevance of V-A coupling in critically ill patients. We sought to analyse the effects of two types of interventions: fluid challenge or norepinephrine infusion on systemic oxygenation parameters (as indicators of cardiovascular efficacy) and on V-A coupling (as an indicator of cardiovascular efficiency).

The main objective of this study was to investigate the relationship between Eₐ/Eᵥ ratio and changes in VO₂ upon treatment of hemodynamic instability following cardiac surgery. The second objectives were to compare V-A coupling and oxygenation-derived parameters [central venous saturation (ScVO₂), gap of CO₂] as predictor of VO₂ changes following hemodynamic treatment.

METHODS

Ethics
The study's objectives and procedures were approved by the local independent Ethics Committee (Comité de Protection des Personnes Nord-Ouest II CHU - Place V. Pauchet, 80054 AMIENS Cedex 1). All patients received written information and gave their verbal consent to participate. The present manuscript was drafted in compliance with the STROBE checklist for cohort studies (15).

Patients
This observational cohort study was performed in a university-affiliated cardiothoracic ICU between 2015 and 2017. We included patients aged 18 or over, under controlled positive ventilation, with hemodynamic instability, for whom the clinician decided to perform a fluid challenge and/or start a norepinephrine infusion. The indications for fluid challenge were: (1) arterial hypotension, defined as systolic arterial pressure (SAP) below 90 mmHg and/or a mean arterial pressure (MAP) below 65 mmHg, and/or (2) stroke volume (SV) variation of more than 10%, and/or (3) clinical signs of hypoperfusion. In the present study, fluid challenge always consisted of a 10-min infusion of 500 ml of lactated Ringer’s solution (16). The indication for norepinephrine was persistent arterial hypotension (SAP <100 mmHg and/or MAP <65 mmHg) despite fluid challenge (11, 16). The exclusion criteria were permanent/persistent chronic atrial fibrillation, heart conduction block (type I, II and III atrioventricular blocks, left and right bundle branch blocks), the presence of an active pacemaker, poor acoustic window, more than mild aortic regurgitation, and right heart failure.

Measurement and Calculation of Left Ventricular Elastance, Arterial Elastance, and Ventriculo-Arterial Coupling
Stroke volume (SV; mL) and cardiac output (CO; l min⁻¹) were measured using transthoracic echocardiography performed with a commercially available machine (CX50 ultrasound system Philips Medical System, Suresnes, France) equipped with a S5-1 Sector Array Transducer. The echocardiographic parameters were averaged from five measurements (regardless of the respiratory cycle). Ev was estimated at the bedside using the non-invasive single beat method described by Chen et al. (17). This method is based on the assumption that time-variation of LV elastance is not influenced by loading conditions or heart rate. Eᵥ was calculated by the formula: Eᵥ = (Pd – (Eₐ(test) * Pes * 0.9)) / (SV * Eₐ(test)). Eₐ(test) was obtained from a group-averaged normalized elastance curve value at this same time tc (Eₐ(avg)), baseline LV ejection fraction (LVEF) and the ratio of diastolic to systolic arterial pressure (17). We calculated the coefficient of variation (CV), precision and least significant change (LSC) for Eᵥ in ten patients. CV was 7.7% ± 0.6 and LSC was 10.9% ± 0.8. Eₐ was estimated by using the formula Eₐ = end-systolic pressure (ESP) = 0.9 * SAP/SV (18). SAP was measured by using invasive radial artery catheters. In healthy men and women, the mean Eₐ/Eᵥ, Eₐ, and Eᵥ values measured invasively at rest are...
respectively 1.0 ± 0.36, 2.2 ± 0.8 mmHg ml⁻¹, and 2.3 ± 1.0 mmHg.ml⁻¹ (18, 19). An abnormal E/A/E ratio was defined as a value >1.36 (19).

The total energy generated by each cardiac contraction is called the “pressure-volume area” (PVA), which is 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 (19). The PVA has been demonstrated to be linearly related to myocardial oxygen consumption (7, 19). SW is calculated as ESP x SV. Potential energy is calculated as ESP x (ESV-V₀)/2 and assumes that V₀ is negligible when compared with ESV. We calculated total indexed peripheral resistance (TPRi) as TPRi = MAP-central venous pressure (CVP)/cardiac index (mmHg ml⁻¹ m⁻²).

