Ventriculo-arterial uncoupling is associated with VO$_2$ dependency in cardiac surgical patients.

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**Abbreviated title: Ventricular-arterial coupling and VO$_2$ dependency**

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Abstract:

Background: The clinical relevance of V-A (un)coupling in critically ill patients is under investigation. In this study we measured the association between V-A coupling and oxygen consumption (VO$_2$) response in patients with acute circulatory instability following cardiac surgery.

Methods and results: Sixty-one cardio-thoracic ICU patients who received fluid challenge or norepinephrine infusion were included. Arterial pressure, cardiac output (CO), heart rate (HR), arterial (E$_A$), and ventricular elastances (E$_V$), total indexed peripheral resistance (TPRi) were assessed before and after hemodynamic interventions. VO$_2$ responders were defined as VO$_2$ increase $> 15\%$. V-A coupling was evaluated by the ratio E$_A$/E$_V$. Left ventricle stroke work (SW) to pressure volume area (PVA) ratio was calculated. In the overall population, 24 patients (39\%) were VO$_2$ responders and 48 patients were uncoupled (i.e., E$_A$/E$_V$ ratio $> 1.3$): 1.9 (1.6-2.4). Most of the uncoupled patients were classified as VO$_2$ responders (28 of 31 patients, $p=0.031$). Changes in VO$_2$ were correlated with those of TPRi, E$_A$, E$_A$/E$_V$ and CO. E$_A$/E$_V$ ratio predicted VO$_2$ increase with an AUC of 0.76 [95 % CI: 0.62-0.87]; $p=0.001$. In multivariate and principal component analyses, E$_A$/E$_V$ and SW/PVA ratios were independently associated (P $< 0.05$) with VO$_2$ response following interventions.

Conclusions: VO$_2$ responders were characterized by baseline V-A uncoupling 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. These results further underline the pathophysiological significance of V-A uncoupling in patients with hemodynamic instability.
Introduction

Acute circulatory failure following cardiac surgery is characterized by an imbalance between oxygen delivery ($\text{DO}_2$) and oxygen consumption ($\text{VO}_2$) which results in tissue hypoxia and organ dysfunction (1). In clinical practice, the difficulty is to identify parameters that are clinically relevant to become endpoints for titration of interventions. Increasing $\text{DO}_2$ is an accepted goal for optimization following cardiac surgery (2, 3) especially if decreased $\text{DO}_2$. Thus, predicting $\text{VO}_2$ responsiveness could identify the patients for which $\text{DO}_2$ increase is the most beneficial.

The ventriculo-arterial coupling (V-A coupling), describes the interactions between the ventricles and the large arteries from an integrated pressure-volume relationship (4-6). The left ventricle and the arterial system are described by their elastances (ventricular elastance ($E_V$), arterial elastance ($E_A$)), and V-A coupling is defined by the ratio of $E_A/E_V$ (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 the left ventricular function is altered (8, 9). There is wide evidence that V-A (un)coupling is a hemodynamic parameter that is associated with patient outcomes (8, 10-13). The relevance of V-A (un)coupling as a parameter of hemodynamic optimization in patients with acute circulatory failure could be related to the fact that V-A (un)coupling is a parameter of cardiovascular efficiency whereas the classical hemodynamic parameters are exclusively parameters of cardiovascular efficacy (2, 3).

In our continuous attempt to investigate the clinical relevance of V-A (un)coupling in critically ill patients we designed the present study in order to analyse the effects of two types of interventions: fluid challenge (FC) 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 $E_A/E_V$ ratio and changes in $\text{VO}_2$ upon treatment of hemodynamic instability following cardiac surgery. The second objectives were to compare V-A coupling and oxygenation derived parameters (central venous saturation ($\text{ScVO}_2$), gap $\text{CO}_2$) as predictor of $\text{VO}_2$ changes following hemodynamic treatment.
METHODS

Ethics

Ethical approval for this study (RNI2014-39) was provided by Comité de Protection des Personnes Nord-Ouest II, Amiens, France (Chairperson T Bourgueil) on 9 February 2015. All patients received written information and gave their verbal consent to participation. The present manuscript was drafted in compliance with the STROBE checklist for cohort studies (12).

