Ejection Fraction May Not Reflect Contractility: Example in Veno-Arterial Extracorporeal Membrane Oxygenation for Heart Failure

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Precise assessment of left ventricular (LV) contractility during veno-arterial extracorporeal membrane oxygenation (VA-ECMO) support is crucial. However, changes in loading conditions may mask changes in LV function when assessed with load-dependent parameters. We compared end-systolic elastance (Ees, mm Hg/ml), the reference load-independent parameter of LV contractility, with LV ejection fraction (LVEF) in two patients. The first patient was a 54-year-old patient supported with femoro-femoral VA-ECMO for a cardiogenic shock. Afterload was calculated by using arterial elastance (Ea, mm Hg/ml). Although Ees near doubled from day 0 to day 3, no significant change was observed in LVEF. The second patient was a 61-year-old patient supported with femoro-femoral VA-ECMO for severe heart failure complicated with sepsis. We retrospectively showed that discrepancy between LVEF and Ees resulted from changes in LV-arterial coupling. We concluded that LVEF may be misleading in the assessment of LV function during VA-ECMO for heart failure. *ASAIO Journal* 2017; XX:00–00.

Key Words: ventricular function, ventriculo-arterial coupling, end-systolic elastance, ejection fraction

Peripheral veno-arterial extracorporeal membrane oxygenation (VA-ECMO) is now the first-line device for refractory acute cardiogenic shock. Veno-arterial extracorporeal membrane oxygenation system pumps venous blood from the right atrium and reinjects oxygenated blood countercurrent into the descending aorta. Precise evaluation of left ventricular (LV) function in patients under assistance is a key point, in particular during weaning, and largely based on LV ejection fraction (LVEF).[1] However, the use of this load-dependent parameter is questionable. Indeed, more than 25 years ago, Robotham *et al.*[2,3] already pointed out that LVEF reflects the coupling between LV contractility and LV afterload but not the LV intrinsic contractility.

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Case Reports

A 54-year-old man presented a cardiogenic shock in relation with a stunned myocardium after coronary artery by-pass. He was supported with femoro-femoral VA-ECMO as a bridge to recovery (or transplantation). After 3 days, because we observed a normalization of blood lactates, an improvement in hemodynamics, and a normalization of liver and renal functions, the question of ECMO weaning was raised. We compared LVEF with end-systolic elastance (Ees), the reference parameter of LV contractility, known to be independent of loading conditions. End-systolic elastance was calculated as Ees = ESP/(ESV – Vo), where Vo is the intercept of end-systolic pressure–volume (ESPV) line with the x-axis, ESP is LV end-systolic pressure and ESV is LV end-systolic volume. Ees corresponds to the slope of the ESPV relationship (ESPVR) (**Figure 1**). Left ventricular systolic pressure was derived from femoral arterial line, whereas ESV was derived from transthoracic 2D echocardiography with automated border detection (VIVID S6; GE Healthcare). Arterial line was placed in contralateral femoral artery to cannulation site, far downstream from the VA-ECMO injection, in such a way that aortic pressure at the end-systole was equilibrated with LV ESP. The dicrotic arterial pressure and the corresponding ESV were plotted to determine one point of ESPVR in the pressure–volume (PV) graph. Several points of ESPVR were determined by changing pump speed, which resulted in load variation. Stroke volume (SV) was calculated as (EDV – ESV), where EDV is LV end-diastolic volume and LVEF (%) was calculated as SV/EDV. The afterload imposed to the left ventricle was also described by an arterial elastance (Ea) (mm Hg/ml), characterizing arterial properties including wall stiffness, compliance, outflow resistance, and wave's reflections.[4] Arterial elastance (mm Hg/ml) was calculated as the ratio of ESP to SV. Basal recordings were performed at day 0, and a new set of measurements was performed in the same manner described previously at day 3. Results are depicted in **Table 1** and **Figure 2**. Compared with measurements performed at day 0, LVEF and SV slightly decreased by 3% and 7 ml at day 3. However, Ees increased from 0.51 to 1.09 mm Hg/ml, and Ea increased from 2.63 to 4.45 mm Hg/ml, leading to a worsening of LV-arterial coupling. Mean arterial pressure (MAP) increased by 18 mm Hg, whereas heart rate (HR) did not significantly change. Unfortunately, during the night between day 3 and day 4, although heart function was improving and weaning was discussed, the patient presented a bleeding diathesis and evolved to a multiple organ failure and died.