**Oxygenation Parameters**

We recorded the ventilator settings (tidal volume, plateau pressure and end-expiratory pressure) at baseline. All parameters were measured on arterial and central venous blood gases (Supplementary File 1).

**Study Procedures**

Anesthesia and cardiopulmonary bypass procedures were standardized for all patients. During the study period, the patients were mechanically ventilated in volume-controlled mode, with a tidal volume set to 7–9 ml kg⁻¹ ideal body weight, and a positive end-expiratory pressure (PEEP) of 5–8 cm H₂O, and sedated with Propofol (20). Ventilator settings (oxygen inspired fraction, tidal volume, respiratory rate and end positive pressure) were not modified during the study period.

The following clinical parameters were recorded: age, gender, weight, ventilation parameters, and primary diagnosis. After an equilibration period, HR, SAP, MAP, diastolic arterial pressure (DAP), CVP, SV, CO, and arterial/venous oxygen content were measured at baseline.

**Statistical Analyses**

In the absence of preliminary data, we designed an observational study with a convenience sample of 61 consecutive patients. Such size could enable to demonstrate a correlation (0.3–0.5) between E/A/E ratio and VO₂ response with a power of 0.8 and alpha error of 0.05. The variables’ distribution was assessed using a D’Agostino-Pearson test. Data are expressed as the number, proportion (in percent), mean ± standard deviation (SD) or the median [interquartile range (IQR)], as appropriate. Patients were classified as VO₂ responders or non-responders as a function of the effect of hemodynamic interventions (fluid challenge or norepinephrine) on VO₂. VO₂ response was defined as an increase of more than 15% in the VO₂. The non-parametric Wilcoxon rank sum test, Student’s paired t-test, Student’s t-test, the Mann-Whitney test, and the Fisher’s test were used to assess statistical significance, as appropriate. Correlations were tested using Pearson’s or Spearman’s rank test, as appropriate.

Because we have analyzed several correlated hemodynamic and perfusion variables, we performed an exploratory principal component analysis to avoid collinearity. The principal component analysis transforms correlated variables into uncorrelated variables that may explain VO₂ changes. A principal component analysis was carried out by including fourteen baseline variables. The VO₂ changes following therapeutic interventions were included as a supplementary variable. Considering there were some differences between baseline characteristics between VO₂ responders vs. non-responders in univariate, we performed a multivariate regression logistical model in order to determine the independent adjusted associations. The conditions of validity of the multivariate model were checked, in order to have at least 5 responders for each variable included in the model. A receiver-operating characteristic (ROC) curve was established for the ability of ScVO₂, CO₂ gap, EVA/E ratio to predict an increase of more than 15% in VO₂.

The threshold for statistical significance was set to p < 0.05. R software (version 3.5.0) with FactoMineR package was used for all statistical analyses.

**RESULTS**

Of the 65 included patients, four were excluded (Supplementary File 2), and so the final study population consisted of 61 subjects (Table 1). At baseline 48 patients (78%) were categorized as uncoupled, with a median E/A/E ratio of 1.9 (1.6–2.4) mainly related to abnormally low EV (1.1 (0.9–1.6)), as compared to preserved EVA (2 (1.5–2.7)). In the overall population, 31 patients (48%) were classified as VO₂ responders. The percentage of VO₂ responders did not differ between the two groups [16 (48%) out of 33 vs. 15 (54%) out of 28, p = 0.799].

Of the 6 patients with mitral regurgitation surgery, 2 were in the group of VO₂ responders and 4 in the group of VO₂ non-responders (Fisher’s test, p = 1).

**Combined Analysis of the Effects of the Two Therapeutic Interventions on Systemic Parameters**

At baseline, VO₂ responders had higher EVA/E ratio, and lower SW/PVA ratio and VO₂ than VO₂ non-responders (Table 2, Figure 1). They also had a lower LVEF. Therapeutic interventions increased SAP, MAP, CO and DO₂ in the overall population. VO₂ responders were characterized by an increased SW/PVA ratio, and a decreased HR, and TPRi. VO₂ non-responders were characterized by an increased EVA, EV, ScVO₂, TPRi, and a decreased gapCO₂.