Patients

This prospective, observational study was performed in the cardiothoracic ICU at University Hospital between 2015 and 2017. The main inclusion criteria were as follows: age 18 or over, controlled positive ventilation, and a clinical decision to treat hemodynamic instability by FC and/or norepinephrine. The indications for FC were arterial hypotension: a systolic arterial pressure (SAP) below 90 mmHg and/or a mean arterial pressure (MAP) below 65 mmHg, and/or stroke volume (SV) variation of more than 10%, and/or clinical signs of hypoperfusion (skin mottling, and a capillary refill time of more than 3 sec). In the present study, FC always consisted of a 10-minute infusion of 500 ml of lactated Ringer's solution. The indications for norepinephrine were persistent arterial hypotension (SAP less than 100 mmHg and/or MAP less than 65 mmHg) despite FC (13). The non-inclusion criteria were permanent arrhythmia, heart conduction block, the presence of an active pacemaker, poor echogenicity, aortic regurgitation, and right heart failure.

Measurement and calculations of left ventricular elastance, arterial elastance, and ventriculo-arterial coupling

Stroke volume (SV; mL) and cardiac output (CO; l min⁻¹) were calculated by using transthoracic echocardiography (CX50 ultrasound system and an S5-1 Sector Array Transducer, Philips Medical System, Suresnes, France). Mean echocardiographic parameters were retrospectively calculated 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. and validated by conference expert (14, 15). Eₐ was estimated by using the formula Eₐ = end-systolic pressure (ESP=0.9 * SAP)/SV (16). SAP was measured by using invasive radial artery catheter. 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 (17). The PVA has been demonstrated to be linearly related to myocardial oxygen consumption (17, 18). SW is calculated as ESP ×
SV. PE 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**

Maintenance or withdraw of preoperative medications followed guidelines. Anaesthesia and cardiopulmonary bypass procedures were standardised 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 cmH₂O, and sedated with Propofol. 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 analysis**

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 to 0.5) between Eₐ/Eₐ 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 (FC or norepinephrine) on VO₂. VO₂ response was defined as an increase of more than 15% in the VO₂ (19). 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. Because, we have analysed several correlated hemodynamic and perfusion variables, we performed three different analysis to evaluate the association between ventriculo-arterial coupling and VO₂: a linear correlation analysis, principal component analysis and predictability analysis. Linear correlations were
tested using Pearson's or Spearman's rank method. The principal component analysis transforms correlated variables into uncorrelated variables that may explain VO$_2$ changes. A principal component analysis was carried out by including fourteen baseline variables. The VO$_2$ changes following therapeutics was included as a supplementary variables. A receiver-operating characteristic curve was established for the ability of ScVO$_2$ and E$_V$/E$_A$ ratio to predict an increase of more than 15% in VO$_2$. 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 analysis concerned 61 subjects (Table 1). At baseline 48 patients (78%) were uncoupled with a median $E_A/E_V$ ratio of 1.9 (1.6-2.4) in relation to abnormally low $E_V$ (1.1 (0.9-1.6)), as compared to preserved $E_A$ (2 (1.5-2.7)). In the overall population, 31 patients (48 %) were classified as VO$_2$ responders. The percentage of VO$_2$ responders did not differ between the two groups (16 (48%) out of 33 vs 15 (54%) out of 28, $p=0.799$).

Combined analysis of the effects of the two therapeutic interventions on systemic parameters (Table 2, Figure 1)

At baseline, VO$_2$ responders had higher $E_A/E_V$ ratio, and lower SW/PVA ratio and VO$_2$ than VO$_2$ non-responders. Therapeutic interventions increased SAP, MAP, CO and DO$_2$ in the overall population. VO$_2$ responders were characterized by an increased SW/PVA ratio, and a decreased HR, and TPRi. VO$_2$ non-responders were characterized by an increased $E_A$, $E_V$, ScVO$_2$, TPRi, and a decreased gapCO$_2$.

Effects of FC on systemic oxygenation parameters (Supplementary File 2)

At baseline, VO$_2$ responders had lower VO$_2$, gapCO$_2$, and higher $E_A/E_V$ ratio, ScVO$_2$ than VO$_2$ non-responders. FC increased SAP, MAP, and SV in VO$_2$ responders and non-responders. VO$_2$ responders were characterized by an increase in SV and CO decreased TPRi, $E_A$, and an increased SW/PVA ratio and gapCO$_2$. $E_V$ did not change. VO$_2$ non-responders were characterized by an increase in SV, ScVO$_2$, and a decreased HR.