A 61-year-old man was admitted in intensive care unit (ICU) for severe heart failure. He presented tachycardia-induced cardiomyopathy with severe dyspnea, signs of poor tissue

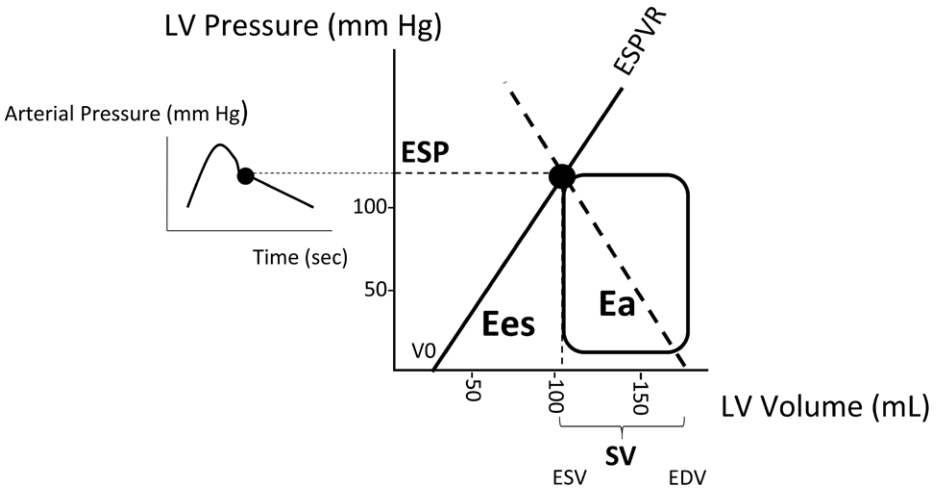

Figure 1. Schematic representation of LV P-V loop: SV is given by the intersection between ESPVR and Ea line. Ees is the slope of ESPVR; ESP is given by arterial pressure (at the dicrotic notch). V0, dead volume; ESV, end-systolic volume; EDV, end-diastolic volume; LV P-V, left ventricular pressure–volume; SV, stroke volume; ESPVR, end-systolic pressure–volume relationship; Ea, arterial elastance; Ees, end-systolic elastance; ESP, end-systolic pressure.

perfusion, and moderate hypotension. Echocardiography demonstrated low LVEF (9%) and aortic velocity time integral (8.1 cm). Despite effective antiarrhythmic therapy, there was no improvement neither in aortic flow nor in LVEF, and the patient was rapidly supported with VA-ECMO. Hypotension was enhanced by vasoplegia resulting from pulmonary sepsis with MAP = 56 mm Hg despite vasopressor treatment. After empirical antibiotic treatment, vasopressors were weaned after 3 days, and the patient paradoxically developed systemic hypertension with MAP reaching 126 mm Hg. However, echocardiography did not show any improvement in LVEF while vasopressors were weaned. When antihypertensive drugs (*i.e.,* vasodilators) were administrated, a significant increase in LVEF (28% *vs.* 9%) was observed. Veno-arterial extracorporeal membrane oxygenation was weaned at day 4 and outcome was favorable: LVEF increased to 34 % when VA-ECMO was removed. The patient left ICU a few days later. In this second case report, we retrospectively analyzed LV-arterial coupling by considering Vo = 0 ml because VA-ECMO flow was not changed intentionally to precisely determine Ees. In these circumstances, an approximation of Ees (Ees′) was simply given by ESP-to-ESV ratio. Between day 0

Table 1. Catecholamine Levels, ECMO Flow, and Hemodynamic Parameters at Days 0 and 3

	Day 0	Day 3
Dobutamine (μg/kg/min)	5	5
Norepinephrine (μg/kg/min)	5	15
ECMO flow (L/min)	5.80	5.50
MAP (mm Hg)	71	89
HR (bpm)	86	88
SV (mL)	27	20
LVEF (%)	17	14
LVEDV (mL)	156	137
LVESV (mL)	129	127
Ees (mm Hg/mL)	0.51	1.09
Ea (mm Hg/mL)	2.63	4.45
Ees/Ea	0.33	0.24

MAP, mean arterial pressure; HR, heart rate, SV, stroke volume; LVEF, left ventricular ejection fraction; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; Ees, end-systolic elastance; Ea, arterial elastance; Ees/Ea, ventriculo-arterial coupling index; ECMO, extracorporeal membrane oxygenation.