**Effects of Fluid Challenge on Systemic Oxygenation Parameters**

At baseline, VO₂ responders had lower VO₂, gapCO₂, and higher EVA/E ratio, ScVO₂ than VO₂ non-responders. Fluid challenge increased SAP, MAP, and SV in VO₂ responders and non-responders. VO₂ responders were characterized by an increase in SV and CO decreased TPRi, EVA, and an increased SW/PVA ratio and gapCO₂. EV did not change. VO₂ non-responders were characterized by an increase in SV, ScVO₂, and a decreased HR.
TABLE 1 | Characteristics of the study participants on inclusion.

| Variables                      | Overall population (n = 61) |
|--------------------------------|----------------------------|
| Age (years), mean±SD           | 67 ± 12                    |
| Gender (female), n (%)         | 12 (20)                    |
| BMI (kg m⁻²), mean±SD          | 28.7 ± 5                   |
| Comorbidities, n (%)           |                            |
| - High blood pressure          | 44 (72.1)                  |
| - Heart failure                | 21 (34.4)                  |
| - Right ventricle dysfunction  | 9 (14.8)                   |
| - Diabetes                     | 16 (26.2)                  |
| - Dyslipidaemia                | 28 (45.9)                  |
| - Active smoking               | 22 (36.1)                  |
| - COPD                         | 5 (8.2)                    |
| - Chronic kidney disease       | 5 (8.2)                    |
| SAPS 2 score, mean±SD          | 41 ± 14                    |
| ASA score, n (%)               |                            |
| - I                            | 1 (1.6)                    |
| - II                           | 2 (3.3)                    |
| - III                          | 54 (88.5)                  |
| - IV                           | 4 (6.6)                    |
| Type of surgery, n (%)         |                            |
| - Vavular only                 | 29 (47.5)                  |
| - Mitral regurgitation surgery | 6 (9.8)                    |
| - CABG only                    | 10 (16.4)                  |
| - Combined surgery             | 12 (19.7)                  |
| - Other                        | 10 (16.4)                  |
| Ventilation parameters         |                            |
| Tidal volume (ml kg⁻¹ of predicted body weight), mean±SD | 7.7 ± 0.6 |
| Total PEEP (cmH₂O), mean±SD    | 5 ± 1                      |
| Patients treated with norepinephrine, n (%) | 26 (48) |
| Median dose (mcg Kg⁻¹min⁻¹), (IQR) | 0.08 [0.06–0.18] |
| Patients treated with fluid expansion, n (%) | 35 (52) |
| In-hospital death, n (%)       | 3 (6)                      |

SD, standard deviation; BMI, body mass index; COPD, chronic obstructive pulmonary disease; SAPS 2, simplified acute physiology score 2; ASA score, American Society of Anesthesiology score; CABG, coronary artery bypass graft surgery; PEEP, positive end expiratory pressure; IQR, 25–75% interquartile range.

Effects of Norepinephrine on Systemic Oxygenation Parameters

At baseline, VO₂ responders had lower SV, CO, SW/PVA ratio, VO₂, and higher gapCO₂, Eᵥ/Eᵥ ratio than VO₂ non-responders. Norepinephrine infusion increased SAP, MAP, CO and DO₂ in both groups. VO₂ responders were characterized by an increased SV and CO, SW/PVA ratio. VO₂ non-responders were characterized by an increased Eᵥ, Eᵥ, ScVO₂.

TABLE 2 | Comparison of haemodynamic parameters in VO₂ responders and VO₂ non-responders. Values are expressed as the mean (SD) or the median (interquartile range).