Effects of norepinephrine on systemic oxygenation parameters (Supplementary File 2)

At baseline, VO$_2$ responders had lower SV, CO, SW/PVA ratio, VO$_2$, and higher gapCO$_2$, $E_A/E_V$ ratio than VO$_2$ non-responders. Norepinephrine infusion increased SAP, MAP, CO and DO$_2$ in both groups. VO$_2$ responders were characterized by an increased SV and CO, SW/PVA ratio. VO$_2$ non-responders were characterized by an increased $E_A$, $E_V$, ScVO$_2$.

Correlations between systemic oxygenation parameters (efficacy) versus $E_A$, $E_V$, $E_A/E_V$ 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).

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). With an AUC [95%CI] of 0.72 [0.59-0.85] (p=0.004), baseline ScVO\(_2\) was predictive of VO\(_2\) responsiveness. When analysing patients separately for FC or norepinephrine infusion, baseline E\(_A\)/E\(_V\) was predictive of VO\(_2\) responsiveness in FC group (AUC: 0.77 [0.59-0.95] (p=0.008) and norepinephrine group (AUC: 0.74 [0.56-0.93] (p=0.045).

When using the principal component analysis, the 3 first principal components explained 61% of the variance (Supplementary file 2 and Figure 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) the majority of patients for whom FC or norepinephrine infusion increased VO$_2$ had V-A uncoupling with lower SW/PVA ratios; (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 analysing together FC 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); which 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 the $E_A/E_V$ was part of components that explain VO$_2$ responsiveness, and was independently associated with VO$_2$ responsiveness. Both approaches credibly establish at least the statistical relevance of analysing V-A (un)coupling in patients with hemodynamic instability following cardiac surgery.

_A pathophysiological perspective on V-A coupling_

Burkhoff and Sagawa have shown that mechanical efficiency is greatest when $E_A = E_V$ (i.e $E_A/E_V$ ratio =1) (4, 6, 17). The patients of the present study were characterized by “normal” $E_A$ but much lower than normal $E_V$ values thus resulting in 78% patients having V-A uncoupling. 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 (4, 6, 17). “Sacrificing” efficiency to preserve efficacy for a limites period of time is a “physiological choice” observed in athletes (20). The patients with the highest V-A coupling ratio (uncoupled) had the lowest VO$_2$ (20). The consequences of long term “sacrificing”, i.e. days for ICU patients are not known. For instance, the fact that catecholamine use is associated with increased mortality could be an example of long-term consequences of better cardiovascular performance with a high energetic cost (21).

Investigating the effects of two interventions on V-A coupling comes down to ask the question already raised many years ago: how effectively an increase in myocardial performance (an increase in SV) is transmitted to the peripheral circulation (22). This transmission may be mediated by the V-A coupling (22). In this respect, if the increase in cardiac performance is transmitted to the circulation, this should result into opening of new vascular beds, and if DO$_2$ limits the VO$_2$, this should result into an increase in VO$_2$. This is exactly 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*

The clinical relevance of the statistical relationship between V-A (un)coupling and VO$_2$ in the context of goal-directed therapy in critically-ill patients is still to be demonstrated. Septic shock is characterised by different profiles of V-A uncoupling (i.e different hemodynamic profiles) for which hemodynamic treatment may differ (23). The use of beta-blockers is an illustration of hemodynamic optimisation based on V-A coupling perspective (24, 25). Cardiologists have already integrated this hemodynamic approach in the treatment of chronic heart failure or arterial hypertension (9, 18, 25). Moreover, V-A coupling has been demonstrated as a factor limiting patients' adaptability to effort (8, 20). 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, 26). To the best of our knowledge, this is the first attempt that has specifically focused on VO$_2$. Previous authors have studied the association of V-A coupling improvement and the time course of systemic oxygenation parameters in trauma patients (26, 27). Our results support their findings by demonstrating an association between V-A coupling, SW/PVA ratio, to perfusion parameters and further VO$_2$ changes. One advantage of V-A coupling may be the fact that it can be non-invasively measured at bedside. On contrary to perfusion parameters, it does not need blood sample. The final clinical relevance of V-A (un)coupling for cardiac surgery patients will require well designed interventional trials such as the one published by Borlaug et al that used LV afterload reduction (28).