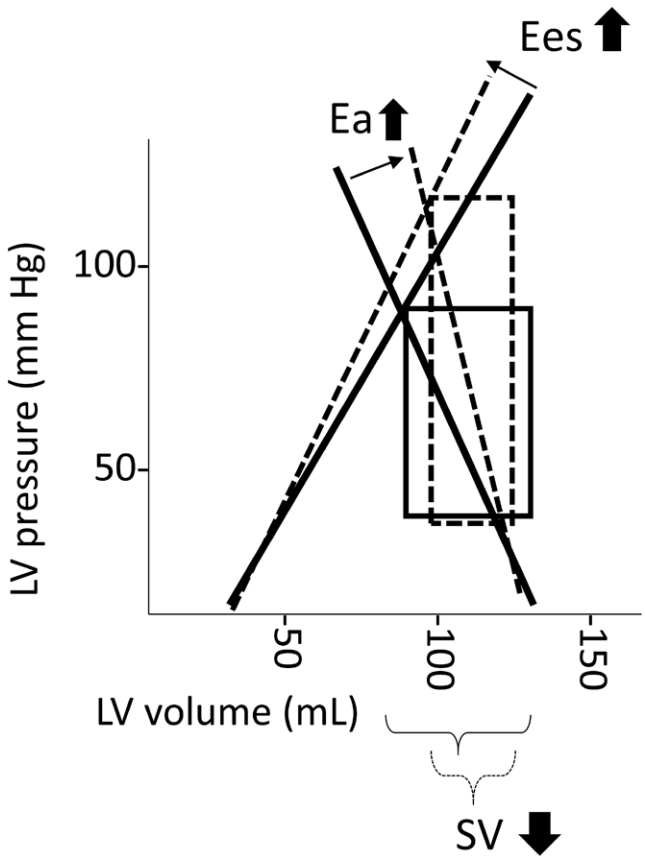

Figure 2. Schematic representation of LV P-V loop at day 0 (solid line) and at day 3 (dotted line): SV decreased while contractility Ees increased because Ea increased. LV P-V, left ventricular pressure–volume; SV, stroke volume; Ees, end-systolic elastance; Ea, arterial elastance.

and day 3, Ees′ increased from 0.46 to 0.86 mm Hg/ml and Ea increased from 4.66 to 6.24 mm Hg/ml when vasoplegia was ruled out. As a result, Ees′-to-Ea ratio did not significantly change (0.11 *vs*. 0.14). When vasodilators were administrated, Ea decreased to 2.24 mm Hg/ml, whereas Ees′ did not changed, leading to an improvement in LV-arterial coupling, with Ees′-to-Ea ratio = 0.41 (**Table 2**).