| Hemodynamic variables | VO₂ responders (n = 31) | VO₂ non-responders (n = 30) | p value |
|-----------------------|-------------------------|-----------------------------|---------|
| HR (bpm)              | 78 (21)                 | 82 (19)                     | 0.410   |
| Post                  | 75 (20)                 | 80 (16)                     | 0.274   |
| SAP (mmHg)            | 99 (19)                 | 91 (14)                     | 0.093   |
| Post                  | 124 (19)                | 116 (29)                    | 0.333   |
| MAP (mmHg)            | 68 (15)                 | 65 (13)                     | 0.260   |
| Post                  | 84 (14)                 | 80 (12)                     | 0.707   |
| SV (ml)               | 41 (14)                 | 46 (18)                     | 0.413   |
| Post                  | 57 (19)                 | 50 (16)                     | 0.118   |
| CO (L min⁻¹)          | 3.2 (1.1)               | 3.6 (1)                     | 0.159   |
| Post                  | 4.1 (1)                 | 3.8 (0.9)                   | 0.357   |
| TPRi (mmHg ml⁻¹ m⁻²)  | 42 (14)                 | 34 (15)                     | 0.056   |
| Post                  | 39 (17)                 | 39 (14)                     | 0.945   |
| Eᵥ (mmHg ml⁻¹)        | 2.3 (1)                 | 2.1 (1)                     | 0.358   |
| Post                  | 2.2 (0.8)               | 2.4 (1.1)                   | 0.343   |
| Eᵥ (mmHg ml⁻¹)        | 1.2 (0.6)               | 1.3 (0.6)                   | 0.252   |
| Post                  | 1.2 (0.6)               | 1.6 (0.7)                   | 0.036   |
| Eᵥ/Eᵥ                 | 2.2 (0.6)               | 1.6 (0.6)                   | 0.002   |
| Post                  | 2 (0.9)                 | 1.6 (0.5)                   | 0.023   |
| SW/PVA ratio          | 0.55 (0.12)             | 0.62 (0.11)                 | 0.008   |
| Post                  | 0.62 (0.15)             | 0.62 (0.12)                 | 0.891   |
| DO₂ (ml min⁻¹)        | 482 (179)               | 504 (148)                   | 0.603   |
| Post                  | 635 (219)               | 593 (149)                   | 0.047   |
| VO₂ (ml min⁻¹)        | 132 (54)                | 180 (53)                    | 0.001   |
| Post                  | 198 (61)                | 167 (53)                    | 0.041   |
| ScVO₂ (%)             | 67 (12)                 | 60 (8)                      | 0.01    |
| Post                  | 63 (9)                  | 65 (8)                      | 0.842   |
| GapCO₂ (mmHg)         | 9 (4)                   | 9 (2)                       | 0.842   |
| Post                  | 9 (4)                   | 7 (5)                       | 0.061   |

CO, cardiac output; DO₂, oxygen delivery; FC, fluid challenge; HR, heart rate; LVEF, left ventricular ejection fraction; MAP, mean arterial pressure; SAP, systolic arterial pressure; SV, stroke volume; TPRi, total indexed peripheral resistance; VO₂, oxygen consumption. $p < 0.05$ within groups (pre-/post-FC).
Correlations Between Systemic Oxygenation Parameters (Efficacy) vs. $E_A$, $E_V$, $E_A/E_V$ Ratio and SW/PVA Ratio (Efficiency) With the Two Therapeutic Interventions

In the overall cohort, changes in VO$_2$ were correlated with those in SW/PVA ratio ($r = 0.362$, $p = 0.003$), $E_A$ ($r = -0.446$, $p < 0.001$), $E_A/E_V$ ($r = -0.256$, $p = 0.046$), CO ($r = 0.495$, $p < 0.001$), ScVO$_2$ ($r = -0.522$, $p < 0.001$), TPRI ($r = -0.444$, $p < 0.001$). The baseline SW/PVA ratio was correlated with DO$_2$ ($r = 0.339$, $p = 0.004$), VO$_2$ ($r = 0.258$, $p = 0.045$), and gapCO$_2$ ($r = -0.304$, $p = 0.017$).

**VO$_2$ Responsiveness Prediction**

Baseline $E_A/E_V$ was predictive of VO$_2$ responsiveness, with an area under the curve (AUC) [95% confidence interval (95%CI)] of 0.76 ([0.62–0.87]; $p = 0.001$). The best cut-off was 2.1 with a gray zone between 1.8 and 2.4. With an AUC [95%CI] of 0.72 [0.59–0.85] ($p = 0.004$), baseline ScVO$_2$ was predictive of VO$_2$ responsiveness. With an AUC [95%CI] of 0.44 [0.29–0.58] ($p = 0.05$), gapCO$_2$ was not predictive of VO$_2$ responsiveness. When analyzing patients separately for fluid challenge or norepinephrine infusion, baseline $E_A/E_V$ was predictive of VO$_2$ responsiveness in fluid challenge group (AUC: 0.77 [0.59–0.95] ($p = 0.008$) and norepinephrine group (AUC: 0.74 [0.56–0.93] ($p = 0.045$).