Potential limitations of the present study

The analysis of two therapeutics 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 and extensively studied (14). On the contrary, we would like to demonstrate that hemodynamic approach based on the V-A coupling makes it possible to dispense with the hemodynamic treatment and a detailed analysis of each parameters. 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$_2$ (29). The VO$_2$/DO$_2$ relationship is not linear. The VO$_2$ responder group has lower value of VO$_2$ that is below the value of the VO$_2$ non-responder group, even after hemodynamic treatment. We
believe the lower value of VO$_2$ in responder group may have not 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 (14). We calculated ESP from a radial artery signal, which may differ from the aortic pressure signal. However, radial artery pressure has been reported to provide a good estimate of ESP (30). 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 cardiologic and cardiac surgical area (14, 18).

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 ICU by individualising hemodynamic treatment and by analysing both the efficacy and efficiency of hemodynamic interventions.

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The authors declare that they have no competing interests.

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References

1. Schumacker PT, Cain SM. The concept of a critical oxygen delivery. Intensive Care Med 1987;(13):223–229
2. Osawa EA, Rhodes A, Landoni G et al. Effect of Perioperative Goal Directed Hemodynamic Resuscitation Therapy on Outcomes Following Cardiac Surgery: A Randomized Clinical Trial and Systematic Review. Crit Care Med 2016;(44):724-33
3. De Backer D. Detailing the cardiovascular profile in shock patients. Critical care 2017;(21):311
4. 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
5. Starling MR. Left ventricular-arterial coupling relations in the normal human heart. Am Heart J.1993;(125):1659–1666
6. Asanoi H, Sasayama S, Kameyama T. Venticulo arterial coupling in normal and failing heart in humans. Circulation Research 1989;(65):483–493
7. Takaoka H, Takeuchi M, Odake M, et al. Assessment of myocardial oxygen consumption (VO\textsubscript{2}) and systolic pressure volume area (PVA) in human hearts. Eur Heart J 1992;(13):85-90
8. Aslanger E, Assous B, Bihry N, et al. Association between baseline cardiovascular mechanics and exercise capacity in patients with coronary artery disease. Anatol J Cardiol 2016;(16):608-613
9. Maurer MS, Sackner-Bernstein JD, El-Khoury Rumbarger L, et al. Mechanisms Underlying Improvements in Ejection Fraction With Carvedilol in Heart Failure. Circ Heart Fail 2009;(2):189-96
10. Chang MC, Mondy JS, Meredith JW, et al. Redefining cardiovascular performance during resuscitation: ventricular stroke work, power, and the pressure-volume diagram. J Trauma 1998;(45):470-8
11. Guinot PG, Longrois D, Kamel S, et al. Venticulo-Arterial Coupling Analysis Predicts the Hemodynamic Response to Norepinephrine in Hypotensive Postoperative Patients: A Prospective Observational Study. Crit Care Med 2018;46:e17-e25
12. Von Elm E, Altman DG, Egger M, et al. 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
13. Guinot PG, Abou-Arab O, Guilbart M, et al. Monitoring dynamic arterial elastance as a means of decreasing the duration of norepinephrine treatment in vasoplegic syndrome following cardiac surgery: a prospective, randomized trial. Intensive Care Med. 2017;(43):643-651
14. Chen CH, Fetics B, Nevo E, et al. Noninvasive single-beat determination of left ventricular end-systolic elastance in humans. J Am Coll Cardiol 2001; 38 2028-34
15. Kelly RP, Ting CT, Yang TM, et al. Effective arterial elastance as index of arterial vascular load in humans. Circulation 1992;(86):513-21
16. Kass DA. Ventricular arterial stiffening: integrating the pathophysiology. Hypertension 2005; (46):185–193
17. Takaoka H, Takeuchi M, Odake M, et al. Assessment of myocardial oxygen consumption (Vo2) and systolic pressure volume area (PVA) in human hearts. Eur Heart J 1992;(13):85-90
18. Ikonomidis I, Aboyans V, Blacher J, et al. The role of ventricular-arterial coupling in cardiac disease and heart failure: assessment, clinical implications and therapeutic interventions. A consensus document of the European Society of Cardiology Working Group on Aorta & Peripheral Vascular Diseases, European Association of