Discussion

Assessment of LV function during VA-ECMO is mainly based on LVEF. However, it is well established that LVEF is the result of a continuous interaction between LV intrinsic contractility and afterload (**Figure 1**). During assistance, when aortic valve opens, SV is transferred into the aorta against arterial load which is the combination of arterial tone and injection from the VA-ECMO pump. As LV volume decreases from EDV to ESV, the actual ESV is a function of not only intrinsic heart contractility, but also of this arterial load. For the same EDV and intrinsic heart contractility, if arterial pressure at end-systole decreases (*i.e.,* Ea decreases), then ESV is lower and LVEF greater (**Figure 1**). Reversely, increasing arterial pressure (*i.e.,* increasing Ea) has the opposite effect by increasing ESV and decreasing LVEF. This is even more significant when LV contractility is low. Indeed, the lowest the slope of ESPVR, the greatest the influence of afterload on SV and LVEF (**Figure 2**). Importantly, if arterial load is independently varied (*e.g.,* by changing VA-ECMO flow), the ESPVR can be easily determined. The slope of the ESPVR (Ees) precisely determines the intrinsic contractility of the heart (**Figure 1**). The steeper the slope, the greater the contractility. Ees (mm Hg/ml) is a useful, load-independent index of myocardial contractility. Ees is the reference measure of LV systolic performance derived from the complex association between the inotropic efficiency and the functional, structural, and geometric characteristics of the left ventricle. This case report clearly demonstrates discrepancy between LVEF and contractility which may lead to improper assessment of LV function, when using load-dependent parameters. Current recommendations for VA-ECMO weaning consider that VA-ECMO could be withdrawn when LVEF is > 20% at minimal VA-ECMO flow. However, in addition to VA-ECMO flow, others components of Ea (like vascular tone) can also mask change in LV contractility. In our case, afterload was severely increased at day 3, because of vasopressors. This was responsible for a severe increase in Ea, leading to a drop in LVEF while LV contractility increased (**Figure 2**). Similarly, the same mechanism applies in sepsis when vasoplegia is corrected, resulting in a decrease in LVEF while LV contractility has not changed.[3,5] This is well illustrated in the second case report; LVEF did not change while "estimated" Ees (Ees′) increased at day 3, when vasoplegia was corrected. Ees'-to-Ea ratio (LV-arterial coupling index) did not significantly change because of increased Ea resulting from vasoplegia correction and hypertension. As LVEF is the result of LV-arterial coupling, no improvement was observed, based on LVEF assessment. When Ea decreased, resulting from vasodilators administration, LV-arterial coupling improved (Ees′-to-Ea ratio increased) and finally LVEF increased (**Figure 3**). Interestingly, this "load sensitivity" is enhanced in failing hearts because the slope of the end-systolic line (Ees) is lower than in normal hearts. Afterload burden induced by VA-ECMO injection is responsible for worsening of LV-arterial uncoupling, leading to impaired energetic efficiency and increased oxygen consumption by the myocardium.[6] As a result, determination of weaning time is crucial, and assistance should only be left in place while the heart is unable to achieve adequate blood flow. In such a way, other devices (*e.g.,* Impella or CentriMag) may be preferred in circumstances where recovery is an option specifically because they do not impose such an afterload burden. In fact, weaning protocols, by turning down the VA-ECMO flow, intuitively improve ventriculo-arterial coupling and determine whether its result (*i.e.,* SV) is adequate. However, as shown in the last discussion, these weaning tests are strongly influenced by loading conditions.

In conclusion, these two case reports clearly show that LV-arterial coupling is a key factor when assessing LV function in heart failure and that focusing only on load-dependent parameters can lead to improper assessment of LV function. Discrepancy between LVEF and contractility, which may at first appear paradoxical, is well explained by LV PV analysis.

Table 2. Catecholamine Levels, ECMO Flow, and Hemodynamic Parameters at Days 0, 3, and 4

	Day 0	Day 3	Day 4
Norepinephrine (µg/kg/min)	0.8	0	0
Isosorbide dinitrate (mg/h)	0	0	4
ECMO flow (L/min)	5.1	4.8	4.6
SAP (mm Hg)	56	126	84
MAP (mm Hg)	56	126	84
HR (bpm)	109	86	93
SV (mL)	19	25	56
LVEF (%)	9	12	28
LVEDV (mL)	199	206	202
LVESV (mL)	181	177	138
Ees (mm Hg/mL)	0.47	0.87	0.91
Ea (mm Hg/mL)	4.66	6.24	2.24
Ees/Ea	0.11	0.14	0.41

MAP, mean arterial pressure; HR, heart rate, SV, stroke volume; LVEF, left ventricular ejection fraction; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; Ees, end-systolic elastance; Ea, arterial elastance; Ees/Ea, ventriculo-arterial coupling index; ECMO, extracorporeal membrane oxygenation.

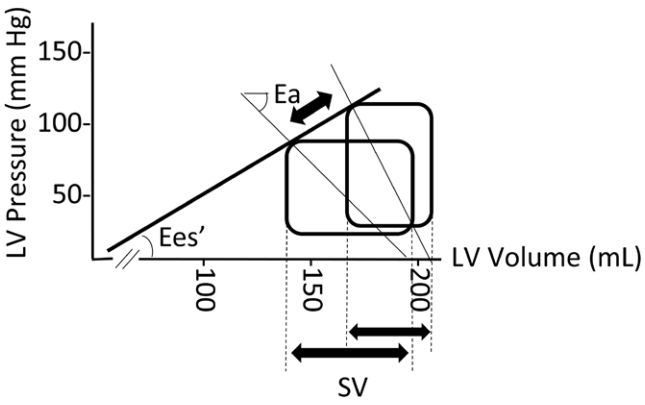

Figure 3. Schematic representation of LV P-V loop. Although "estimated" Ees ((Ees′) did not change, SV and consequently ejection fraction varied as a function of Ea. LV P-V, left ventricular pressure–volume; Ees, end-systolic elastance; SV, stroke volume; Ea, arterial elastance.

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