These results were confirmed by the multivariate regression model adjusted on differences at baseline (LVEF, ScVO$_2$, SW/PVA ratio, $E_A/E_V$ ratio). Baseline $E_A/E_V$ ratio (OR: 3.4 [1.1–10.3], $p = 0.033$) and ScVO$_2$ (OR: 1.08 [1.01–1.15], $p = 0.016$) were independently associated with VO$_2$ responsiveness, but not the baseline LVEF (OR: 1 [0.93–1.07], $p = 0.993$) and SW/PVA ratio (OR: 0.5 [0.3–1.3], $p = 0.297$). When using the principal component analysis, the 3 first principal components explained 61% of the variance (Supplementary Table 1, Supplementary Figures 1, 2). VO$_2$ changes were significantly associated with the first ($r = 0.31$) and the third component ($r = 0.52$). $E_A$, $E_V$, $E_A/E_V$, and SW/PVA ratio were variables included in components associated to VO$_2$ changes.

**DISCUSSION**

The main results of the present study are as follow: (1) most patients for whom fluid challenge or norepinephrine infusion increased VO$_2$ had high V-A coupling ratio with lower left ventricle stroke work to pressure volume area ratio (SW/PVA) at baseline; (2) baseline $E_A/E_V$ and SW/PVA ratios were associated...
with perfusion parameters and VO$_2$ changes independently of the therapeutic intervention used.

When analyzing together fluid challenge or norepinephrine infusion, the only common profile is the increase in arterial pressure. VO$_2$ responders have an increase in SV, CO and a decrease in TPRi. VO$_2$ responder patients were uncoupled before interventions as they adapted to maintain tissue perfusion with a higher energetic cost for the same efficacy (preserving efficacy over efficiency). This was reflected by the lower E$_A$/E$_V$ ratio in VO$_2$-responders. Equally, VO$_2$-responder patients had significantly lower SW/PVA values before hemodynamic intervention, which were associated to perfusion parameters. We demonstrated that the E$_A$/E$_V$ ratio partly explains VO$_2$ responsiveness and was independently associated with VO$_2$ responsiveness. Both approaches credibly establish at least the statistical relevance of analyzing V-A coupling in patients with hemodynamic instability following cardiac surgery.

### A Pathophysiological Perspective on V-A Coupling

It has been shown that mechanical efficiency is greatest when E$_A$ = E$_V$ (i.e., E$_A$/E$_V$ ratio = 1) (4, 6, 21). The patients of the present study were characterized by “normal” E$_A$ but much lower than normal E$_V$ values, resulting in 78% patients having high V-A coupling ratio. Burkhoff and Sagawa have also shown that the mechanical efficiency of the heart is more sensitive to E$_A$, especially when E$_V$ is impaired, which is observed at baseline in the patients of the present study (21). “Sacrificing” efficiency to preserve efficacy for a limited period of time is a “physiological choice” observed in athletes (22). Patients with the most severe V-A coupling (i.e., the highest V-A coupling ratio) had the lowest VO$_2$ (22). The consequences of long term “sacrificing efficiency,” (i.e., days) for the ICU patients are not known. For instance, the fact that catecholamine use is associated with increased mortality could be an example of deleterious long-term consequences of providing better cardiovascular performance at a high energetic cost (23).

Investigating the effects of two interventions on V-A coupling comes down to answering the question already raised many years ago: how effective is an increase in myocardial performance (i.e., an increase in SV) transmitted to the peripheral circulation (24). This transmission may be mediated by the V-A coupling (24). In this respect, if the increase in cardiac performance is transmitted to the circulation, this should result into opening new vascular beds, and if DO$_2$ limits the VO$_2$, this should result in an increase in VO$_2$. This is what our results demonstrate, linking the increase in cardiac performance with the peripheral circulation through the V-A coupling.

### Clinical Relevance of V-A Coupling in ICU Patients

Cardiologists have already integrated V-A coupling based hemodynamic approach in the treatment of chronic heart failure or arterial hypertension (9, 14, 25). In the ICU, several attempts of hemodynamic optimisation based on V-A coupling perspective were published (25, 26). Few studies have investigated the relationship between V-A coupling on one side and DO$_2$ and VO$_2$ on the other in ICU patients (10, 27). To the best of our knowledge, this is the first attempt that has specifically focused on VO$_2$. V-A coupling has been already demonstrated as a factor limiting patients’ adaptability to effort (8). Previous authors have studied the association of V-A coupling improvement and the time course of systemic oxygenation parameters in trauma patients (27, 28). Our results support their findings by demonstrating an association between V-A coupling, SW/PVA ratio, to perfusion parameters and further VO$_2$ changes.