Cardiovascular Imaging, and Heart Failure Association. Eur J Heart Fail. 2019 Mar 12. doi: 10.1002/ejhf.1436
19. Abou-Arab O, Braik R, Huette P, et al. The ratios of central venous to arterial carbon dioxide content and tension to arteriovenous oxygen content are not associated with overall anaerobic metabolism in postoperative cardiac surgery patients. PLoS One. 2018 Oct 26;13(10):e0205950.
20. Sahlén A, Shahgaldi K, Aagaard P, et al. Altered ventriculo-arterial coupling during exercise in athletes releasing biomarkers after endurance running. Eur J Appl Physiol 2012;(112):4069-79
21. Fellahi JL, Fischer MO, Daccache G, et al. Positive inotropic agents in myocardial ischemia-reperfusion injury: a benefit/risk analysis. Anesthesiology 2013;(118):1460-5
22. Freeman GL, Colston JT. Role of ventriculovascular coupling in cardiac response to increased contractility in closed-chest dogs. J Clin Invest 1990;(86):1278-84
23. Bouhemad B, Nicolas-Robin A, Arbelot C, et al. Acute left ventricular dilatation and shock-induced myocardial dysfunction. Crit Care Med 2009;(37):441-7
24. Morelli A, Ertmer C, Westphal M, et al. Effect of heart rate control with esmolol on hemodynamic and clinical outcomes in patients with septic shock: a randomized clinical trial. JAMA 2013;(310):1683-91
25. Chirinos JA, Sweitzer N.Card.Ventricular-Arterial Coupling in Chronic Heart Failure. Fail Rev 2017;(3):12-18
26. Chang MC, Martin RS, Scherer LA, et al. Improving ventricular-arterial coupling during resuscitation from shock: effects on cardiovascular function and systemic perfusion. J Trauma 2002;(53):679-85
27. Martin RS, Norris PR, Kilgo PD, et al. Validation of stroke work and ventricular arterial coupling as markers of cardiovascular performance during resuscitation. J Trauma 2006;(60):930-4
28. Borlaug BA, Olson TP, Abdelmoneim SS, et al. A randomized pilot study of aortic waveform guided therapy in chronic heart failure. J Am Heart Assoc 2014;(3):e000745
29. Scheeren TW, Arndt JO. Different response of oxygen consumption and cardiac output to various endogenous and synthetic catecholamines in awake dogs. Crit Care Med 2000;(28):3861-8
30. Haedersdal C, Madsen JK, Saunamäki K. The left ventricular end-systolic pressure and pressure-volume index. Comparison between invasive and auscultatory arm pressure measurements. Angiology1993;(44):959-64

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Figure legend

**Figure 1.** V-A coupling ratio according to VO$_2$ change

**Figure 2.** Variable factors map for the first and third component of the principal component analysis. The 10 more contributory variable are represented.
**Table 1.** Characteristics of the study participants on inclusion. Values are expressed as the mean or the number (%).

| Variables                                           | Overall population (n=61) |
|-----------------------------------------------------|--------------------------|
| Age (years; mean (SD))                              | 67 (12)                  |
| Gender (F/M)                                        | 12/49                    |
| SAPS 2                                              | 41 (14)                  |
| Ventilation parameters                              |                          |
| Tidal volume (ml kg⁻¹ of predicted body weight; mean (SD),) | 7.7 (0.6)                |
| Total PEEP (cmH₂O; mean (SD))                       | 5 (1)                    |
| Number of patients treated with norepinephrine (n, %) | 26 (48)                  |
| Median dose (mcg Kg⁻¹min⁻¹)                         | 0.08 (0.06-0.18)         |
| Number of patients treated with fluid expansion (n, %) | 35 (52)                  |
| In-hospital death (n, %)                            | 3 (6)                    |
Table 2. Comparison of haemodynamic parameters in VO\textsubscript{2} responders and VO\textsubscript{2} non-responders. Values are expressed as the mean (SD) or the median [interquartile range]. CO, cardiac output; DAP, diastolic arterial pressure; DO\textsubscript{2}, 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; VO\textsubscript{2}, oxygen consumption; $^s$: $p<0.05$ within groups (pre-/post-FC).

| Hemodynamic variables | VO\textsubscript{2} Responders (n=31) | VO\textsubscript{2} Non-responders (n=30) | $P$ value |
|-----------------------|--------------------------------------|----------------------------------------|-----------|
| HR (bpm)              |                                      |                                        |           |
| Pre                   | 78 (21)                              | 82 (19)                                | 0.410     |
| Post                  | 75 (20)$^s$                          | 80 (16)                                | 0.274     |
| SAP (mmHg)            |                                      |                                        |           |
| Pre                   | 99 (19)                              | 91 (14)                                | 0.093     |
| Post                  | 124 (19)$^s$                         | 116 (20)$^s$                          | 0.333     |
| MAP (mmHg)            |                                      |                                        |           |
| Pre                   | 68 (15)                              | 65 (10)                                | 0.260     |
| Post                  | 84 (14)$^s$                          | 80 (12)$^s$                           | 0.707     |
| DAP (mmHg)            |                                      |                                        |           |
| Pre                   | 52 (13)                              | 52 (10)                                | 0.971     |
| Post                  | 62 (14)                              | 62 (12)                                | 0.961     |
| SV (ml)               |                                      |                                        |           |
| Pre                   | 41 (14)                              | 46 (18)                                | 0.413     |
| Post                  | 57 (19)$^s$                          | 50 (16)$^s$                           | 0.118     |
| CO (L min\textsuperscript{-1}) |                                      |                                        |           |
| Pre                   | 3.2 (1.1)                            | 3.6 (1)                                | 0.159     |
| Post                  | 4.1 (1)$^s$                          | 3.8 (0.9)$^s$                         | 0.357     |
| TPRi (mmHg ml\textsuperscript{-1} m\textsuperscript{-2}) |                                      |                                        |           |
| Pre                   | 42 (14)                              | 34 (15)                                | 0.056     |
| Parameter                        | Pre       | Post      | $p$-value |
|---------------------------------|-----------|-----------|-----------|
| $E_A$ (mmHg ml$^{-1}$)          |           |           |           |
| EA                               | 2.3 (1)   | 2.1 (1)   | 0.358     |
| EV                               | 1.2 (0.6) | 1.3 (0.6) | 0.252     |
| $E_A/E_V$                       | 2.2 (0.6) | 1.6 (0.6) | 0.002     |
| SW/PVA ratio                    |           |           |           |
| Pre                             | 0.55 (0.12) | 0.62 (0.11) | 0.008     |
| Post                            | 0.62 (0.15) | 0.62 (0.12) | 0.891     |
| $DO_2$ (ml min$^{-1}$)          |           |           |           |
| Pre                             | 482 (179) | 504 (146) | 0.603     |
| Post                            | 635 (219) | 539 (149) | 0.047     |
| $VO_2$ (ml min$^{-1}$)          |           |           |           |
| Pre                             | 132 (54)  | 180 (53)  | 0.001     |
| Post                            | 198 (61) | 167 (53) | 0.041     |
| $SeVO_2$ (%)                    |           |           |           |
| Pre                             | 67 (12)   | 60 (9)    | 0.01      |
| Post                            | 63 (9) | 65 (8) | 0.842     |
| Gap$CO_2$ (mmHg)                |           |           |           |
| Pre                             | 9 (4)     | 9 (2)     | 0.842     |
| Post                            | 9 (4)     | 7 (5) | 0.061     |
| Arterial lactate (mmol l$^{-1}$)|           |           |           |
|       | Pre     | Post    | LVEF (%)       |
|-------|---------|---------|----------------|
|       | 1.5 (1.3-2.1) | 1.6 (1.3-2.1) | 0.882          |
|       | 1.5 (1.2-2.1) | 1.7 (1.3-2.1) | 0.468          |
|       | 42 (13)  | 50 (11) | 0.007          |
|       | 46 (12)  | 49 (9)  | 0.209          |
Variables factor map (PCA)

Figure