Sepsis and septic shock are characterized by different profiles of V-A coupling (i.e., different hemodynamic profiles) for which hemodynamic treatment may differ (29). More than two thirds of sepsis patients are V-A uncoupled (30, 31). The fact that most uncoupled patients showed an increase in VO$_2$ after therapeutic interventions could be a further argument for targeting V-A coupling during resuscitation, as marker of tissue perfusion. This therapeutic option might help in better choosing the responsive patients, as a vasopressor-sparing strategy (32). The norepinephrine infusion alters V-A coupling with an increase in E$_A$ > E$_V$ (30, 33). Targeting primarily the MAP of 65 mmHg might sustain an unnecessary (34) and possibly an unfavorable prolonged energetic state because of increased cardiac afterload (32). Algorithms using the monitoring dynamic arterial elastance were proposed in ICU and they demonstrated that early weaning of norepinephrine may be associated with better tissue perfusion (12, 35). As the dynamic arterial elastance was shown to be correlated with V-A coupling and microcirculation (36, 37), the connection with VO$_2$ in our study might contribute with a new puzzle piece. One advantage of V-A coupling is that it can be non-invasively measured at bedside. Contrary to perfusion parameters, it does not require blood sampling. Further randomized study evaluating a hemodynamic strategy based on V-A coupling may confirmed these points.

### Potential Limitations of the Present Study

Firstly, the analysis of two therapeutic interventions can make interpretation of the results difficult. The present objective was not to precisely analyze the individual effect of each therapy. Such demonstrations have been previously published (17). On the contrary, we would like to demonstrate that a hemodynamic approach based on the V-A coupling makes it possible to dispense with the hemodynamic treatment and a detailed analysis of each parameter. The fact that the association between V-A coupling and perfusion parameters was demonstrated in the population as a whole and in each treatment, group reinforces our results. As discussed, we believe that the effects of norepinephrine on VO$_2$ may be due to its effects on CO and DO$_2$ (38).

Secondly, the VO$_2$/DO$_2$ relationship is not linear. The VO$_2$ responder group has lower values of VO$_2$ that are below those in the non-responder group, even after hemodynamic treatment. We believe the lower value of VO$_2$ in responder group may not have introduce bias. These observations are in relation with the fact that the hemodynamic response was defined by VO$_2$ changes. The methods used to calculate E$_V$ and E$_A$ can potentially be criticized because we did not use a high-fidelity ventricular pressure catheter (17). We calculated ESP from a radial artery...
signal, which may differ from the aortic pressure signal. However, radial arterial pressure has been reported to provide a good estimate of ESP (39). 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 $E_V$, but not the $E_A/E_V$ ratio, as the error in end-systolic pressure would be similar. Despite these limitations, non-invasive evaluation of $E_V$ 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 $E_V$ must be considered to be approximations of $E_A$ and $E_V$. Despite these limitations, non-invasive evaluation was validated against the gold standard method, and have been used in the cardiology and cardiac surgical fields (14).

Thirdly, our findings generalizability is restricted by the low number of patients analyzed in this cohort. Considering the known heterogeneity of intensive care unit (ICU) patients, larger cohorts are required to perform a properly matching on different confounding factors. The clinical relevance of the relationship between V-A coupling and VO$_2$ in the context of goal-directed therapy in critically ill patients is still to be validated. The results of well-designed interventional trials, such as the one published by Borlaug et al. that used LV afterload reduction, are awaited (40).

### CONCLUSIONS

In VO$_2$ responders, V-A coupling was characterized by a high $E_A/E_V$ ratio (due to high $E_A$ and low $E_V$). Baseline $E_A/E_V$ and SW/PVA ratios were associated with VO$_2$ changes independently of the hemodynamic intervention used. Measuring V-A coupling may offer a new perspective of hemodynamic optimisation in the ICU by individualizing hemodynamic treatment and by analyzing both the efficacy and efficiency of hemodynamic interventions.

### DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

### ETHICS STATEMENT

The studies involving human participants were reviewed and approved by (Comité de Protection des Personnes Nord-Ouest II CHU - Place V. Pauchet, 80054 AMIENS Cedex 1). The patients/participants provided their written informed consent to participate in this study.

### AUTHOR CONTRIBUTIONS

SA, MN, and P-GG conceived the study, analyzed the data and drafted the manuscript. P-GG collected the data. DL, BP, and BB provided a critical review. All authors contributed to the article and approved the submitted version.

### SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2022.842554/full#supplementary-material

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